Diffuse alveolar hemorrhage associated with thrombotic thrombocytopenic purpura after allogeneic bone marrow transplantation

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ABSTRACT

Alveolar hemorrhage is an early complication after bone marrow transplantation (BMT) and often associated with inflammatory pulmonary processes. We present a case of diffuse alveolar hemorrhage associated with BMT associated thrombotic thrombocytopenic purpura (BMT-TTP). An 18-years-old man with acute myeloid leukaemia (FAB; M5) underwent ABO incompatible BMT from his HLA-identical sister. On the 37th day of BMT, BMT-TTP was diagnosed with the occurrence of red cell fragmentation and rise in serum lactic dehydrogenase (LDH) level with severe sudden decrease in hemoglobin and platelet levels. Cyclosporine A (CsA) was ceased and plasma infusion with plasma exchange was started. On the 42nd day of BMT, the diagnosis of diffuse alveolar hemorrhage was made by the clinical, bronchoscopic and bronchoalveolar lavage fluid findings. Alveolar hemorrhage among patients with BMT-TTP has been scarce reported. These two complications may be regarded as related, as small vessel injury is a central feature in both and they may share aetiological and pathogenetic factors.

Key Words: Alveolar, Hemorrhage, Thrombotic thrombocytopenic purpura, Bone marrow transplantation.

ÖZET

Allogeneik kök hücre nakli sonrası trombotik trombositopenik purpuraya eşlik eden yaygın alveoler hemoraji

Alveolar hemoraji kök hücre nakli (KHN) sonrası erken komplikasyonlardandır ve sıklıkla inflamatuvar süreçlere eşlik eder. Burada allogeneik KHN sonrası trombotik trombositopenik purpura (TTP)'ya eşlik eden bir yaygın alveoler hemoraji olgusu sunmaktayız. Akut miyeloblastik lösemili (AML-M5) 18 yaşında erkek hastaya HLA uyumlu kız kardeşinden ABO uyumsuz KHN yapıldı. KHN'nin 37. günü alyuvar fragmantasyonu, serum LDH yükselmesi, hemoglobin ve trombosit sayılarında hızlı düşme ile karakterize KHN-TTP tanısı kondu. Siklosporin-A kesilerek, plazma değişimi ile birlikte plazma infüzyonu yapıldı. KHN'de TTP'ye eşlik eden alveoler hemoraji seyrek görülen bir bulgudur. Bu iki komplikasyon birbiri ile ilişkili kabul edilmekte ve küçük damar hasarı her ikisinde de bulunmaktadır. Etyolojik ve patogenetik faktörler de ortak olabilir.

Anahtar Kelimeler: Alveoler, Hemoraji, Trombotik trombositopenik purpura, Kök hücre nakli.

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INTRODUCTION

Alveolar hemorrhage may occur in all severe disorders of hemostasis. It is an early complication after bone marrow transplantation (BMT) and often associated with inflammatory pulmonary processes (including infection)[1]. Thrombotic thrombocytopenic purpura (TTP) is another serious complication after BMT and characterized by thrombocytopenia, microangiopathic hemolytic anemia, and ischemic manifestations resulting from platelet agglutination in the arterial microvasculature[2]. Thrombotic microangiopathies (TMA) after BMT results from widespread endothelial cell damage, leading to microangiopathic erythrocyte fragmentation, platelet consumption and vital organ dysfunction due to small vessel occlusion[3]. The endothelial cell injury leading to TMA, was due to toxic conditioning regimens [high-dose chemotherapy and total body irradiation (TBI)], cytomegalovirus (CMV) infection, the use of cyclosporine A (CsA), and a possible graft-versus-host effect on the endothelium[4-7]. Because anemia, thrombocytopenia, renal impairment, and changes in mental status are common and may have multiple causes in the transplant population, diagnosis of TTP can be difficult after BMT.

Here we present a case of diffuse alveolar hemorrhage associated with BMT associated thrombotic thrombocytopenic purpura (BMT-TTP).

