



Transfusion-Related Immune Hemolytic Anemia in Two Children with β -Thalassemia

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Abstract

Patients with β -thalassemia major require long-term blood transfusions. However, these patients are at increasing risk of developing anti-red blood cell autoantibodies and alloantibodies due to multiple allogenic blood transfusions. Here, we report the clinical features and management of two patients with β -thalassemia with autoimmune hemolytic anemia followed shortly after last blood transfusions. At the beginning, the patients responded well to the immunoglobulin and prednisolone treatments, but after a short period of time, first patient developed recurrent autoimmune hemolytic anemia. At the end, this patient remained well in the follow up period with corticosteroid treatment. As a result, it is recommended that thalassemia patients should receive blood that matches Rh and Kell antigens, and prestorage leukodepleted erythrocyte suspensions to reduce allo and autoantibody formation.

Key Words: β -Thalassemia; Autoimmune Hemolytic Anemia; Childhood.

İki Pediatrik Beta Talasemi Hastasında Transfüzyon İlişkili İmmün Hemolitik Anemi

Özet

β -talasemi major hastaları yaşam boyu kan transfüzyonlarına ihtiyaç duyarlar. Ancak, bu hastalarda çoklu allojenik kan transfüzyonlarından dolayı eritrositlere karşı otoantikör ve alloantikör geliştirme riski artmıştır. Burada, son transfüzyonlarından kısa süre sonra otoimmün hemolitik anemi gelişen iki β -talasemi hastasının klinik özellikleri ve tedavi yaklaşımları sunulmuştur. Başlangıçta hastalar immünglobulin ve prednizolon tedavilerine iyi yanıt vermişken, kısa bir süre sonra ilk hastada otoimmün hemolitik anemi tekrarladı. Ancak takiplerinde kotikosteroid tedavisi ile bu hastanın da otoimmün hemolitik anemisi düzeldi. Sonuç olarak talasemi hastalarında allo ve otoantikör oluşumunu azaltmak için kan transfüzyonlarının Rh ve Kell uyumlu olarak yapılması ve eritrosit süspansiyonlarının depolanmadan önce filtrelenmesi önerilmektedir.

Anahtar Kelimeler: β -Talasemi; Otoimmün Hemolitik Anemi; Çocukluk Çağı.

INTRODUCTION

Beta thalassemia is a hereditary hemolytic anemia, which is defined as absent or reduced production of globin chain. Patients with β -thalassemia major require life-long blood transfusions which increase the risk of developing anti-red blood cell (RBC) antibodies. Alloimmunization to RBC antigens is an immune response often stimulated by recurrent transfusions of RBC products (1). Alloimmunization may cause a variety of problems in long-term medical and transfusion management of thalassemic patients (2). In addition to RBC alloimmunization, the development of RBC autoantibodies is also a potential risk. Although RBC autoantibodies occur less frequently than alloimmunization, these autoantibodies can lead to the reduction of the life span of transfused RBCs with life threatening hemolysis, and can cause difficulty in cross-matching (3).

Autoimmune hemolytic anemia (AIHA) is characterized by the production of autoantibodies against patient's own RBCs leading to increased hemolysis (4). Therefore, AIHA developing in addition to thalassemia, which is also a hemolytic disease, may be easily overlooked. The

reported incidence of anti-RBC antibody development in thalassemic patients varies from 5% to 20% (1,2). Antibodies can be clinically insignificant, but in some cases it may cause severe and life-threatening hemolytic reactions (5).

Here, we report two cases of thalassemia patients with direct coombs positive autoimmune hemolytic anemia after recurrent erythrocyte transfusions.

CASE REPORT

Patient 1: A 4-year-old boy was referred to the Pediatric Hematology Clinic with fever, cough, tea-colored urine, anemia and hepatosplenomegaly. He was born after a full term uncomplicated normal delivery to parents of third degree of consanguineous marriage. His medical history was significant for thalassemia intermedia. Four weeks after the last blood transfusion, complete blood count (CBC) showed that his hemoglobin concentration had fallen to 5.5 g/dl. At the same time, the direct antiglobulin test (DAT) was positive for C3d, and he had gross hemoglobinuria. Indirect antiglobulin test was negative. The physical examination revealed that the patient showed paleness, jaundice, and tachycardia. A systolic murmur with a grade of 3/6 was present over the

entire precordium. Auscultation of the lung revealed fine moist rales as suitable with pneumonia. He had also hepatosplenomegaly (liver 6 cm, spleen 8 cm below the costal margins).

Antibiotics for pneumonia, and intravenous immunoglobulin (IVIG) with the dose of 1g/kg/d (5 day) for autoimmune hemolytic anemia were administered. The treatment was continued with prednisolone with the dose of 2 mg/kg daily. The treatment was successful. The DAT was negative 5 weeks after corticosteroid therapy. However, the DAT became positive again (Ig G +2, polyspecific +2) three months after the DAT negativity. Prednisolone treatment was started again with the dose of 2 mg/kg/d. The patient had been discharged after 3 weeks of hospital stay with the advice to continue steroids. Five weeks later, the DAT became negative. Prednisolone dose was decreased, and then came to an end at the end of the fifth month.

Patient 2: An 8-year-old boy with thalassemia major was referred with continuing hemolysis despite ABO and Rh matched erythrocyte transfusion. Physical examination revealed marked pallor, fever, tachycardia, tachypnea, icterus and hepatosplenomegaly (liver 12 cm, spleen 18 cm below the costal margins). There was no lymphadenopathy, edema, rash, petechiae or any bruises. Cardio vascular examination revealed a 3/6 systolic murmur along the left sternal border. Complete blood count showed significant anemia (hemoglobin 3.3 g/dl) and mild thrombocytopenia (platelets $115 \times 10^9/L$). Peripheral blood smear showed anisocytosis and poikilocytosis. Total bilirubin was 5.5 (normal 0.0-1.0 mg/dl), and mono specific DAT showed both +3 anti IgG and anti C3d antibodies and indirect antiglobulin test was negative.

