Management of Hyperhemolysis in β-Thalassemia with Complement Blockade

Richard Zanetti[1], Lauren Vasta[2], Kristen Romanelli[1], and Thomas Newton[3]

[1]WRNMMC
[2]Walter Reed National Military Medical Center
[3] Fairfax, VA, USAPediatric Specialists of Virginia

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Abstract

Introduction: Hyperhemolysis is a life-threatening condition of exaggerated hemolysis of red blood cells which occurs in patients receiving chronic transfusion therapy. Results: We present a 19-year-old male with β-thalassemia major with an episode of hyperhemolysis. Hemolysis was initially unresponsive to immunosuppression, but responded to with the addition of eculizumab. Several weeks after stabilization, hemolysis returned which was also successfully managed with immunosuppression and eculizumab. Discussion: Hyperhemolysis is unique in β-thalassemia due to the underlying dysfunctional erythropoiesis and transfusion dependence. Immunosuppression with eculizumab successfully slowed the hemolysis and allowed for resumption of transfusions.

Introduction

Hyperhemolysis is a rare, life-threatening condition, commonly occurring in the setting of chronic transfusion therapy. Hyper hemolysis results in hemolysis of both transfused and patient red blood cells.[1] Delayed transfusion reactions, including hyperhemolysis reactions, have been shown to involve complement mediated hemolysis.[2] Complement triggers the hemolytic reaction, and also amplifies the inflammatory response leading to enhanced tissue damage.[3]

A hyperhemolytic crisis is a grave situation with limited treatment options. Aggressive immunosuppression is often implemented to dampen the level of hemolysis. Eculizumab is a complement inhibitor currently approved for the treatment of complement mediated hemolysis in atypical hemolytic uremic syndrome (HUS) and paroxysmal nocturnal hemoglobinuria (PNH). There are several previously reported cases of eculizumab use in hyperhemolytic crises in sickle cell disease.[4-9]However, there is a paucity of evidence for eculizumab in transfusion-dependent β-thalassemia. Dysfunctional erythropoiesis and ineffective hemoglobin within red cells in β-thalassemia presents a unique challenge in the management of a hyperhemolytic crisis. We demonstrated effective management of acute and chronic hyperhemolysis in a patient β-thalassemia using eculizumab.

Case Description

Our patient is a 19-year-old male with β-thalassemia major on chronic transfusion therapy. He received phenotypically-matched RBC transfusions (matched for E- K- S- Fya- antigens) every 3 weeks. Twelve days after a transfusion, he presented with myalgias, fatigue, and low-grade fever, and was found to have a hemoglobin (hgb) of 5.5 g/dL with concurrent evidence of hemolysis, concerning for a delayed hemolytic transfusion reaction. The direct antiglobulin test (DAT) revealed panagglutination. He was admitted and transfused one unit of matched packed red blood cells (PRBC). Immediately after the transfusion he produced

dark urine with urobilinogen and proteinuria concerning for hemolysis of the transfused unit. Hyperhemolysis was suspected and aggressive immunosuppression was initiated consisting of intravenous methylprednisolone (2mg/kg) every 6 hours and intravenous immunoglobulin G (IVIG) (1 gram/kg). Despite these interventions, his hemoglobin dropped from 4.7 g/dL to 4.3 g/dL. Intravenous (IV) eculizumab (900mg) was initiated in conjunction with continued IV corticosteroids and two additional doses of IVIG. Figure 1 details the lab trend and interventions during his acute hospitalization.

The patient was monitored in the intensive care unit and further transfusions were avoided while immune control was attempted. He remained stable with hemoglobin 3.1-3.4 g/dL until hospital day 8. At that time, he had a hemoglobin of 2.9 g/dL with evidence of stable bilirubin and lactase dehydrogenase (LDH) levels. The decision was made to start him on Rituximab (375mg/m^2 IV) and transfuse one half of a unit of phenotypically-matched PRBCs over four hours. He tolerated this well and followed with the second half of the unit that evening. Repeat laboratory evaluation post-transfusion remained stable. He continued to receive transfusions over several days with improvement in hgb, but without significant worsening of hemolysis.

