Delayed Hemolytic Transfusion Reaction Presenting as Sickle-Cell Crisis

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Eighteen patients with sickle-cell disease underwent partial exchange transfusion. Three developed delayed hemolytic reactions, with selective disappearance of transfused cells. All reactions occurred within 6 days of transfusion, and patients presented with the clinical features of painful crises. The two most severe reactions were associated with antibodies to Jk^a. These patients developed fever, arthritis, and a clinical course suggesting serum sickness. In both patients, other alloantibodies had previously been seen. A fourth patient developed multiple alloantibodies, accelerated destruction of transfused cells, but milder illness. Such reactions may be commoner than is appreciated and should be suspected when patients have recurrent or severe sickle crises after transfusion. Blood that is nonimmunogenic in antigen systems frequently associated with delayed hemolytic reactions (Rh, Kell, Duffy, and Kidd) is preferred for sickle-cell patients who lack these antigens, especially if these patients have previously demonstrated capability to form erythrocyte alloantibodies.

BLOOD TRANSFUSION remains the major therapeutic and prophylactic measure for managing the complications of sickle-cell disease (1, 2). With the advent of modern cytapheresis technology, partial exchange transfusions have become more feasible and more widely used. The use of exchange transfusion, however, exposes the sickle-cell patient to an increased risk of hepatitis, potential iron and fluid overload, and alloimmunization to foreign erythrocyte antigens. The last problem results in more sickle-cell patients who are difficult to cross-match, and may result in an increased number of delayed hemolytic transfusion reactions.

We have recently seen four patients with sickle-cell anemia who developed a severe clinical disorder associated with delayed hemolysis after transfusion therapy. These reactions were strikingly similar and could easily be mistaken for sickle-cell pain crises. We describe one illustrative case in detail and outline the relevant clinical findings in the other cases.

Case Reports

PATIENT 1

A 36-year-old black man with sickle-cell anemia was admitted for treatment of recurrent left malleolar ulceration. The patient had frequent pain crises from early childhood and was treated with multiple transfusions during adolescence. The last 12 years had been marked by one to two pain crises per year, usually responding to hydration and analgesia. His right ankle received a skin graft in 1974 with good results, and his last blood transfusions were given to promote healing during that hospital admission. However, the left medial malleolus showed continued active ulceration requiring use of parenteral analgesics for the last 2 years.

Physical examination revealed scleral icterus, mildly enlarged heart, and 1 to 2 cm shallow left medial malleolar ulceration. Laboratory findings revealed normal urinalysis, hematocrit 26.4%, leucocyte count 11 500/mm^3 with a normal differential, platelet count 483 000/mm^3, reticulocyte count 18.6%, total bilirubin 2.1 mg/dL, direct bilirubin 0.4 mg/dL, no free plasma haptoglobin, and hemoglobin electrophoresis showing sickle (S) hemoglobin. The patient's blood group was B Rho(D) positive, and he was negative for E (rh"), C (rh'), K, Kp^a, Fy^a, Jk^a, Le^a, and Le^b red-cell antigens. He had an anti-E (rh") alloantibody detectable with enzyme treated red cells and a negative direct antiglobulin test.

Shortly after admission the patient underwent partial exchange transfusion using a Haemonetics Model 30 blood processor (Haemonetics Corporation, Natick, Massachusetts) according to a research protocol designed to evaluate the effect of partial exchange transfusion on cardiopulmonary performance. Sixteen-hundred millilitres of the patient's red cells was replaced with 1270 mL of pooled, group O, E(rh") negative, frozen deglycerolized red cells. The donor units were selected with a specific antigenic marker so that the fate of the transfused cells could be followed by differential agglutination. Four of the six units were positive for the C(rh') and Jk^a antigens. The patient tolerated the procedure well.

