Fatal Delayed Transfusion Reaction in a Sickle Cell Anemia Patient with Serratia Marcescens Sepsis

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Patients with sickle cell anemia may require repeated red cell transfusion, putting them at risk for minor blood group alloimmunization and the development of delayed hemolytic transfusion reactions. Although *Streptococcus pneumoniae* is the most common cause of life-threatening infection in patients with sickle cell anemia, those who have been recently hospitalized are at risk for infection with resistant hospital-associated organisms, and blood transfusion may put the patient at risk of infection with transfusion-associated organisms such as *Serratia marcescens* and *Yersinia enterocolitica*. We recently cared for an adolescent with sickle cell anemia who presented to the emergency department with a severe, delayed hemolytic transfusion reaction and *Serratia marcescens* infection. The patient had been discharged from the hospital five days previously, and had been transfused and treated with antibiotics while hospitalized. In addition to demonstrating the potential severity of delayed hemolytic transfusion reactions, our case illustrates the importance of providing relatively broad-spectrum antibiotic coverage to patients with sickle cell anemia and possible infection who have recently been hospitalized.

Key words: sickle cell anemia ■ infection ■ blood transfusion ■ *Serratia marcescens*

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INTRODUCTION

Red cell transfusion is commonly required in patients with sickle cell anemia. Repeated transfusion can result in minor blood group alloimmunization, putting the patient at risk for the development of a delayed hemolytic transfusion reaction. In some cases, the delayed hemolytic transfusion reaction may cause severe hemolysis, resulting in the delayed hemolytic transfusion reaction with hyperhemolysis syndrome (DHTRH).[1] A DHTRH may result in significant morbidity or mortality due to the effects of intravascular hemolysis and anemia. We discuss a patient with sickle cell anemia who developed DHTRH complicated by *Serratia marcescens* sepsis six days following red cell transfusion. She presented with severe anemia, shock and acidosis, and expired 12 hours after admission.

CASE REPORT

A 16-year-old female with hemoglobin-SS disease came to the emergency department with a one-day history of respiratory distress, and pain in the legs and lower back. There was no history of fever. She had been discharged from the hospital five days previously, after having been hospitalized with pneumonia and aplastic crisis. She had been treated with ampicillin-sulbactam and clarithromycin while in the hospital, and she continued to receive clarithromycin as an outpatient. She had received two units of packed red cells during that admission and had been transfused on one other occasion at 11 years of age.

The patient was seizing on arrival in the emergency department. She was afebrile, blood pressure was 144/89 mmHg, heart rate 144 beats per minute and respiratory rate 38 breaths per minute. Arterial blood gas was pH 7.04, pO2 65 torr and pCO2 19 torr; lactate was 19.0 mmol/L. Her seizures were controlled with lorazepam and fosphenytoin, and she was intubated. Computed tomography of the head was normal. On admission to the pediatric intensive care unit, blood pressure was 92/36 mmHg, and peripheral perfusion was poor. The patient was jaundiced, the lungs were clear and a gallop rhythm was present; there was no organomegaly. Neurologic examination was nonfocal. In the pediatric intensive care unit, she received ceftriaxone and a 10 ml/kg bolus of 0.9% NaCl, and a dopamine infusion was begun. Complete blood count was WBC 42.8 x 10^9/L (30% polymorphonuclear cells

and 32% bands), hemoglobin 20 g/L, platelet count 264 x 10^9/L and reticulocyte count 16.33%. The posttransfusion hemoglobin had been 85 g/L six days previously; pretransfusion hemoglobin had been 56 g/L. Lactate dehydrogenase was 3,785 U/L, and bilirubin was 85.5 μmol/L. Direct antiglobulin test was positive. Anti-JKB antibody was present, which had not been identified at the time of the previous transfusion. Cardiomegaly with pulmonary vascular congestion was present on chest radiograph.

