

Diffuse alveolar hemorrhage due to donor lymphocyte infusion in a case of acute lymphoblastic leukemia

Akut lenfoblastik lösemili bir olguda donör lenfosit infüzyonuna bağlı gelişen diffüz alveolar hemoraji

Gülsan Sucak, Zeynep Arzu Yegin, Münci Yağcı, Nurdan Köktürk
Gazi University Faculty of Medicine, Ankara, Turkey

Abstract

Diffuse alveolar hemorrhage, with a mortality rate between 60-100%, is a life-threatening complication in hematopoietic stem cell transplant recipients. A 34-year-old man, with precursor B acute lymphoblastic leukemia diagnosed in July 2003, relapsed after allogeneic peripheral blood hematopoietic stem cell transplantation from his human leukocyte antigen- identical brother in July 2005. He received a donor lymphocyte infusion of 2×10^7 /kg CD3 positive cells. He developed fever, dyspnea and hypoxemia four days after donor lymphocyte infusion. The patient was diagnosed as diffuse alveolar hemorrhage based on the clinical, radiological and bronchoscopic data. He was immediately started on high-dose methylprednisolone. Two days after the onset of the steroid therapy, he recovered with significant improvement in oxygenation. Diffuse alveolar hemorrhage can be a late-onset transplant complication that could also be associated with a recent donor lymphocyte infusion. (*Turk J Hematol 2008; 25: 101-3*)

Key words: Diffuse alveolar hemorrhage, donor lymphocyte infusion, stem cell transplantation, acute lymphoblastic leukemia.

Özet

Diffüz alveolar hemoraji, hematopoetik kök hücre alıcılarında %60-100 oranında mortalite ile sonuçlanabilen bir akciğer komplikasyonudur. Temmuz 2003 'te prekürsör B akut lenfoblastik lösemi tanısı almış 34 yaşındaki bir erkek hastaya tam uyumlu kardeş vericisinden allojeneik periferik kök hücre nakli yapıldı. Takibinde gelişen hematolojik relaps nedeniyle 2×10^7 /kg CD3 pozitif hücreden oluşan donör lenfosit infüzyonu uygulanan hastada infüzyondan 4 gün sonra ateş, nefes darlığı ve hipoksemi gelişti. Klinik, radyolojik ve bronkoskopik veriler ile desteklenen diffüz alveolar hemoraji tanısı ile hastaya yüksek doz metil prednizolon tedavisi başlandı. Steroid tedavisinin ikinci gününden itibaren hastada belirgin klinik düzelme sağlandı. Diffüz alveolar hemoraji, transplant sonrası geç dönemde ortaya çıkabilen, donör lenfosit infüzyonunun da tetikleyebileceği bir komplikasyondur. (*Turk J Hematol 2008; 25: 101-3*)

Anahtar kelimeler: Diffüz alveolar hemoraji, donör lenfosit infüzyonu, kök hücre nakli, akut lenfoblastik lösemi

Introduction

Pulmonary complications, including infectious and non-infectious etiologies, occur in about 30-60% of hematopoietic stem cell transplant (HSCT) recipients and contribute signifi-

cantly to morbidity and mortality [1-8]. Diffuse alveolar hemorrhage (DAH), with a reported incidence of 1-24% in HSCT recipients and a mortality rate between 60-100%, is a life-threatening complication [1-4,6-12]. Here, we present a late-onset DAH due to donor lymphocyte infusion (DLI) in a case of acute lymphoblastic leukemia (ALL).

Case Report

A 34-year-old man, with precursor B ALL diagnosed in July 2003, underwent allogeneic peripheral blood HSCT from his human leukocyte antigen-identical brother in July 2005, while in remission. His conditioning regimen consisted of busulfan and cyclophosphamide.

His early posttransplant course was uneventful, without any graft versus host disease (GVHD) or pulmonary complications. He relapsed 186 days after HSCT. He received a reinduction chemotherapy with cytosine arabinoside (100 mg/m²/day for 7 days) and idarubicin (12 mg/m²/day for 3 days), followed by a DLI of 2×10^7 /kg CD3 positive cells performed on day 196 of HSCT. He developed fever, dyspnea, hypoxemia, hypotension and non-productive cough four days after DLI. He was pancytopenic with a platelet count of 21,000/ μ L. The chest radiograph showed bilateral patchy alveolar opacities. An urgent high resolution computed tomography (HRCT) demonstrated bilateral alveolar infiltrates, predominantly in the lower zones (Figure 1). Fiberoptic bronchoscopy, which was performed seven days after DLI, revealed progressively bloodier return of bronchoalveolar lavage (BAL).

His prothrombin time (PT) and activated partial thromboplastin time (aPTT) were 12.2 and 29.9 seconds, respectively, and D-dimer was 135- μ g/L, within normal limits. There was no other identifiable sign of hemorrhage at the time of the event. Cultures for bacteria and fungus were negative and polymerase chain reaction (PCR) for cytomegalovirus (CMV) and *Pneumocystis carinii* was also negative. Pathological examination of the BAL revealed hemosiderin-laden macrophages. Broad spectrum antibiotics were started empirically because of the high risk of systemic infection, despite negative sputum, urine, blood and BAL cultures. Aggressive platelet transfusions

were performed to maintain the platelet count above 50,000/ μ L and packed red blood cell transfusions to keep the hemoglobin level at 9 g/dl or higher. In the absence of any other identifiable cause, the patient was diagnosed with DAH based on the clinical, radiological and bronchoscopic data. He was immediately started on high-dose methylprednisolone [1000 mg/day (3 days), 500 mg/day (3 days), 250 mg/day (3 days)], followed by slow taper. Two days after the onset of the steroid therapy, he recovered with significant improvement in oxygenation. A follow-up HRCT performed two weeks after the initiation of steroid therapy revealed complete disappearance of pulmonary infiltrates (Figure 2).

