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Anti-s Antibody-Associated Delayed Hemolytic Transfusion Reaction in Patients With Sickle Cell Anemia

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Purpose: Signs and symptoms of delayed hemolytic transfusion reaction (DHTR) may resemble those of vaso-occlusive crises in patients with sickle cell anemia (SCA). The diagnosis of DHTR therefore presents a challenge to the clinician when treating such patients. The current study describes a patient with SCA and DHTR secondary to red cell anti-s antibody, manifesting as painful extremeties, severe hemolytic anemia, and acute oliguric renal failure.

Patient and Methods: A 17-year-old patient with homozygous hemoglobin S presented 8 days after partial exchange transfusions with severe anemia and signs and symptoms resembling vaso-occlusive crisis. Clinical course was complicated by intravascular hemolysis and acute renal failure.

Results: Anti-s antibody was detected in the eluate. Diagnosis of DHTR was made. Treatment included single volume whole blood exchange transfusion and continuous veno-venous hemofiltration with dialysis.

Conclusions: The possibility of DHTR should be considered in a patient with SCA with hemolytic anemia. Acute renal failure is a rare complication of anti-s antibody-associated DHTR. Such reactions can be successfully managed with exchange transfusion and continuous hemofiltration with dialysis.

Key Words: Hemolytic transfusion reactions—Sickle cell anemia—Direct anti-globulin test.

Blood transfusion continues to be the mainstay of therapy for prevention and treatment of various complications of sickle cell anemia (SCA). Alloimmunization is an important complication of transfusion therapy and it results in an increased risk of transfusion reactions and difficulty in obtaining compatible blood during subsequent illness. Transfusion reactions can be immediate (usually intravascular) or delayed (usually extravascular). A delayed hemolytic transfusion reaction (DHTR) results from antibodies to minor blood groups which are not routinely tested for transfusion compatibility. Such reactions are unexpected because they occur in the face of an apparently compatible match. The current study reports a patient with SCA who developed DHTR and acute renal failure due to anti-s antibody intravascular-related hemolysis. The patient was successfully treated with exchange transfusion and continuous veno-venous hemofiltration with dialysis.

CASE REPORT

A 17-year-old girl with homozygous hemoglobin S presented with fever and lower extremity pain. The patient was exclusively followed at our institution since the age of 6 years for all her care. Her SCA-related hospitalizations were all for uncomplicated pain and febrile episodes except for 1 episode of acute chest syndrome at 15 years of age for which she received exchange transfusion (6 donor exposures). Three weeks after the acute chest syndrome, she was found to have anti-E antibody without evidence of hemolysis during a retrospective alloimmunization study protocol. Eight days before the current hospitalization, she had undergone two partial exchange transfusions (4 donor exposures) for suspected impending cerebrovascular accident. Magnetic resonance imaging and angiography were performed subsequently, and results

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were normal. Partial exchange transfusion was performed by removing 5 mL/kg blood by phlebotomy, followed by transfusing 12 mL/kg packed red cells. After transfusion, her hemoglobin level increased from 7.0 g/dL to 13.3 g/dL with a hemoglobin S level of 47%. Between detection of anti-E antibody and the most recent transfusion with E-negative blood, the patient had not received any other donor exposure.

Admission examination revealed temperature of 38.8°C, heart rate of 103 beats/min, blood pressure 153/91 mm Hg, and severe lower extremity tenderness. Laboratory examination showed hemoglobin level of 9.6 g/dL, hematocrit 28%, reticulocyte count 2.6%, and platelet count 84.000/μL. The patient was treated with intravenous fluids and meperidine, acetaminophen, ibuprofen, and cefuroxime. Twenty-four hours later, the hemoglobin decreased to 5.0 g/dL and reticulocyte count to 1.0%. Serum albumin and alanine transaminase levels were normal. The prothrombin time was 15.2 seconds (normal, < 10.6-13.1 seconds), activated partial thromboplastin time 47.1 seconds (normal, 19.5-31.1 seconds) and D-Dimer 0.5-1.0 μg/mL (normal 0.25 μg/mL). Bacterial and viral cultures were negative.