Anemic cardiac failure due to DHTRH complicated by possible infection was diagnosed. One unit of compatible packed red cells was transfused over two hours and transfusion of a second compatible unit, planned to be administered over six hours, was begun. There was initial improvement. Arterial blood gas six hours after admission was pH 7.32, pO2 231 torr and pCO2 22 torr; lactate was 11.6 mmol/L and hemoglobin 34 g/L. Midway through the transfusion of the second unit, the patient developed a temperature of 38.2°C. Acetaminophen was administered, and the transfusion was continued. The patient remained febrile, urine output decreased and, approximately four hours after the second transfusion was begun, she developed bradycardia with widened QRS complexes. Arterial blood gas at this time was pH 7.09, pO2 183 torr, pCO2 18 torr; potassium was 8.1 mmol/L, lactate 18.0 mmol/L and hemoglobin 40 g/L. She went on to develop cardiac arrest and could not be resuscitated. Blood culture drawn in the emergency department, prior to blood transfusion, grew *Serratia marcescens* sensitive to ceftriaxone, resistant to ampicillin-sulbactam. Permission for autopsy was not given.

DISCUSSION

A DHTRH typically occurs 4–14 days following red cell transfusion in a patient who has been alloimmunized to a minor blood group antigen during a previous transfusion.[1] Following the initial alloimmunization, antibody levels decline and may become undetectable. Should the patient be transfused at a later time with red cells positive for the offending antigen, pretransfusion testing—including the direct antiglobulin test—will be negative. However, re-exposure to that antigen during the transfusion will cause an anamnestic response, with accelerated antibody production and hemolysis several days later.[1] Clinical findings of a DHTRH may include fever, pallor, myalgia, bone pain, and pain and swelling of joints. Laboratory findings may include indirect hyperbilirubinemia, decreased haptoglobin, hemoglobinemia, hemoglobinuria and reticulocytosis or reticulocytopenia. Activated components of complement produced during a DHTRH may attach to and hemolyze the patient's own red cells by a "bystander effect,"[2,3] and the transfusion itself may suppress endogenous red cell production.[1,3] As a result, the presenting hemoglobin may be less than the pretransfusion hemoglobin, as was the case with our patient. The direct antiglobulin test may be either positive or negative, and the responsible red cell alloantibody may be identified in the serum or may be undetectable.[3] Even if the direct antiglobulin test is positive and the responsible antibody is identified, these abnormalities will not have been present at the time of pretransfusion testing.[2]

Our patient had evidence of anemic cardiac failure and sepsis. Exchange transfusion would have allowed for an isovolumetric increase in hemoglobin and potentially would have had the additional benefit of removing bacterial toxins and alloantibody. We did not perform an exchange transfusion because our patient was hypotensive, acidotic and required inotropic support. Also, an exchange transfusion would have required a relatively large volume of blood; at the time of our patient's admission to the pediatric intensive care unit, only a single compatible red cell unit was available.

There are additional concerns regarding exchange transfusion in patients with DHTRH. During exchange, the patient's own red cells are removed and replaced with donor cells. While there may be a component of autohemolysis in these patients, transfused cells may be at greater risk of destruction than the patient's own red cells. Removal of a large volume of autologous cells by exchange transfusion may put the patient at risk for the development of an even more severe anemia should accelerated destruction of the transfused cells occur.

Transfusion of uncrossmatched blood is particularly hazardous in patients with DHTRH because of the risk of an acute hemolytic transfusion reaction due to the presence of alloantibody. Additional transfusions may worsen hemolysis and should be avoided if possible.[1,3] Pretreatment with steroids and/or intravenous immune globulin may reduce hemolysis should additional transfusions be necessary, and these agents, along with erythropoietin, may have a role in stabilizing hemoglobin and helping to avoid the need for future transfusion.[1,3] It would be reasonable to initiate therapy with 1–2 mg/kg of methylprednisolone every six hours until the patient improves, and to then place the patient on 2 mg/kg/day of prednisone and to wean the patient off the prednisone over a 1–3-month period. Intravenous immune globulin at a dose of 1 gm/kg/day for up to five days would also be reasonable, either alone or in combination with steroids. If significant hemoglobinuria is present during an episode of DHTRH, an alkaline diuresis should be induced with bicarbonate and diuretics to reduce the risk of pigment nephropathy.[4] Despite the increased risk of transfusion-related complications in patients with DHTRH, transfusion and, in some cases, exchange transfusion, will still be necessary in those with significant hemodynamic compromise due to anemia, such as our patient.

