Open Access Case Report

Refractory Autoimmune Hemolytic Anemia in a Child with Beta thalassemia Major

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Abstract

Autoimmune hemolytic anemia (AIHA) in Thalassemia major is a challenging entity. This is a case of 1 year old Thalassemia major patient who developed AIHA after few transfusions and became refractory to all available medical modalities. Before transplant, patient did not respond to high dose steroid therapy, two cycles (5 days) of Fludarabine- dexamethasone, two doses of Rituximab and IV immunoglobulin. After 100% HLA matched bone marrow transplant, patient remained stable till day +10, but than his AIHA worsened along with development of severe veno-occlusive disease. In addition to Cyclosporine and methotrexate he received high dose of steroids, Rituximab and IVIG with no response. He rejected to 100% HLA matched bone marrow transplant with persistent refractory AIHA. For refractory AIHA, the Proteasome inhibitor Bortezomib was also given. This case reflects that refractory AIHA associated with Beta Thalassemia can be a challenging clinical condition requiring new or redefined treatment modalities and it can adversely affect transplant outcome even in young patients undergoing 100% HLA matched bone marrow transplant

Keywords: Autoimmune hemolytic anemia, Thalassemia major, bone marrow transplant

Introduction

Beta-thalassemia is the most prevalent form of hemoglobinopathy resulting from decreased or absence of beta chain synthesis. As a result of ineffective erythropoiesis and hemolysis patients of beta-thalassemia major are dependent on lifelong red cell component (RCC) transfusion. This results in exposure of the patient to multiple foreign antigens expressed on red blood cells(RBC). 360 antigens are recognized on the surface of red blood cells among which 322 antigens are clustered in 36 blood groups system.[1] The development of anti-RBC antibodies, either autoantibodies or alloantibodies, remains a major problem in multi-transfused patients.[2,3] The development of alloantibodies and/or autoantibodies against RBC antigens complicates cross match compatibility, shortens RBC survival in vivo,causes clinical hemolysis, delays provision of safe transfusions and may accelerate tissue iron loading.

Case Report

A 1 year old male child, known patient of Thalassemia major with autoimmune hemolytic anemia (Direct Coombs test positive) presented to us with increased requirement of red cell transfusion. PCR studies for hemoglobinopathy at the age of 4 months showed homozygous Fr(8-9) gene mutation. Initially transfusion frequency was once a month but after 4 months transfusion frequency increased to twice a month. Transfusion requirement improved after receiving prednisolone (PDN)3 mg/kg/day. But on tapering prednisolone, the transfusion requirement increased again. No response to Azathioprine noted after receiving 1 month of treatment. On examination he was pale, liver was 3 cm and spleen 2.8 cm palpable below the costal margin. His initial workup showed autoimmune hemolytic anemia. (Table I)

Table I: Initial workup.

Investigations	Results
CBC	hypochromic microcytic anemia
Direct Coombs Test	2+
Indirect Coombs test (ICT)	1+
Monospecific anti C3d	3+
C3c	+
Ig M	2+
anti IgG	4+
Reaction with Auto cells	Positive.
Antibody screen	Pan reactive
Antibody identification	Pan reactive (No allo antibody detected using Adsorbed serum)

