Case Report

Resolution of alloimmunization and refractory autoimmune hemolytic anemia in a multi-transfused beta-thalassemia major patient

Joseph Philip, Neelesh Jain

Department of Transfusion Medicine, Armed Forces Medical College, Pune, Maharashtra, India

Abstract:

Beta-thalassemia is one of the most prevalent autosomal disorders, which affect more than 400,000 newborn per year worldwide. In India, the carrier rate of beta-thalassemia varies from 3-17%. The overall rate of alloimmunization in thalassemia patients has been reported to be 5-30% in the world, which is mostly contributed by the alloimmunization to minor blood group antigen. Among Asians, the incidence of red cell alloimmunization is 22%. The recommended treatment for beta-thalassemia major is regular blood transfusion every 3 to 4 weeks. The development of anti-red cell antibodies (alloantibodies and/or autoantibodies) can significantly complicate transfusion therapy. Alloantibodies are commonly associated with red cell hemolysis. Red cell autoantibodies appear less frequently, but they can result in clinical hemolysis called autoimmune hemolytic anemia (AIHA), and in difficulty in cross-matching blood. Patients with autoantibodies may have a higher transfusion rate and often require immunosuppressive drugs or alternative treatments including intravenous immunoglobulin (IVIg) and rituximab (anti-CD20 monoclonal antibody).

Key words:

Thalassemia major, auto immune hemolytic anemia, alloimmunization

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Correspondence to:
Dr. Joseph Philip,
Department of Transfusion Medicine, Armed Forces Medical College, Pune - 40, Maharashtra, India.
E-mail: eoj_in@yahoo.com

Introduction

Beta-thalassemia is one of the most prevalent autosomal disorders, which affect more than 400,000 newborns per year worldwide.[1] In India, the carrier rate of beta-thalassemia varies from 3-17%.[2] The overall rate of alloimmunization in thalassemia patients has been reported to be 5-30% in the world, which is mostly contributed by the alloimmunization to minor blood group antigens.[3] Among Asians, the incidence of red cell alloimmunization is 22%.[3] The recommended treatment for beta-thalassemia major is regular blood transfusion every 3 to 4 weeks. The development of anti-red cell antibodies (alloantibodies and/or autoantibodies) can significantly complicate transfusion therapy. Alloantibodies are commonly associated with red cell hemolysis. Red cell autoantibodies appear less frequently, but they can result in clinical hemolysis called autoimmune hemolytic anemia (AIHA), and in difficulty in cross-matching blood. Patients with autoantibodies may have a higher transfusion rate and often require immunosuppressive drugs or alternative treatments including intravenous immunoglobulin (IVIg) and rituximab (anti-CD20 monoclonal antibody).[4,5]

Case Report

An 11-year-old male child, known case of beta-thalassemia major who was the recipient of transfusions from several centers, was detected to have positive Direct as well as Indirect Coomb's Test (DCT and ICT). His hemoglobin was 6.7 g/dl. Total and unconjugated bilirubin levels were increased (4.4 mg/dl and 3.6 mg/dl, respectively). He has been on regular blood transfusion since 5 months of age. Initial transfusion frequency was 1 unit packed red cells every 3 weeks. Transfusion frequency came down to 1 unit PRBCs every 2 weeks at 3 years of age. Transfusion frequency further came down to 1 unit PRBCs once a week since June 2009, at which time he was 8 years old. Patient developed jaundice, which was diagnosed as Coomb's positive hemolytic anemia, for which he was started on prednisolone 45 mg once daily. 20 mg IVIg was also given in Nov 2009. After a stable period of 1 year, ICT and DCT became positive again. Hence, a trial of rituximab (anti-CD20 monoclonal antibody) was given at a dose of 375 mg/m^2 body surface area. Total 4 doses were given from Feb 2011 to April 2011. As the patient became ICT-positive, finding a compatible donor blood unit was the major challenge. The patient was thoroughly investigated serologically; all the necessary serological investigations performed, which included major blood grouping (forward and reverse) and Rh phenotyping [Table 1].