Patients with sickle cell anemia appear to be at increased risk of developing minor blood group alloimmunization and DHTRH.[5] Extended phenotypic red cell

matching may reduce the risk of alloimmunization, but is time consuming and expensive and will not prevent all cases of alloimmunization and not fully protect against DHTRH. At most institutions, a limited extended crossmatch is performed prior to transfusing patients with sickle cell anemia. At our hospital, patients with sickle cell anemia are matched for the Kell and non-D Rhesus blood group antigens (C and E), the most common minor blood groups implicated in alloimmunization. In addition, patients should be matched for those minor blood groups against which they have formed alloantibody in the past, even if the alloantibodies are not detectable at the time of pretransfusion testing. The management of patients with hidden alloantibodies[6] has recently been discussed, as has the management of hemolytic transfusion reactions in patients with sickle cell anemia.[3]

While our patient's clinical presentation was consistent with DHTRH, it is also possible that her anemia was caused or exacerbated by an infection-induced hemophagocytic syndrome. It was not possible to exclude this entity because neither bone marrow examination nor autopsy was performed. Hemophagocytic syndrome may respond to treatment with corticosteroids or intravenous immune globulin.

Our patient had *Serratia marcescens* sepsis. Her recent hospitalization and antibiotic treatment may have increased her risk of developing this gram-negative infection. While *Serratia marcescens* is a common contaminant of stored blood units, our patient's blood culture was obtained prior to the blood transfusion. She had received red cells six days prior to this admission, and it is possible, though unlikely, that the *Serratia marcescens* was acquired at that time. Cultures were not done at that time because the transfusion was apparently uncomplicated. Clinicians should consider the possibility of infection with transfusion-associated organisms such as *Serratia marcescens* and *Yersinia enterocolitica* in recently transfused patients who develop fever and signs of infection. While *Streptococcus pneumoniae* is a leading cause of serious infection in patients with sickle cell anemia, patients who have been recently hospitalized and treated with antibiotics are at increased risk of colonization and infection with resistant bacteria. It is interesting to note that gram-negative infections have been reported to be relatively common in patients with sickle cell anemia in Africa and the West Indies.[7,8] A potentially fatal ceftriaxone-induced hemolytic reaction has been described in patients with sickle hemoglobinopathy.[9] Because of this, the use of ceftriaxone is best confined to the treatment of patients who are managed on an ambulatory basis, where its long half-life is of substantial benefit. Ampicillin-sulbactam is preferred for the empiric treatment of infection in hospitalized patients with sickle cell anemia. However, resistance to ampicillin-sulbactam is not uncommon, and it should not be considered adequate treatment for critically ill patients with sickle cell anemia, particularly those recently hospitalized or treated with antibiotics, who are at increased risk of colonization with resistant organisms. Recommendations for the antibiotic treatment of critically ill patients with presumed infection have recently been published.[10]

The diagnosis of DHTRH may not be obvious in patients with sickle cell anemia. Some degree of hemolysis is normal in these patients. Bone and joint pain and fever may mimic vaso-occlusive crisis or infection. Reticulocytopenia, if present, may suggest aplastic crisis. Recently transfused patients with sickle cell anemia who present with bone or joint pain, fever, anemia or evidence of accelerated hemolysis should be evaluated for possible DHTRH. Since antibody levels may decline and make future pretransfusion testing unreliable, it is important to identify the responsible red cell antigen at the time of the DHTRH, so that the patient can be matched for that antigen should additional transfusions be required at a later date. The risk of minor blood group alloimmunization and the potential development of DHTRH, as well as the risk of transfusion-associated bacterial infections, are additional reasons to limit transfusion in patients with sickle cell anemia if possible.

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