A CASE REPORT

An 18-years-old man developed acute myeloid leukaemia (FAB; M5) after two years of autologous peripheral blood stem cell transplantation for second chemosensitive relapse of Hodgkin's disease. Following two courses of induction therapy he achieved complete remission and underwent ABO incompatible BMT from his HLA-identical sister. The conditioning regimen consisted of cyclophosphamide (60 mg/kg on days -3 and -2) and total body irradiation (TBI; 12Gy). Cyclosporine A (12.5 mg/kg, daily) and short-term methotrexate (15 mg/m^2/day on day +1 and 10 mg/m^2/day on days +3, +6 and +11) were given as acute graft-versus-host disease (GVHD) prophylaxis. Engraftment occurred on the 18th day of BMT. On day +23, he gradually became hypertensive and his serum creatinine level increased from 1.2 mg/dL to 2.1 mg/dL (Figure 1). Meanwhile blood CsA level was found to be 500 ng/mL that was in the toxic range (normal range 200-400 ng/mL). Doxazocin mesylate (4 mg/day) and furosemide (40 mg/day) were added to the treatment and CsA was discontinued until CsA level was decreased to the therapeutic range and serum creatinine level returned to the normal. On the 37th day, he received methyl prednisolone (2 mg/kg/day) for acute GVHD grade II. Despite a prompt response in few days, the clinical picture was deteriorated and he developed malaise, headache, nausea and vomiting. Despite the regression of acute GVHD, BMT associated TTP was noted. The diagnosis was based on the occurrence of red cell fragmentation (10% fragmented red cells) and rise in serum lactic dehydrogenase level (LDH 920 U/L; normal range 100-230 IU/L) with severe sudden decrease in hemoglobin (Hb) level from 8.4 g/dL to 6.4 g/dL and platelet (Plt) count from 61 x 10^9/L to 41 x 10^9/L (Figure 1). The indirect bilirubin level was 1.08 mg/dL. CsA was ceased again and plasma infusion with plasma exchange was started. Because of the difficulties in obtaining fresh frozen plasma, plasmapheresis could be given three times in a week until the levels of Hb, LDH and Plt were stabilized, then the frequency of plasmapheresis was reduced. On the 42nd day of BMT, the patient developed hemoptysis, which was followed by cough and dyspnea. Bilateral diffuse alveolar opacities were seen on chest radiograph (Figure 2a, 2b). There was no evidence of an infection. Coagulation profile was in normal limits. Anemia progressed and arterial oxygen partial pressure was lowered. Fiberoptic bronchoshopy showed blood emerging diffusely from the airways and bronchoalveolar
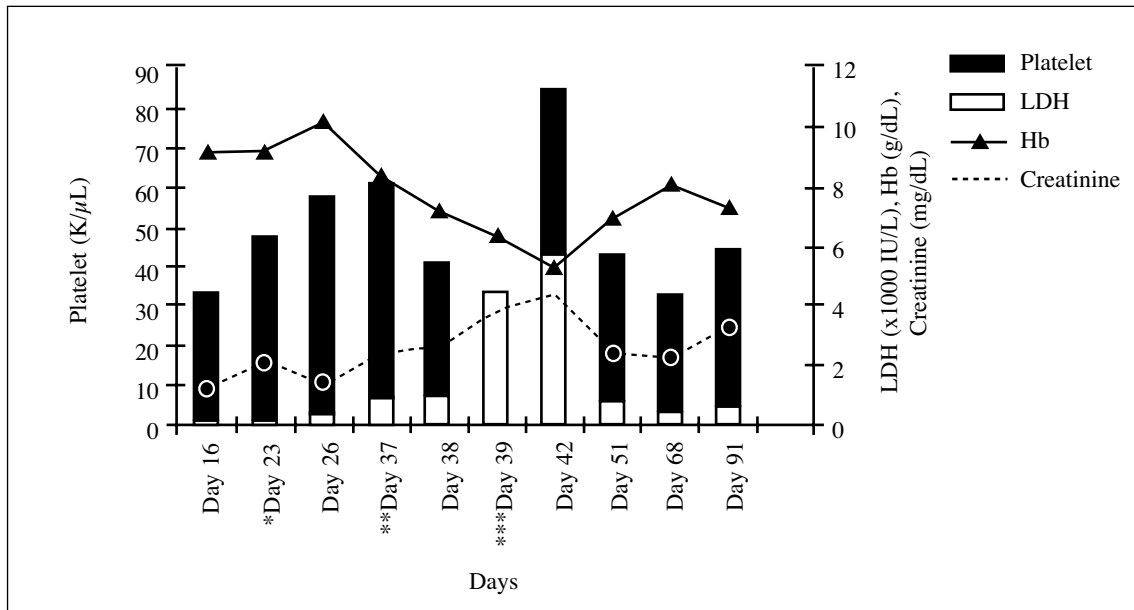
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Figure 1. Serum LDH, platelet, hemoglobin and creatinine levels of patient. With the increasing LDH levels, platelet and hemoglobin levels showed decrements and microangiopathic hemolytic anemia/TTP occurred. *On day +23, serum creatinine level increased from 1.2 mg/dL to 2.1 mg/dL with a blood CsA level of 500 ng/mL and CsA was ceased. **On day +37, acute GVHD grade II was diagnosed. ***On day +39, despite the regression of acute GVHD, BMT associated TTP was noted. Cyclosporine A was ceased again and plasmapheresis was started.
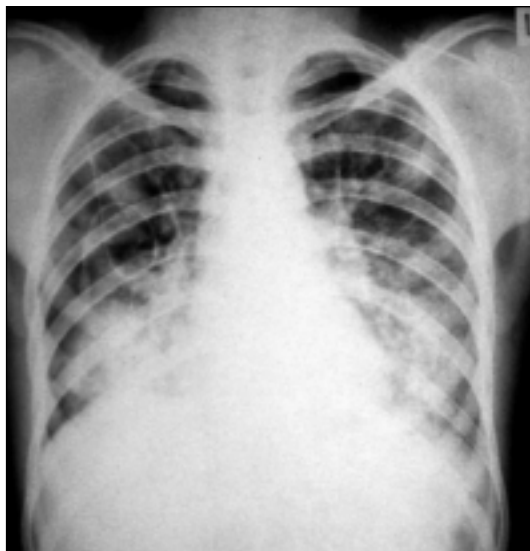

Figure 2a. Posteroanterior chest X ray film showing bilateral diffuse alveolar opacities.

