Syngeneic peripheral blood stem cell transplantation with immunosuppression for hepatitis-associated severe aplastic anemia

Hepatite bağlı şiddetli aplastik anemi için immunosüpresyonla singeneik periferik kan kök hücre transplantasyonu

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Abstract

Hepatitis-associated aplastic anemia occurs in up to 10% of all aplastic anemia cases. Syngeneic bone marrow transplantation is rare in patients with severe aplastic anemia and usually requires pre-transplant conditioning to provide engraftment. We report on a 29-year-old male patient with hepatitis-associated severe aplastic anemia who had a series of severe infectious conditions before transplantation, including tracheal inflammation. Life-threatening bleeding, which developed after bronchoscopy, was successfully treated with activated recombinant factor VII and platelet transfusions. Syngeneic peripheral blood stem cell transplantation using immunosuppressive treatment with antithymocyte globulin and cyclosporin A without high-dose pre-transplant conditioning was performed, followed by complete hematologic and hepatic recovery. *(Turk J Hematol 2010; 27: 294-8)*

Key words: Aplastic anemia, hepatitis, peripheral blood stem cell transplantation, trachea, infection, bleeding

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Özet

Hepatite bağlı aplastik anemi, tüm aplastik anemi olgularının %10'undan daha az bir oranda meydana gelir. Şiddetli aplastik anemili hastalarda singeneik kemik iliği transplantasyonu nadir olup, genellikle hibritleşmeyi sağlamak için nakil öncesi şartlandırma gerektirmektedir. Transplantasyondan önce, trakea enflamasyonu da dahil olmak üzere şiddetli enfeksiyonlar geçiren hepatite bağlı şiddetli aplastik anemili 29 yaşında erkek bir hastaya ilişkin bir rapor sunulmuştur. Bronkoskopiyi takiben gelişen yaşamı tehdit eden kanama, aktive edilmiş rekombinant faktör VII ve platelet transfüzyonlarıyla başarılı şekilde tedavi edilmiştir. Yüksek doz nakil öncesi şartlandırma olmaksızın, antitimosit globu-

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lin ve siklosporin A ile immunosüpresif tedavi yöntemiyle singeneik periferik kan kök hücre transplantasyonu gerçekleştirilmiş ve ardından tam hematolojik ve hepatik iyileşme gözlenmiştir.
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Anahtar kelimeler: Aplasti Anemi, hepatit, periferik kan kök hücre transplantasyonu, trake, enfeksiyon, kanama

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Introduction

Hepatitis-associated aplastic anemia is a well-described disease that occurs in 2 to 5% of aplastic anemia cases in the West, and in 4 to 10% in the Far East [1]. Hepatitis of the hepatitis-associated aplastic anemia does not appear to be caused by any of the known hepatitis viruses [1,2]. Syngeneic bone marrow transplantation in patients with severe aplastic anemia (SAA) is rare, and usually requires pre-transplant conditioning to provide engraftment [3,4].

We report a patient with hepatitis-associated SAA who was successfully treated with syngeneic peripheral blood stem cell (PBSC) transplantation after a series of infectious and bleeding complications. To our best knowledge, this is only the second published case of syngeneic PBSC transplantation in hepatitis-associated SAA [5]. The patient gave informed consent for review of his medical records and publication of this case.

Case Report

A 29-year-old male patient presented with fatigue, fever and skin and mucosal bleeding at the end of January 2008. He has a twin brother.

Initial laboratory findings showed severe pancytopenia and elevation of bilirubin and liver enzymes (Table 1, Day -116). Acquired idiopathic SAA was diagnosed following bone marrow biopsy, which indicated less than 10% cellularity. A series of tests were performed including hepatitis C virus (HCV), HBV, human immunodeficiency virus (HIV), antinuclear antibody (ANA), and Ham and Hartman test, which were all negative. Cytogenetics evaluation was normal. The patient was completely dependent on platelet and packed red blood cell (RBC) transfusions in order to control the bleeding and anemia.

There was a severe deterioration in the patient's liver condition, with development of jaundice and an increase in blood liver enzyme concentrations, at the beginning of March 2008 (Table 1, Day -77). In mid-March, the patient received mycophenolate mofetil 750 mg twice daily, together with 5 μg/kg/d of recombinant human granulocyte colony-stimulating factor (G-CSF) and 1 mg/kg/day of methylprednisolone. The patient developed diabetes mellitus, which required regular short-acting insulin treatment and necessitated discontinuation of corticosteroid treatment. Combined mycophenolate mofetil and G-CSF treatment caused elevation of granulocytes to 1.3 x 10^9/L in the second half of April, but showed no improvement in the platelet count (Table 1, Day -30). The improvement in RBC was the result of RBC transfusions. From the beginning of the disease until the end of April, the patient suffered two episodes of enterococcal sepsis and pneumonia and four febrile episodes.

HLA typing was performed after repeated attempts. His twin brother was HLA identical (PCR-SSP A*01-, B*08 B*35, DRB1*03-). We decided to perform syngeneic PBSC transplantation using antithymocyte globulin (ATG) and cyclosporin A as an immunosuppressive regimen without high-dose chemotherapy conditioning.