The patient was started on intravenous antibiotics (sulbactam and cefoperazone) for fever, and given 2 units of packed red cells to improve his Hb status. With the diagnosis of β -thalassemia major with AIHA confirmed by positive DAT, patient was started on IVIG (1 g/kg 2 days), and followed by corticosteroids (methyl prednisolone at 10 mg/kg/d 3 days, 5 mg/kg/d 5 days, and following prednisolone 2 mg/kg/d). Significant hemolysis persisted, and Hb did not rise for another two weeks. The DAT remained positive for over 3 weeks. Blood culture revealed *Micrococcus spp.*, so imipenem treatment was offered for 10 days. The control blood cultures were negative after imipenem therapy. Severe anemia necessitated transfusion with packed red cells. The treatment process encountered difficulties during grouping and cross matching due to excessive agglutination of red blood cells. However group specific packed red cells that were 'least incompatible' were transfused. Subsequently, the patient had an uneventful course with the regression of hepatosplenomegaly and maintenance of Hb levels at 8.5 g/dl. After 4 weeks of steroids, the steroid dose was gradually tapered to a maintenance dose of 0.5 mg/kg/d. On follow up, his polyspecific and monospecific DAT became negative. The patient was then put on routine transfusion schedule for thalassemia, retaining an Hb level ≥ 9.5 g/dl, and

continued to be in remission 3 months later with DAT being negative. He has been seen regularly for 3 months and is still in remission on daily low dose steroids.

DISCUSSION

The pathophysiology of AIHA complicating β -thalassemia major or intermedia is unclear. The sequestered red cells in the enlarged spleen might enhance immunological activity to attached or coincidental antigens (6,7). In addition, infections may induce AIHA in patients with thalassemia. It has been reported that thalassemic patients with mycoplasma or parvovirus B19 virus infections are at high risk of developing AIHA (8,9). The number of blood units transfused is an important factor for increased allo and autoimmunization in thalassemia patients (10). Diagnosis of AIHA is based on evidence of hemolytic anemia consisting of anemia, jaundice, splenomegaly, reticulocytosis, raised serum bilirubin and a positive DAT (11). Once AIHA has been identified, differentiation between warm and cold antibodies can be carried out by monospecific DAT, which also identifies responsible mechanisms. If the reaction is positive with anti IgG and negative with anti C3d, it is usually due to warm antibodies which are common in idiopathic or drug associated AIHA. If the reaction is positive with both anti IgG and anti C3d, however, it also indicates warm autoantibodies and is more common in patients with systemic lupus erythematosus and idiopathic AIHA. In cold agglutinin disease, the reaction is positive with anti C3d but negative with anti IgG (11). Both of our patients had positive DAT test with both anti IgG and anti C3d, so they had a warm type AIHA. Patients with AIHA exhibit normal granulocyte and platelet counts. Combination of AIHA with immune thrombocytopenia (Evans syndrome) has already been identified (12). Our second patient's platelet count was slightly low initially, though during the course of treatment, platelet counts kept normal and there was no sign of bleeding throughout his stay in hospital. It was thought to be due to hypersplenism.

Singer et al. studied the frequency of alloimmunization and erythrocyte autoimmunization among 64 thalassemia patients of Asian descent who received regular transfusions (1). They found that 22% of the 64 patients in total developed alloantibodies, and 25% developed autoantibodies of which 18% had a significant clinical hemolysis. They also discovered higher alloimmunization or erythrocyte autoimmunization risk in patients who had a splenectomy, transfusion with unmatched for RBC antigen phenotype, and no prestorage leukodepleted blood products. They proposed that the absence of spleen might enhance the immune response to the infused foreign antigens, which are not effectively filtered. Neither of our patients received any phenotype-selected and prestorage leukodepleted red cells before admission to our hospital. They did not have any splenectomy either. Phenotype-selected red blood cell transfusions reduce the alloimmunization rate down to 5% (13). Immune system also has an important role in allo or autoantibody

formation. It was clear that B lymphocytes increased in number in splenectomized thalassemic patients (14). Ameen et al. showed that erythrocyte alloantibodies were most frequent among patients from 2 to 10 years old. They also discovered that anti-K was most frequently detected alloantibody, followed by anti-E and anti-C (2).

The clinical features and management of AIHA complicating β -thalassemia major have not been well documented. Corticosteroid therapy is the mainstay of treatment in warm type AIHA. Both of our patients had warm AIHA, and had good responses to corticosteroid therapy. Transfusions are of transient benefit but may be required initially because of severity of anemia. Transfusion of red cells in AIHA can be complicated because of cross matching problems and rapid in vivo destruction of transfused cells due to the presence of autoantibodies (15). Our first patient received only two transfusions and responded well to corticosteroids. However, the second patient needed multiple blood transfusions until a stable Hb level could be reached.

In conclusion, physicians dealing with thalassemic patients should look for hemolysis associated with autoimmunization, or alloimmunization, especially in patients who are unusually anaemic or who develop hemolytic crisis in which hemoglobin levels fail to return to the precrisis level in due time. We recommend performing blood transfusions with RBC phenotype-selected red cells, and providing prestorage leukodepleted blood products for thalassemic patients.

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