Discussion

DAH is a life-threatening complication of HSCT with non-specific clinical and radiological features [8]. The presented case, with non-productive cough, progressive dyspnea, hypoxemia, fever, acute onset of alveolar infiltrates, progressively bloody alveolar lavage and finally increased number of hemosiderin-laden macrophages in BAL fluid, had almost all the typical signs and symptoms defined for DAH [1-3,9,12,13]. Infection and coagulopathy were excluded as the etiologic factors with negative hemostatic tests, cultures and molecular tests for CMV and *P. carinii* pneumonia (PCP). However, the contribution of low platelet counts to the development of DAH cannot be excluded. Lung tissue injury, cytokine release and mainly inflammatory response are the implicated etiological factors in the pathogenesis of DAH, rationalizing the suppression of the inflammatory response with high-dose steroids [1-3,6,8,11]. Damage to the alveolar microcirculation has also been claimed to be the common pathophysiologic theme shared by the different etiologic factors [13].



Figure 1. HRCT demonstrates bilateral alveolar infiltrates, predominantly in the lower zones



Figure 2. Control HRCT (2 weeks after steroid therapy) reveals complete disappearance of pulmonary infiltrates

Thrombocytopenia, which is thought to be one of the risk factors for DAH [1,11], was also present in our patient. Our aggressive replacement therapy might have played a role in the dramatic response of the patient as well. However, it has been reported that favorable responses have not been obtained with correction of coagulopathy or platelet transfusions alone [5,8,9].

DAH is reported to be among the early posttransplant complications; 28 of the 48 DAH cases in one of the largest DAH series had developed in the early posttransplant period, in the peri-engraftment period particularly [3]. However, late-onset DAH cases are also not uncommon, with DAH cases being reported even 1322 days after the transplant [3,5,8].

To the best of our knowledge, this is the first published case of DAH secondary to DLI in the late posttransplant period. Our case could have developed DAH as a complication of his initial HSCT rather than the DLI. However, in the absence of any previous pulmonary symptoms and complications and of course GVHD, DAH in this case does not seem to be secondary to the initial HSCT. On the contrary, having developed four days after DLI, similar to the neutrophil influx in the peri-engraftment period in the posttransplant DAH, donor lymphocytes might have infiltrated the lung tissue causing alveolar damage directly or via causing inflammatory response to the released cytokines. Low platelet counts and the reinduction chemotherapy possibly had an additive effect. Our patient had a very favorable course with no requirement of ventilatory support, which we attribute to the prompt diagnosis and treatment. This case indicates that DLI may be considered as a risk factor in the development of late-onset DAH after HSCT.

In conclusion, DAH can be a late-onset transplant complication that can also be associated with a recent DLI. A high index of suspicion and early intervention can be life-saving. Early diagnosis and administration of high-dose steroids are crucial to alter the natural course of the disease.

References

1. Khurshid I, Anderson LC. Non-infectious pulmonary complications after bone marrow transplantation. *Postgrad Med J* 2002;78:257-62.
2. Scaglione S, Hofmaister CC, Stiff P. Evaluation of pulmonary infiltrates in patients after stem cell transplantation. *Hematology* 2005;10:469-81.
3. Afessa B, Tefferi A, Litzow MR, Peters SG. Outcome of diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med* 2002;166:1364-8.
4. Roychowdhury M, Pambuccian SE, Aslan DL, Jessurun J, Rose AG, Manivel JC, Gulbahce HE. Pulmonary complications after bone marrow transplantation: an autopsy study from a large transplantation center. *Arch Pathol Lab Med* 2005;129:366-71.
5. Kotloff RM, Ahya VN, Crawford SW. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. *Am J Respir Crit Care Med* 2004;170:22-48.
6. Lewis ID, DeFor T, Weisdorf DJ. Increasing incidence of diffuse alveolar hemorrhage following allogeneic bone marrow transplantation: cryptic etiology and uncertain therapy. *Bone Marrow Transplant* 2000;26:539-43.
7. Sharma S, Nadrous HF, Peters SG, Tefferi A, Litzow MR, Aubry MC, Afessa B. Pulmonary complications in adult blood and marrow transplant recipients: autopsy findings. *Chest* 2005;128:1385-92.
8. Afessa B, Tefferi A, Litzow MR, Krowka MJ, Wylam ME, Peters SG. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med* 2002;166:641-5.
9. Ben-Abraham R, Paret G, Cohen R, Szold O, Cividalli G, Toren A, Nagler A. Diffuse alveolar hemorrhage following allogeneic bone marrow transplantation in children. *Chest* 2003;124:660-4.
10. Hicks K, Peng D, Gajewski JL. Treatment of diffuse alveolar hemorrhage after allogeneic bone marrow transplant with recombinant factor VIIa. *Bone Marrow Transplant* 2002;30:975-8.
11. Raptis A, Mavroudis D, Suffredini A, Mollidrem J, Rhee FV, Childs R, Phang S, Barrett A. High-dose corticosteroid therapy for diffuse alveolar hemorrhage in allogeneic bone marrow stem cell transplant recipients. *Bone Marrow Transplant* 1999;24:879-83.
12. Weisdorf DJ. Diffuse alveolar hemorrhage: an evolving problem? *Leukemia* 2003;17:1049-50.
13. Collard HR, Schwarz MI. Diffuse alveolar hemorrhage. *Clin Chest Med* 2004;25:583-92.