DCT, ICT, Antibody screening, and identification were also done subsequently. All of these tests were performed by using LISS Coomb's ID Gel

Cards from Diamed GmbH, Switzerland. Patient was found to be positive for both DCT and ICT. Elution was done to identify the type of antibody coated over the red cells, which showed the presence of warm reactive anti C_3d antibody. Non-specific mixed field (mf) pan-agglutination reaction was seen on 11 cell antibody identification panel. We tried to give him Rh phenotype matched blood, but it showed +1 reactivity in compatibility testing. Later, we did extended red cell antigen profiling of the patient, which is described in Table 2.

But, finding an antigen profile-matched donor was again a major issue. The antigen profiling of 84 voluntary blood donors were done, and out of them, 9 donors showed the same antigen profile as the patient. Cross-matching between matched donor's red cells with patients serum was performed, which showed a significant reduction in the incompatibility reaction. We motivated these matched voluntary blood donors for regular blood donation to our center on a rotation basis, and the blood was given to this patient. After 6-7 months, his DCT and ICT became negative. A donation schedule has been made for these compatible donors, and regular motivation has been provided. The patient has now started improving as the frequency of transfusion has gone down to every 27 days. The patient is on continuous follow-up. We have been doing his DCT and ICT with each blood demand sample and fortunately, all these tests are coming persistently negative. Ultimately, the combined approach of both drug therapy including rituximab, and regular transfusion of red cell antigens (major as well as minor)-matched blood have sorted out the challenging case of thalassemia complicated with AIHA.

Discussion

In this report, we evaluated the importance of doing extended red cell antigen phenotyping for chronically transfused thalassemia patients. We also highlight the effectiveness of rituximab in thalassemia cases, complicated by AIHA. Rituximab is a chimeric monoclonal antibody against the protein CD20, which is found on the surface of B cells. Rituximab destroys B cells, and is, therefore, used to treat diseases, which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells, which is seen in AIHA.[6] The factors for alloimmunization are complex, which involves the RBC antigenic difference between the blood donor and the recipient; the recipient's immune status; and the immunomodulatory effect of the allogeneic blood transfusions. The distribution of various blood groups antigens varies amongst individuals in any given population. Therefore, there is a variable degree of disparity amongst the donors and the recipient as far as minor blood group antigens are concerned, which are not tested for routine transfusions. As a result, alloimmunization can take place during the transfusion management. As regards the risk of alloimmunization, all patients receiving multiple transfusions should be typed for clinically important blood group antigens including ABO, Rh, Kell, Kidd and Duffy systems, etc.[7] Alloimmunization in thalassemia patient was reported from Taiwan (37%),[8] Arab (30%).[9] While to cause AIHA, transfusion-related immunomodulation plays an important role, in which the patients produce autoantibodies that bind to erythrocytes, leading to their destruction and a resultant anemia. There are very few studies that highlighted the concept of AIHA in patients with thalassemia. A Malaysian study has shown a low frequency (1.6%) of auto-antibody formation amongst thalassemics, whereas a study in Kuwait observed that 11% of their patients developed autoantibodies with underlying alloantibodies.[10] AIHA represents a failure of self-tolerance. Although many cases of AIHA are idiopathic, some of the conditions associated with AIHA are autoimmune disorders.

In conclusion, complicated cases of thalassemia, which develop alloimmunization along with refractory autoimmunization leading to AIHA, are very difficult to treat. Corticosteroid drug therapy followed by IVIg and rituximab with the regular transfusion of extended red cell phenotype-matched blood is a very effective regimen for such patients. This combined approach could be a good regimen for other complicated cases of auto and/or alloimmunization also, who require regular periodic blood transfusions.

Table 1: Major blood grouping

ABO		Rh Phenotype				
Forward	Reverse	D	C	c	E	e
O (4+)	O (4+)	4+	4+	Non reactive	Non reactive	4+

Table 2: Patients extended red cell antigen profile

Category	Red cell antigens	Reactivity
I	P_1	Non-reactive
	Le^a	Non-reactive
	Le^b	3+
	Lu^a	Non-reactive
	Lu^b	4+
II	K	4+
	k	4+
	Kp^a	Non-reactive
	Kp^b	2+
	Jk^a	4+
	Jk^b	Non-reactive
III	M	4+
	N	4+
	S	3+
	s	4+
	Fy^a	4+
	Fy^b	3+

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