The peripheral smear demonstrated moderate polychromasia, few sickle cells, target cells, nucleated red blood cells and absence of schistocytes. Plasma hemoglobin level was 163 mg/dL, serum lactate dehydrogenase was 4220 U/L (normal, 100–225 U/L), and carboxyhemoglobin was 5.6%. Direct anti-globulin test was positive (2+) with polyspecific serum (containing anti-immunoglobulin G and C3d) and monospecific serum (containing anti-immunoglobulin G). Anti C3d was not performed. Anti-s red cell antibody was detected in the eluate. Retrospective testing confirmed the presence of red cell s antigen in one of the two donor units that had been used for the partial exchange transfusions 8 days before presentation. The patient was red cell s-antigen negative on a pretransfusion sample from day 1 of hospitalization.

Urinalysis showed tea-colored urine with specific gravity of 1.010, 3+ blood, 2+ protein, and 10 red blood cells and 20 white blood cells per high-power field. Fractional excretion of sodium was 8% and renal failure index 31%. The blood urea nitrogen level increased to 150 mg/dL, creatinine to 7.6 mg/dL, and potassium to 7.3 mmol/L. Antinuclear antibodies and antibodies to neutrophil cytoplasmic antigens were not detected, and complement 3 and 4 levels were normal.

The anemia was initially treated by transfusion of 15 mL/kg of packed red blood cells resulting in only a minimal increase in hemoglobin to 6.1 gm/dL. Subsequent attempts at transfusion were hindered by the discovery of red cell anti-s antibody. To rapidly correct anemia in the face of hypervolemia from acute renal failure, a single volume exchange transfusion (80 mL/kg) was performed. Packed red blood cells without red cell s antigen in fresh-frozen plasma was used. This resulted in an immediate increase in hemoglobin to 13.6 g/dL (Fig. 1) and a decrease in fractional concentration of hemoglobin S from 48% to 9.2%. Severe oliguria ensued on day 3 of presentation, and the patient was treated by continuous veno-venous hemodiafiltration for 4 days and, subsequently, hemodialysis for 8 days. Methylprednisolone treatment was started on day 3 and continued for a period of 7 days. The renal function steadily improved and, on day 22, the creatinine level was normal for the patient's age. At discharge 4 weeks after admission, the patient's blood urea nitrogen level was 5 mg/dL and creatinine was 0.6 mg/dL. No further transfusions were given.

DISCUSSION

Delayed hemolytic transfusion reaction with acute renal failure is a potentially fatal complication of blood transfusion in patients with SCA and alloimmunization (1–4). Adults with SCA have higher alloimmunization rates compared with children (5,6). This may be because adults may be more immunocompetent than children, subjected to greater number of transfusions, and have antigenic exposure during pregnancy. Alloantibodies may be difficult to detect during a cross match, because they can be present in diminishing titers over time or fixed in tissues such as the spleen (7).

The diagnosis of DHTR is based on laboratory and clinical evidence of hemolysis and detection of the alloantibody. In patients with SCA, the clinician may not suspect DHTR because the signs and symptoms resemble those of vaso-occlusive crisis (8). Because of the preexisting reticuloendothelial blockade and ineffective removal of antibody-coated transfused cells, patients with SCA may have more severe signs and symptoms of DHTR (8). The higher frequency of DHTR in patients with SCA may also be caused by chronic activation of the alternate pathway of complement and racial differences in antigen phenotypes

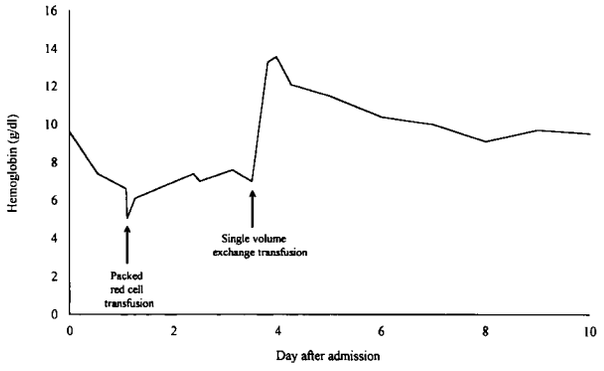

FIG. 1. Serial hemoglobin levels during the hospital course.