Additional transfusions were given and tolerated over the next week, reaching a maximum hgb of 12.3 g/dL by hospital day 11. At this time, the methylprednisolone was transitioned to prednisone with a slow taper. He was able to be discharged in stable condition after 15 total days in the hospital. During the acute phase he received a total of three doses if IVIG daily in the first four days, two doses of weekly eculizumab, two doses of weekly rituximab and high dose steroids followed by taper.

As an outpatient he completed a three-week prednisone taper and he continued weekly Rituximab for four total doses. Unfortunately, 44 days after his initial presentation (three weeks from his last dose of eculizumab), hemolysis resumed with drop in hgb from 11.4g/dL to 7 g/dL and an increase in LDH. Figure 2 outlines the outpatient course with labs and interventions. Eculizumab (900mg) was restarted weekly for four weeks, along with prednisone (0.5mg/kg/day) and sirolimus (2mg) twice daily. He received a total of 11 doses of eculizumab, he was given 900mg weekly for five doses, followed by 1200mg every other week for four doses, then 1200mg every three weeks for two doses. The eculizumab treatment course was completed 176 days from his initial presentation. The patient continues to tolerate transfusions without evidence of recurrence of hemolysis on single-agent sirolimus for immunosuppression.

Discussion:

Hyperhemolysis is a hematologic emergency with limited options for treatment. Hyperhemolysis in individuals with β-thalassemia presents additional challenges, as they are unable to effectively compensate for the hemolysis due to dysfunctional erythropoiesis. In this case presentation, initial immunosuppression slowed the hemolysis, but was insufficient to allow for the resumption of necessary transfusions. His hgb reached a critically low level and his condition was tenuous while waiting for immunosuppression to take effect.

Complement plays a crucial role in red blood cell hemolysis in the hyperhemolytic crisis. In one study, an in vitro model demonstrated complement deposition on healthy cells, sickle cells and cells lines of patients with PNH.[4] In this model, hemolysis was only seen among the PNH cell lines, despite evidence that the sickle cells were similarly decorated.[4] Increased concentrations of complement were seen in the setting of simulated infection supporting that infections and inflammation can trigger complement activation on the RBC surface leading to hemolysis.[4]

Complement mediated hyperhemolysis in β-thalassemia may share similar features to hemolysis in PNH. PNH results from a structural defect in the red cell membrane resulting in a lack glycosyl-phosphatidyl inositol (GPI) anchor protein synthesis. This results in a chronic hemolytic anemia. The anemia in patients with PNH is less severe because they are able to effectively synthesize their own red cells. The downstream effect is a lack of CD55 (Decay Accelerating Factor) and CD59 (Membrane Inhibitor of Reactive Lysis) protection from red cell complement-mediated hemolysis.[10] Decreased expression of CD55 and CD35 has also been demonstrated in patients with β-thalassemia major, suggesting that these cells may exhibit a similar mechanism of red cell lysis during a hyperhemolysis episode.[11]

Thus, complement blockade with eculizumab, through the binding of complement component 5 (C5), was a logical choice for managing this condition. In this case, the use of eculizumab successfully slowed the hemolysis and allowed for safe transfusion. After recovery from the acute episode, hemolysis recurred while his immunosuppression was being managed solely with corticosteroids. He required resumption of complement blockage with eculizumab. This blunted the hemolytic process before it resulted in a critical degree of anemia.

This case demonstrates that ongoing complement blockade with eculizumab allowed for successful resumption of immunosuppression with a prednisone taper and maintenance sirolimus without recurrence of hemolysis. Additionally, this can serve as a model for the successful management of this rare, potentially fatal syndrome in individuals with β-thalassemia.

Conflict of Interest Disclosures : The authors have no conflicts of interest relevant to this article to disclose.

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Figure Legend:

Figure 1: Labs and Interventions During Acute Episode

Figure 2: Labs and Interventions During Chronic Episode