Four days after exchange, the patient complained of diffuse myalgias and arthralgias involving the shoulders, knees, elbows, and ankles. This pattern was distinctly different from his typical sickle-cell crisis, which was characterized by chest and back pain. Within 24 hours he developed swelling of both knees and the left elbow, and severe myalgias. His rectal temperature reached 40 °C. Hematocrit initially remained at the postexchange level of 30%, but a brisk leukocytosis of 18 600/mm^3 occurred. Serum lactate dehydrogenase (LDH) rose to 867 U/mL and total bilirubin to 4.4 mg/dL. Urinalysis showed a moderate amount of free hemoglobin. Antistreptolysin O titer, antinuclear antibody, and rheumatoid factor were all negative. Multiple cultures of blood, urine, joint fluid, pharynx, rectum, and urethra were all normal. Multiple aspirations of the joint fluid from the knees showed no crystals or organisms and only a few polymorphonuclear leukocytes. Over the next 4 days the patient's hematocrit dropped from 30% to 19%, his LDH increased to 2000 U/mL, and his total bilirubin rose to 18 mg/dL. Evaluation of serial differential agglutination and hemoglobin electrophoresis data revealed the specific destruction of the donor group O cells (Figure 1). Transfused cells decreased from 55% to 19% and hemoglobin A from 48% to 20% between Days 7 and 10. The patient did not have a positive direct antiglobulin test, nor could any new alloantibody be seen. He was transfused with 6 units of frozen deglycerolyzed red cells, four of which were positive for the C (rh') and Jk^a antigens, and begun on 60 mg of prednisone daily. The patient developed a weakly positive direct antiglobulin test 13 days after the exchange transfusion, and at 15 days two new alloantibodies, anti-Jk^a and anti-C, were identified. A digitonin eluate was negative. All joint manifestations and signs of toxicity abated after 4 days of prednisone therapy, despite the continued delayed destruction of the transfused units (Figure 1).

PATIENT 2

A 20-year-old black man with sickle-cell anemia was admitted for assessment of pleuritic chest pain and an increasing frequency of sickle-cell crises. He had received four or five blood transfusions since birth. Direct antiglobulin test and serum anti-

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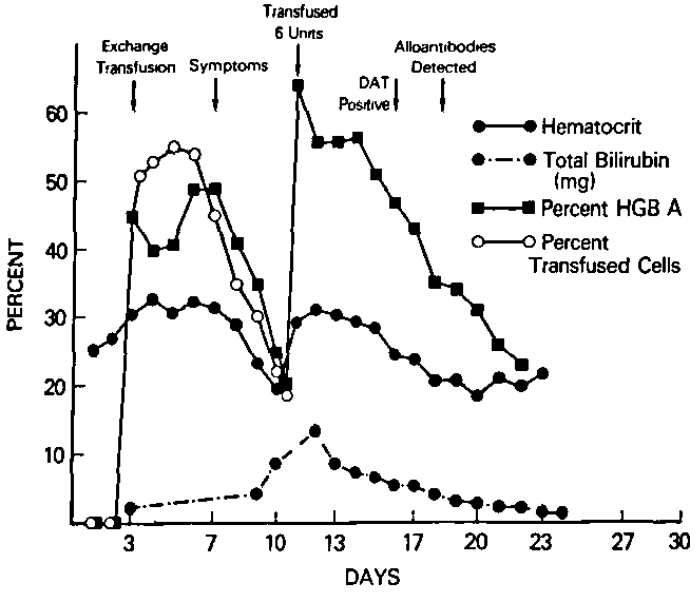

Figure 1. Course of delayed hemolytic transfusion reaction in Patient 1. HGB = hemoglobin; DAT = direct antiglobulin test.

body screen were negative. Hemoglobin electrophoresis was SS.

Ten days after admission the patient underwent partial exchange transfusion. One litre of the patient's red cells was replaced with five units of compatible pooled frozen deglycerolized red cells. Immediately postexchange the patient had 50% hemoglobin A and a hematocrit of 38%.

Six days postexchange the patient complained of malaise, and within 24 hours developed a fever to 38.6 °C accompanied by midepigastric pain with bilious vomiting and gross hemoglobinuria. By eight days postexchange the hematocrit had fallen to 17%, plasma hemoglobin had risen to 76 mg/dL (pre-exchange value, 21 mg/dL), and serum LDH was 1120 U/L. Direct antiglobulin test and antibody screen were negative. Delayed hemolytic transfusion reaction was diagnosed from accelerated disappearance of the hemoglobin A and differential agglutination data showing rapid removal of the transfused cells (Figure 2). Further transfusions were tolerated without difficulty, and the patient recovered uneventfully.

PATIENT 3

A 25-year-old black man with sickle-cell anemia was admitted for evaluation of pain crises. He had been transfused a total of 10 units over the past 15 years, the last transfusion being 1 year before admission.