Two cycles (5 days/ cycle) of Fludarabine-dexamethasone (Flu 200 mg/msq-Dex 125 mg/msq in total) were administered to decrease the antibody load pre bone marrow transplant(BMT), but no response was seen. Patient was switched to irradiate washed, least incompatible RCC transfusion and Oral PDN was restarted. First dose of Rituximab (200 mg/m$^{2)}$ and the first dose of IVIG (200mg/kg/dose) was given on day -33 and -31 and PDN tapering started. No improvement on the transfusion requirement was seen. We proceeded with 100% HLA compatible sibling donor BMT with pre transplant conditioning regimen of Fludarabine 150mg/m^2 from -17 to -13, ATG Genzyme 7mg/kg from day -12 to -10, Busulfan(oral) total dose 14 mg/kg from day -9 to -6 and Cyclophosphamide total dose 200 mg/kg from day -5 to -2. 2nd dose of IVIG (200 mg/kg) and Rituximab (200mg/m^2) was given on day -3 and -1 respectively. GvHD prophylaxis included Cyclosporine-A @ 20 mg/kg/day PO on days -2 to +2 then adjusted to CSA (t) levels and Methotrexate with initial dose of 10mg/m2 at day +1, then 8mg/m2 at +3 & +6 post BMT. Patient remained stable till day +10 post BMT, after this he developed high grade fever, watery diarrhea, jaundice and worsening autoimmune hemolytic anemia. Figure 1 for trend of Bilirubin (mg/dl), Weight (kg), Hemoglobin (g/dl) and platelets (/ul), platelet and Red Cell Concentrate transfused from day 5 to day 26 post BMT.

Increasing trend of Liver size, weight gain (5%) and abdominal girth was noted from day 14 post BMT with dyspnea and oxygen dependency. Our main differential was veno-occlusive Disease (VOD)/Sinusoidal Obstructive Syndrome (SOS) in addition to underlying Refractory Autoimmune Hemolytic Anemia (AIHA). Post-transplant refractory AIHA was managed by IVIG, Rituximab and Methylprednisolone along with RCC Transfusions but no major response was seen. For VOD/ SOS restriction of intravenous fluids, discontinuing hepatotoxic drugs, diuretics and judicious use of platelet transfusion was done. Peripheral donor chimerism on day +22 post BMT was 20% which further declined to 10% on day +44. Cyclosporine was stopped and transplant rejection was declared. No neurological sequelae were observed due to hyperbilirubinemia (87 mg/dl on day 17). From Day 46, 4 doses of a Proteasome inhibitor Bortezomib 1.3mg/m^2 IV was given on days 1, 4,8, 11 for refractory AIHA. After 4 doses of bortezomib and oral steroids slight improvement in transfusion requirements was noted, but the patient remained Coombs test positive. Patient was referred to the surgical department for splenectomy.

Discussion

Beta thalassemia major presents in the early age of life requiring regular RCC transfusions. A transfused RBC minor mismatch can trigger antibody production by the immune system resulting in alloimmunization. The frequencies of RBC alloimmunization in hemoglobinopathies is between 4% and 50%.[4] There exists another entity of autoimmunization in which a TM patient produces antibodies against self RBC antigens.