Figure 2b. Thorax computed tomogram of the chest showing diffuse alveolar hemorrhage.

lavage fluid analysis showed the presence of many red blood cells. The diagnosis of diffuse alveolar hemorrhage was made by the cli-
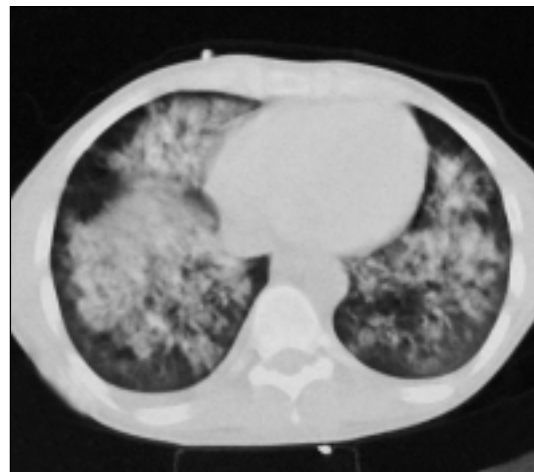
nical, bronchoscopic and bronchoalveolar lavage fluid findings. The clinical symptoms including dyspnea and hemoptysis were disappeared after intensified transfusion support and oxygen therapy. However, a progressive decline in renal function was added

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to the persistent microangiopathic hemolytic anemia. Plasma exchange was performed more often, but there was no significant renal functional improvement. Meanwhile, weekly monitoring of CMV serology showed the detection of CMV antigen. He received dose adjusted gancyclovir and intravenous immunoglobuline, as preemptive therapy. His renal function progressively deteriorated and he required hemodialysis. On the 91st day of BMT he developed abundant hemoptysis and died.

DISCUSSION

Alveolar hemorrhage results from injury to alveolar capillaries leading to extravasation of red blood cells into alveolar lumen. The causes of alveolar hemorrhage are many, and in some patients several causes such as infections, hemostatic disturbances jointly contribute to the development of alveolar hemorrhage. After BMT, it occurs as an early complication. In most cases thrombocytopenia is present, but inflammatory pulmonary processes (including infection) often are associated. TTP is a relatively frequent complication of hematopoietic cell transplantation, especially allogeneic transplantation and it is associated with high mortality, though death is usually caused by multiple factors[8]. Although endothelial injury has been implicated, the exact mechanisms of TTP remain to be defined. Endothelial injury is likely the result of multiple contributing pathogenic factors, including toxic conditioning regimens, CMV infection, use of CsA, and a possible graft-versus-host effect on the endothelium[3-7]. Among patients with microangiopathy and GVHD, a significant correlation between the time of monocyte engraftment and activation of coagulation was reported[3]. Microangiopathic process in these patients was postulated to be the result of inflammatory cytokine production in the course of GVHD. Some investigators thought that inflammatory cytokines in the course of GVHD may mediate microangiopathy directly through endothelial injury or through induction of endothelial cell procoagulant activity[9,10].

Alternatively, through cytokine-induced up-regulation of endothelial HLA class II antigen expression, the endothelium can become a target organ in the GVHD process. These reactions may be aggravated by the vascular toxicity of CsA or prior endothelial damage caused by intensive conditioning regimens[3]. Transplantation from unrelated donors, hepatic venoocclusive disease (VOD), grade 2-4 acute GVHD and bacteremia with diphtheroid organisms were also reported as the other risk factors for the development of TMA in the setting of BMT[11]. The patients with increased serum creatinine levels in the setting of TTP had a significant poorer outcome than those with normal levels. Although there are some remission achieved reports with plasma exchange using fresh frozen plasma or cryosupernatant fraction of plasma, the management of TTP is unsatisfactory and mortality is high. As an antithrombotic agent the beneficial effect of defibrotide in chemotherapy-related hemolytic-uremic syndrome (HUS)/TTP was already reported[12]. Defibrotide, is a single-stranded polydeoxyribonucleotide drug derived from animal tissue, that has antithrombotic, antiischemic and thrombolytic properties[13].

Alveolar hemorrhage among patients with BMT-TTP has been scarce reported[14-16]. However reports that show an association between these syndromes were not clear.

In conclusion, DAH and TMA are very serious and less common complications after BMT with high mortality rates. The occurrence of these syndromes in combination is very rare. The occurrence of concurrent GVHD, may represent a "graft-versus-endothelial" process, aggravated by preceding or concomitant endothelial insults such as extensive prior therapy, use of CsA, and reactivation of CMV. For our case, concomitant occurence of TTP and DAH with many proposed etiological and pathogenetic factors indicated the small vessel injury as a central feature in both clinical syndrome although vascular endothelial damage supported by several factors could

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contribute to that combination, mechanisms of these syndromes appeared to need more investigations.

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