The patient was blood group A Rho(D) positive, and his hemoglobin electrophoresis showed hemoglobin SS. His serum contained anti-C and anti-C^w alloantibodies, and direct antiglobulin test was negative.

One week after admission the patient underwent partial exchange transfusion. He received 6 units of frozen deglycerolized red cells, all of which were negative for the C and C^w antigens, with his postexchange hematocrit being 25.4%. He was discharged 6 days later with a hematocrit of 27.5% and hemoglobin A level of 46%.

Forty-eight hours after discharge, the patient was readmitted with severe pain crisis. Effusions were present in both knees. His hematocrit had fallen to 23.9% and hemoglobin A to 28%. Direct antiglobulin test was positive, and anti-Jk^a was detected in the serum and in the heat eluate (Figure 3). Four of the six donor units used in the red-cell exchange were typed as Jk^a positive.

Pain and joint effusions gradually resolved over the next 8 days. He received an additional 4 units of packed cells that were negative for the C, C^w, and Jk^a antigens. Twenty-eight days postexchange, the direct antiglobulin test was no longer positive, but the anti-Jk^a was still present in the serum.

PATIENT 4

An 18-year-old black woman with sickle-cell anemia was admitted after 1 week of pain that was typical of her sickle-cell pain crises. She had never received blood transfusions and had never been pregnant. Within 4 days of admission the patient appeared to be in aplastic crisis, and transfusion was planned. Direct antiglobulin test and serum antibody screen were negative. Three units of cross-match-compatible washed red blood cells were transfused uneventfully. The patient improved and was discharged 8 days after admission.

Unlike her usual postcrisis course, however, the patient noted continued weakness, pain in her extremities, and malaise. Two weeks after discharge, she was negative by the direct antiglobulin test, but the serum antibody screen was positive. Anti-E, N, Le^a, and I, and an antibody against an unidentified high incidence antigen were identified. Hemoglobin electrophoresis done 18 and 22 days after the 3-unit inpatient transfusion showed no hemoglobin A, indicating complete removal of the transfused cells. The patient gradually improved with complete clearing of symptoms 30 days after discharge.

Discussion

In the course of 18 partial exchange transfusions in sickle-cell patients, we have observed three patients who became acutely ill as a result of delayed hemolytic transfusion reactions. A fourth patient suffered a milder illness after a 3-unit transfusion. Cases 1 and 3 were associated with the rapid appearance of anti-Jk^a, and it is likely that these two patients had anamnestic antibody responses after re-exposure to the Jk^a antigen. Patient 2 had clinical and laboratory findings compatible with a delayed hemolytic transfusion reaction, although no antibody has ever been seen. Patient 4 was a nulliparous female with no transfusion history; therefore, she presumably had a primary immune response to several transfused red cell antigens. Her milder course may be related to the slower elaboration of antibody characteristic of a primary immune response and to the smaller volume of transfused red cells that she received.

There are few published reports of delayed hemolytic transfusion reactions in sickle-cell patients (3, 4). This is not surprising because many of the laboratory variables useful in documenting delayed hemolytic reactions are already abnormal in patients with sickle-cell anemia. Only documentation of the disappearance of transfused

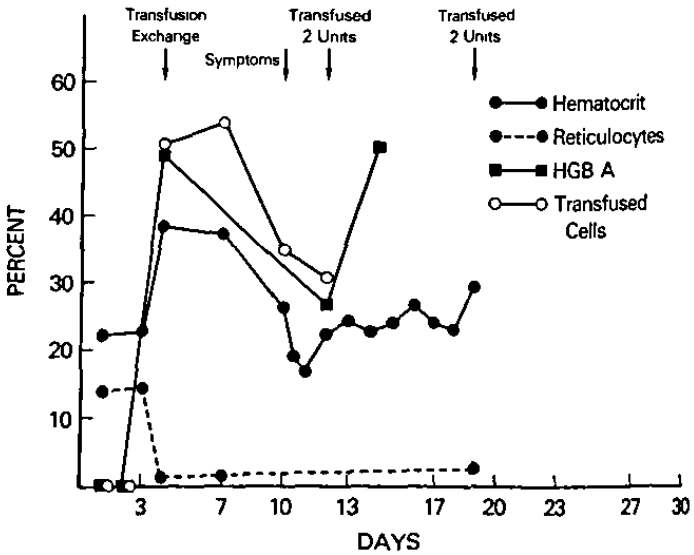

Figure 2. Course of delayed hemolytic transfusion reaction in Patient 2. HGB = hemoglobin.

cells by differential agglutination (5) and hemoglobin electropheresis (6), along with the appearance of one or more alloantibodies, will lead to the diagnosis. Rarely, it may not be possible to detect the offending alloantibody (7), or the antibody may only appear at a much later-than-expected date due to total absorption of the antibody onto transfused cells.