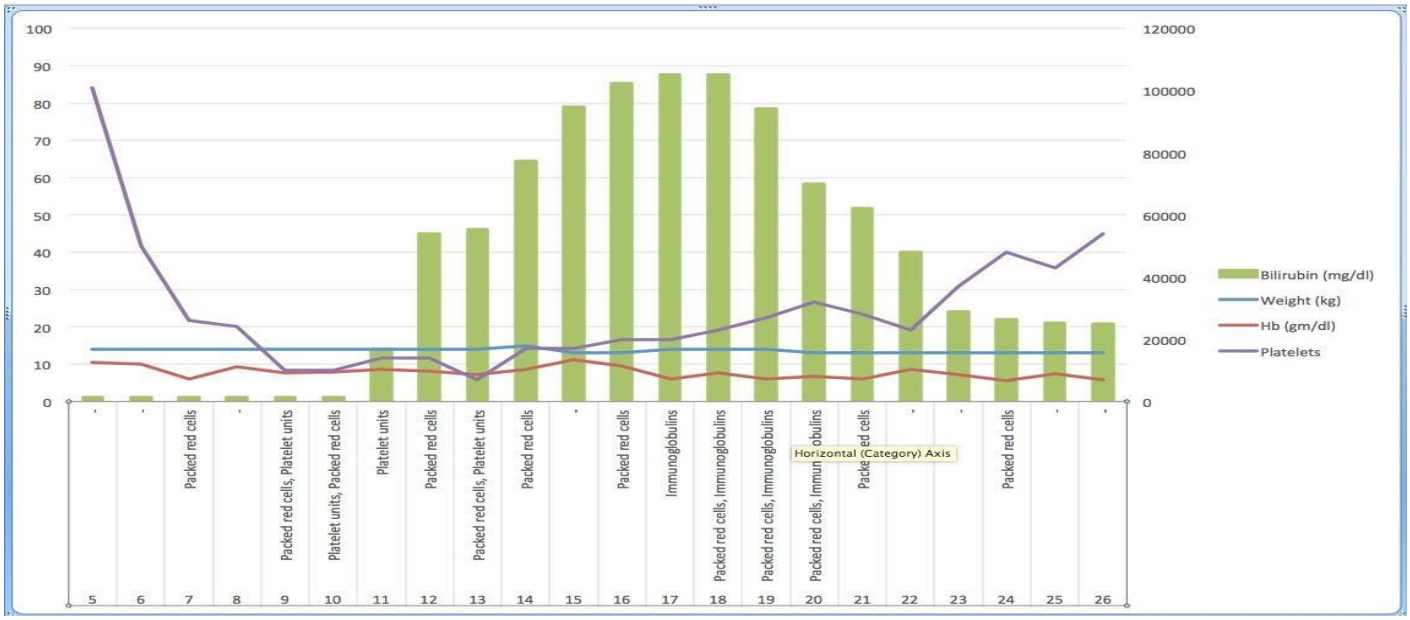

Figure 1. Clinical Parameters and Treatment Trends Post Bone Marrow Transplantation

The underlying etiology may or may not be directly associated with increased exposure to blood transfusion. One explanation is suppression or alteration in the immune system of patient due to exposure to any virus or drug.[5] In a study by Ahrens N et al auto antibodies are identified in patient's plasma after transfusion in the absence or presence of alloantibodies, as a result of hyperactive immune response to transfused RCC antigens epitopes.[6] In another study by Valle Neto et al autoimmunization has been identified in 6.64% of patients in both alloimmunized and non alloimmunized patients while Hormiani et al showed presence of alloantibodies and autoantibodies in 16 (3.1%) and 21 (4.1%) among multi-transfused patients of TM respectively.[7],[8] While AIHA developed in our patient merely after a few transfusions done following the diagnosis of TM which did not respond to any available treatment modalities. Although for primary AIHA steroid alone or combined with Rituximab and or splenectomy has promising results in 80% of the patients but additional studies are recommended for relapsed or refractory cases.[9]A study done by Greco et al analyzed the role of HSCT in autoimmune diseases. The study concluded that there is an improved progression free survival (59.4%) and overall survival (70.2%) at 5 years in large proportion of refractory autoimmune hematological and non-hematological diseases.[10] In our case the patient deteriorated post BMT as on day 10 there was an exaggerated hemolysis requiring daily RCC transfusion instead of improvement.

Another highlighted complication in this case was SOS/VOD post BMT, resulting in severe hyperbilirubinemia of 87 mg/dl. A study by Ashizawa M. et al. showed 40% of patients developed hyperbilirubinemia with bilirubin level of at least 2 mg/dL within 20 days after HSCT with 21% mortality.[11]Kernicterus is a neurological complication due to deposition of bilirubin in basal ganglia and globus pallidus seen in neonates having Bilirubin >20 mg/dl.[12] Unconjugated Hyperbilirubinemia is associated with the Neurological sequelae. The hydrophilic conjugated bilirubin cannot cross the blood brain barrier. Little data is available on side effects of very high levels of unconjugated bilirubin after neonatal age.[13] Neurological sequelae after very high unconjugated hyperbilirubinemia have not been studied extensively. Our patient recovered with supportive care alone without any neurological deficit.

Conclusion

Refractory autoimmune hemolytic anemia associated with Beta Thalassemia can be a challenging clinical condition requiring new or redefined treatment modalities and it can adversely affect transplant outcome even in young patients undergoing 100% HLA matched bone marrow transplant.

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