TABLE 1. *Reported cases of delayed hemolytic transfusion reaction and acute renal failure*

Author (Ref)	Age/ Sex	Signs of renal failure	Involved antibody	Management	Outcome
Pineda (1)	71 yr/F	Kidney shutdown	Jk^a	Not described	Survived
	9 yr/F	Oliguria	Fy^b	Not described	Survived
	36 yr/M	Kidney shutdown	K	Not described	Died
	48 yr/F	Oliguria	A_1	Not described	Survived
Fudenberg (2)	31 yr/F	Anuria	k	Transfusion, hydration	Died
Kraytman (3)	71 yr/F	BUN 460 mg/dL, Creatinine 18 mg/dL	E	Hemodialysis	Died
Hillman (4)	72 yr/M	BUN 109 mg/dL, Creatinine 6.1 mg/dL	E, c	Transfusion, peritoneal dialysis	Died
Milner (13)	15 yr/F	BUN 28 mg/dL, Creatinine 1.8 mg/dL	E	Transfusion, hydration	Survived
Holland (14)	50 yr/M	Oliguria, ↑ K^+, Creatinine 13 mg/dL	Jk^b	Transfusion, fluid restriction	Survived
Meltz (15)	30 yr/F	BUN 116 mg/dL, Creatinine 13 mg/dL	U	Hydration, mannitol, furosemide	Survived
Kalyanaraman (present case)	17 yr/F	Oliguria, ↑ K^+, BUN 150 mg/dL Creatinine 7.6 mg/dL	s	Exchange Transfusion, continuous venovenous hemofiltration/ dialysis	Survived

of the transfused blood (9,10). The red cell antigen s-negative phenotype is found in 11% white and 4% black patients; thus the likelihood of exposure of a red cell antigen s-negative recipient to a red cell antigen s-positive donor is extremely high. Severe hemolytic disease of the newborn caused by anti-s has been described previously (11). Previous alloimmunization to one antigen increases the likelihood of developing alloimmunization to another antigen (12). Therefore, the patient in the current study had a higher risk of developing a severe DHTR because of multiple factors.

Intravascular hemolysis and acute renal failure from DHTR are uncommon, especially in children. In previous studies (only one study reported a patient with SCA) (13), the antibodies involved were in the Rh, Kell, Kidd, Duffy, A_1, and U groups (1–4, 13–15). To date, the current study is the first reported case of red cell anti-s antibody acute renal failure from DHTR (Table 1). Evaluation of all other causes of acute renal failure was noncontributory in our patient. The patients with SCA experiencing DHTR are especially vulnerable to acute renal injury because of increased use of nephrotoxic drugs such as non-steroidal analgesics for pain and inflammation during vaso-occlusive attacks and beta-lactam antibiotics for suspected sepsis episodes. Propensity to develop dehydration from inadequate tubular concentration ability poses additional risk of renal compromise. The possibility of DHTR should be considered in any patient with SCA presenting with acute hemolysis and worsening renal function. Furthermore, the benefits of transfusion therapy should be weighed against the risk of alloimmunization.

Blood transfusion is a standard therapy for severe anemia in patients with sickle cell disease. However, in the patient in the current study, only a minimal increase in hemoglobin occurred after transfusion, probably from persistent red cell anti-s antibody-induced hemolysis. In patients with oliguric renal failure, blood transfusion has the risk of worsening hypervolemia. Previous experience suggests that DHTR with severe renal failure causes a high mortality (Table 1). Whole blood exchange transfusion can effectively, rapidly, and safely correct anemia in antibody-associated hemolysis and hypervolemia (16). In the patient in the current study, the oxygen-carrying capacity was also rapidly restored with a single-volume whole-blood exchange transfusion without worsening fluid overload. The patient also demonstrates that severe renal failure from DHTR is potentially reversible. Early institution of venovenous hemofiltration with dialysis is important in maintaining adequate fluid and metabolic balance and ensuring caloric intake until spontaneous recovery of renal function occurs.

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