Alloantibodies developed by the patients in this series are not different from those detected in other patients who have developed delayed hemolytic transfusion reactions (8, 9). However, the clinical presentation of the reaction itself in sickle-cell patients appears to differ in several respects from that occurring in other patients. First, recognition of the delayed hemolytic reaction relies on a high level of suspicion and use of sophisticated laboratory procedures such as differential agglutination and serial hemoglobin electrophoresis. Second, it may be difficult clinically to separate delayed hemolytic reactions in sickle-cell patients from sickle-cell pain crises, and indeed there may be a causal relation between these reactions and the initiation and clinical severity of the crisis. The hematologic, serologic, and electrophoretic documentation of the delayed hemolytic reactions in our patients coincided with the initiation and course of the sickle-cell pain crises, a relation first reported by Chaplin and Cassell (4). All of our patients were initially treated for the sickle-cell pain crises before the full nature of the pathophysiologic process was recognized. Clinically significant delayed hemolytic reactions may be commoner in transfused sickle-cell patients than is commonly appreciated, and this may in part explain why some patients respond very poorly to transfusion therapy.

The relation between the delayed hemolytic reaction and the occurrence of a sickle-cell crisis is unclear. The chronic nonimmunologic hemolysis in a sickle-cell patient may result in partial blockade of the reticuloendothelial system with subsequent decrease in hemoglobin clearance. When a delayed hemolytic reaction occurs, there may be competition between sickle cells and antibody-coated transfused cells for reticuloendothelial clearance, leading to a more clinically severe presentation of both processes. A case has been reported, however, that suggests patients with sickle-cell anemia have an increased, rather than a decreased, ability to clear free hemoglobin (10). Alternatively, the activation of the complement system by complement-fixing antibodies or the formation of immune complexes might result in an unusual clinical picture similar to serum sickness in these patients. The two patients who developed hemolysis and who had complement-fixing anti-Jk^a antibodies developed a syndrome of arthritis, myalgias, and fever very similar to acute serum sickness.

The frequency of alloimmunization in multitransfused patients with sickle-cell anemia has been reported to range from 4.3% to 36% (11, 12). Certainly, alloimmunization in any patient makes subsequent transfusion more difficult and hazardous. However, the nature and severity of the delayed hemolytic reactions in patients with sickle-cell anemia, as contrasted with the usually clinically unimportant consequences of these reactions in other patients, have tempered our enthusiasm for vigorous transfusion therapy in this patient population.

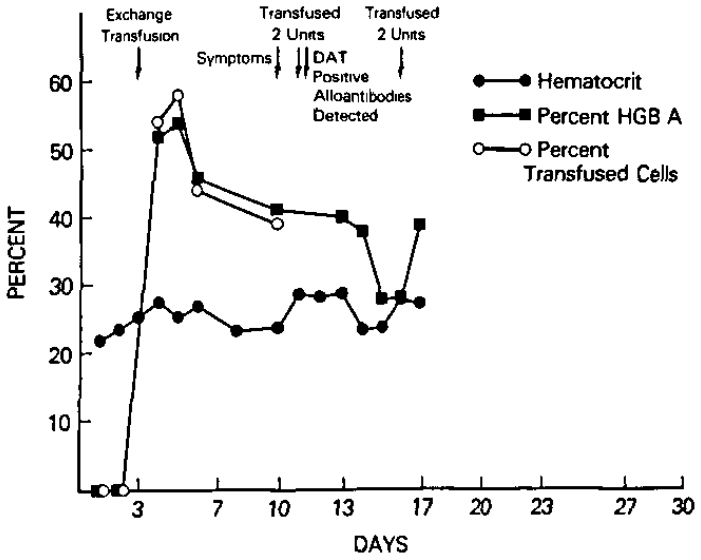

Figure 3. Course of delayed hemolytic transfusion reaction in Patient 3. HGB = hemoglobin; DAT = direct antiglobulin test.