The transplantation procedure was postponed because the patient developed fever, hemoptysis and a sensation of a foreign body in his throat at the initial day of the planned conditioning regimen in April. Inspiratory stridor was auscultated over the trachea. Indirect laryngoscopy showed no signs of a laryngeal disease. A computed tomography (CT) scan showed a thickening of the anterior wall of the trachea, with internal air pockets, mucosal erosion and intraluminal soft tissue formations (Figure 1a). The patient received liposomal amphotericin and antibiotics. A bronchoscopy was performed with a support of platelet transfusions and fresh frozen plasma, because of slightly prolonged prothrombin time. This caused extensive bleeding from the trachea, which was life-threatening given the concurrent development of alveolar hemorrhage and global respiratory insufficiency (Figure 1b). The patient received one dose of recombinant factor

(rF) VIIa 90 μg/kg and platelet transfusion, after which the bleeding was markedly reduced. A week later, the fever stopped and the respiratory insufficiency was eliminated, but the patient still suffered from hemoptysis. A decision was made to start the transplantation procedure. Mycophenolate mofetil and G-CSF were discontinued before transplantation. The patient was still severely pancytopenic before transplantation, and exhibited hepatitis with some signs of improvement (Table 1, Day -4).

G-CSF was given as 10 μg/kg/day to mobilize the donor's PBSCs. A large volume apheresis specimen was obtained using peripheral vein access with a Cobe-Spectra cell separator on Day 5 of mobilization. The cell harvest, with a total of 7.8 x 10^8/kg of MNC, 4.37 x 10^8/kg of CD3+, 11.7 x 10^6/kg of CD34+, and 12.9 x 10^6/kg of CD133+ cells, was infused on Day 0, following immunosuppression, as follows: 8.5 mg/kg/day of ATG (Fresenius) for 4 days (from Day -4 to -1) and 5 mg/kg/day of cyclosporin A intravenous (i.v.) in two equal doses for 7 days (from Day -1 to Day 6), followed by a switch to oral cyclosporin A. Mycophenolate mofetil was added on Day +14 as 1 g twice daily due to persistent thrombocytopenia and anemia. The patient received G-CSF as 5 μg/kg after PBSC infusion until white blood cell (WBC)

Table 1. Laboratory findings for blood and liver function

Parameters*	Day# -116	-77	-30	-4	+8	+48	+250
WBC [x10^9/L]	0.2	0.345	3.15	1.83	4.2	6.09	6.81
Neutrophils [x10^9/L]	0.069	0.107	1.3	0.354	1.57	2.43	2.66
Hb [g/L]	46	80.4	79.9	90.6	78.9	102	117
Hct [l/l]	0.13	0.215	0.218	0.237	0.222	0.27	0.32
Plt [x10^9/L]	15.6	19.2	11.9	23.9	13	106	176
Rtc [%]	0.3	-	0.3	0.3	0.2	4.2	1.68
AST [U/L]	67	835	460	283	32	40	22
ALT [U/L]	197	1835	1360	1099	27	49	13
Gamma–GT [U/L]	95	166	449	285	34	35	13
Total bilirubin [μmol/L]	25	157	51	56	18	26	17
Direct bilirubin [μmol/L]	7.2	68.4	39.9	14.3	4.9	6.7	3.9

*upper normal values: AST 37 U/L, ALT 40 U/L, gamma–GT 55 U/L, Total bilirubin 21 μmol/L, direct bilirubin 4.2 μmol/L