There is some question whether the large volume of blood used in exchange transfusion is more likely to result in alloimmunization of the recipient than simple transfusion alone. Since it has been shown that the risk of stimulating one or more antibodies is about 1% per unit transfused (13, 14), it is unlikely that a single large exposure is more hazardous than an equivalent number of single transfusions. The larger volume transfused in an exchange procedure, however, may result in a more severe delayed hemolytic reaction than multiple single transfusions if several of the units in the exchange are destroyed by antibodies elaborated by the patient. The three patients cited above who had had the most severe clinical reactions were those who received 5 or more units during a partial exchange procedure.

From this experience, we have modified our management of patients with sickle-cell disease who have already formed antibodies and who require transfusion therapy. These patients have proved themselves to be immunologic "responders" to foreign red cell antigens, and are likely to form additional antibodies to newly introduced antigens. We now ascertain the phenotype of the recipient's red cells and do not provide cells that are positive for Rh, Kell, Duffy, and Kidd antigens to recipients who are negative for those antigens. Antibodies to these antigens are usually clinically significant, frequently occurring, and have been responsible for the most severe clinical sequellae in our patients. In addition, we now evaluate all patients with sickle-cell anemia who have pain crises post-transfusion for delayed hemolytic transfusion reactions. It is likely that these reactions are not uncommon and should therefore be considered whenever a recently transfused patient presents in sickle-cell crisis.

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Right and Left Ventricular Exercise Performance in Chronic Obstructive Pulmonary Disease: Radionuclide Assessment

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Right and left ventricular pump performance was assessed at rest and during upright bicycle exercise in 30 patients with chronic obstructive pulmonary disease and in 25 normal control subjects. Right ventricular and left ventricular ejection fractions were ascertained noninvasively using first-pass quantitative radionuclide angiocardiography. The normal ventricular response to exercise was at least a 5% absolute increase in the ejection fraction of either ventricle. In patients the predominant cardiac abnormality involved performance of the right ventricle. Right ventricular ejection fraction was abnormal at rest in eight patients. Twenty-three patients demonstrated an abnormal right ventricular response to submaximal exercise. Airway obstruction and arterial hypoxemia were significantly more severe in patients with abnormal right ventricular exercise reserve than in those with normal reserve. Abnormal left ventricular performance was infrequent either at rest (four patients) or during exercise (six patients). Thus, this radionuclide technique allows noninvasive assessment of biventricular exercise reserve in chronic obstructive pulmonary disease.

IN ITS ADVANCED STAGES, chronic obstructive pulmonary disease is associated with right ventricular enlargement and failure due to long-standing increases in pulmonary vascular resistance (1-3). This augmented right ventricular afterload is present only during exercise in the early stages of the disease (1). However, as the disease progresses, pulmonary artery hypertension and its concomitant effects on cardiac performance become manifest even at rest (1-4).

Evaluation of right ventricular performance at rest and during exercise in chronic obstructive pulmonary disease has been limited predominantly to invasive techniques involving cardiac catheterization. With these techniques, elevated pulmonary artery, pulmonary capillary wedge, and right ventricular end-diastolic pressures have been shown during exercise (1, 5-7). However, little is known about right ventricular systolic pump performance during exercise in chronic obstructive pulmonary disease and, specifically, about how abnormalities in cardiac performance relate to the severity of airways obstruction and arterial hypoxemia. Noninvasive radionuclide techniques have been developed in this laboratory to evaluate biventricular performance at rest and during exercise (8-13). These radionuclide techniques already have been used to detect abnormalities in right ventricular performance at rest in chronic obstructive pulmonary disease and cystic fibrosis and to evaluate therapeutic interventions in these diseases (8, 14, 15).

This study was done to define the right ventricular and left ventricular responses to submaximal upright bicycle exercise in chronic obstructive pulmonary disease using carefully controlled exercise conditions. In the course of this study the relation between ventricular responses and the severity of obstructive ventilatory impairment and arterial hypoxemia was evaluated.

Methods

PATIENT POPULATION

Thirty patients with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) and 25 untrained normal control subjects were studied. None of the control subjects had clinical, electrocardiographic, or radiographic evidence of cardiopulmonary disease. Routine pulmonary function test results were normal in all 25 control subjects. Twenty-one were male, and four were female. Their mean age was 42 years (range, 22 to 59 years).

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