– before transplantation, + after transplantation

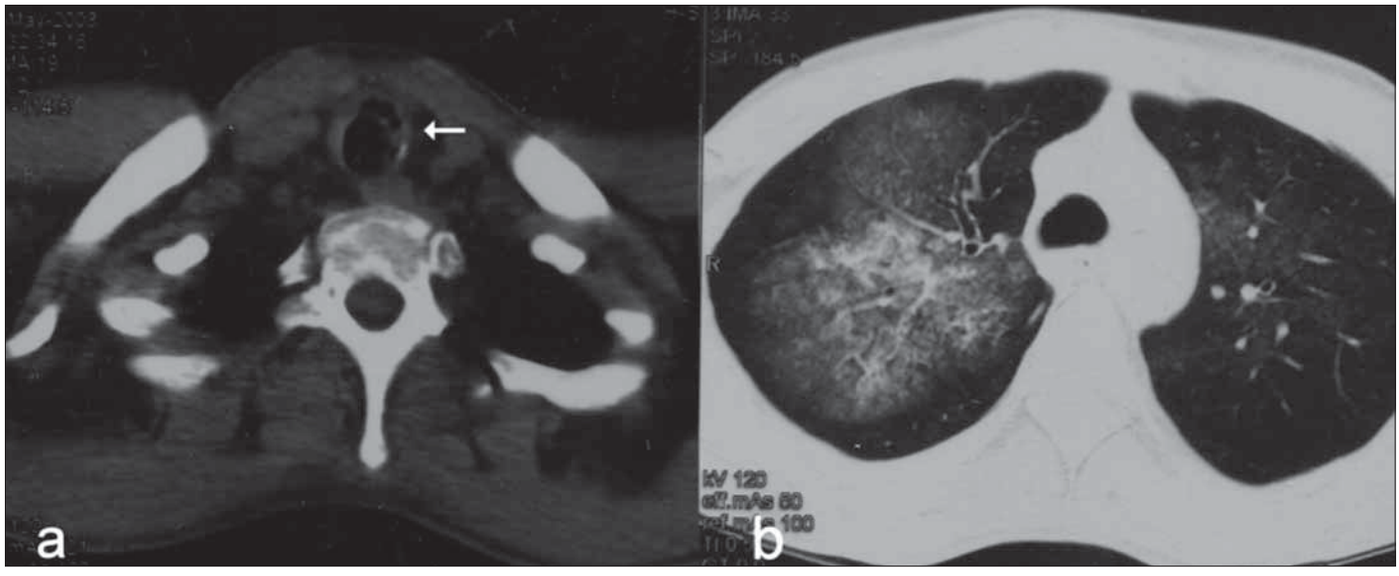

Figure 1. a) The neck CT scan shows a thickened anterior wall of the trachea, with internal air pockets, mucosal erosion and intraluminal soft tissue formations; b) The chest CT scan shows alveolar hemorrhage, particularly in the right lung

recovery. He also received standard prophylactic antibacterial, antifungal and antiviral treatments. The transplant took place without any febrile episodes or other complications. Neutrophil engraftment was rapid. The granulocytes were over 1.0 x 10^9/L on Day +8 (Table 1). The final RBC transfusion was on Day +16, and the final platelet transfusion on Day +27. The platelet number reached 100 x 10^9/L on Day +48 (Table 1), whereas RBC reached 100 g/L on Day +79. The patient was discharged from the hospital on Day +34. A follow-up CT scan of the trachea showed resolution of the lesions, with minor scarring. A complete resolution of the patient's liver disease was established. Diabetes mellitus was well controlled through diet. A follow-up bone marrow biopsy showed normal findings. Mycophenolate mofetil was discontinued, while cyclosporin A was gradually tapered. The patient is well and without signs of rejection 15 months after transplantation.

Discussion

In summary, this case demonstrates concomitant hepatitis of unknown origin and SAA. The patient has a twin brother, but the transplantation was delayed for several reasons, such as severe hepatitis, unusual life-threatening tracheal complications, most likely of infectious origin, and due to repeated, unsuccessful HLA testing.

Inflammation of the tracheal wall is rarely reported in aplastic anemia, and it is usually caused by aspergillosis [6,7]. The situation was further complicated by life-threatening bleeding provoked by bronchoscopy, which was successfully treated by rFVIIa and platelet transfusions. This complication has not been previously reported in aplastic anemia. Successful off-label use of rVIIa has been reported for bleeding in cases of liver disease and in severely injured trauma patients [8,9]. It has been used rarely for bleeding complications in aplastic anemia [10].

Ultimately, we conducted a successful syngeneic transplantation using immunosuppressive treatment without high-dose pre-transplant conditioning, which is rarely reported in hepatitis-associated SAA [4]. Conditioning regimens with cyclophosphamide ± ATG, or with fludarabine, cyclophosphamide ± ATG, are widely used in allogeneic settings with high rates of sustained engraftment and survival [11,12]. In the settings of syngeneic transplantation in aplastic anemia, application of cyclophosphamide in the conditioning regimen provides sustained engraftment, but increases early mortality [3]. Syngeneic transplantation without conditioning is followed by a high rate of graft failure without the adverse effects on overall survival [3]. The concept of syngeneic transplantation without conditioning or with ATG conditioning alone, as in our case, is therefore feasible [4,13]. Hepatitis usually precedes aplastic anemia [1,2]. In this case, hepatitis was present at the time of diagnosis and it severely deteriorated during the course of SAA. We believe that the immunosuppressive treatment may have had an important role both for the hematologic condition and for liver improvement [14]. The liver improvement was rapid and complete following ATG and cyclosporin A treatment applied during the transplantation procedure. In all likelihood, both SAA and hepatitis were probably caused by immune reactions [1,2,14,15]. In light of other studies that have explored the role of stem cells in liver injury, it is even possible that the stem cell transplantation may have contributed, to some extent, to the resolution of the patient's liver disease [16]. Although hematopoietic stem cell transplantation with high-dose conditioning is generally a safe and successful treatment procedure in hepatitis-associated aplastic anemia [1,2,17], there is a risk of liver disease deterioration [18].

This case confirms that rFVIIa, combined with platelet transfusion, may be effective in controlling tracheal bleeding in rare situations of tracheal infection in hepatitis-associated SAA. It also demonstrates the possibility of rapid liver disease resolution and sustained engraftment after syngeneic PBSC transplantation using immunosuppressive treatment without high-dose pre-transplant conditioning in hepatitis-associated SAA.

Conflict of Interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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