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Delayed Hemolytic Transfusion Reaction With Acute Renal Failure

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Fever, hemoglobinemia, hemoglobinuria, oliguria, and a marked fall in hematocrit values developed in a patient with a bleeding peptic ulcer 13 days after he had received 4 units of apparently compatible blood. He went on to become frankly uremic and hyperkalemic, but eventually recovered. Results of routine serologic studies at the time of the transfusion reaction were normal, but an anti-Jk^b antibody could be demonstrated when cells treated with trypsin were used in the indirect Coombs' test; the patient's blood type was found to be Jk (a+b−); the blood type of three of his four donors was Jk(b+).

DELAYED appearance of isoantibodies, first detected 4 to 14 days after the transfusion of apparently compatible blood, has been described by several authors.[1-8] Clinical manifestations range from the asymptomatic development of a positive indirect Coombs' test on repeated cross matching to overt acute hemolytic anemia with chills, fever, jaundice, hemoglobinuria, spherocytosis, reticulocytosis, loss of haptoglobin, and a positive direct Coombs' test. Hemolysis of apparently compatible red blood cells, demonstrated only by a shortened survival of red blood cells tagged with ^{51}Cr, has been reported even without detectable serum isoantibodies.[9] The case presented herein is believed to be the first report of a delayed hemolytic transfusion reaction resulting in acute renal failure.

Report of a Case

A 50-year-old Chinese man was admitted to the San Francisco General Hospital for the first time on March 19, 1967, because of dizziness, weakness, and tarry stools of 1½ days' duration. The patient had a 12-year history of recurrent peptic ulcer. Gastrointestinal bleeding had occurred three times but transfusion had been required only once, five years prior to admission, when 3 units of whole blood had been given. He also had a history of asthma treated intermittently with corticosteroids; the last course of treatment had been five months prior to admission.

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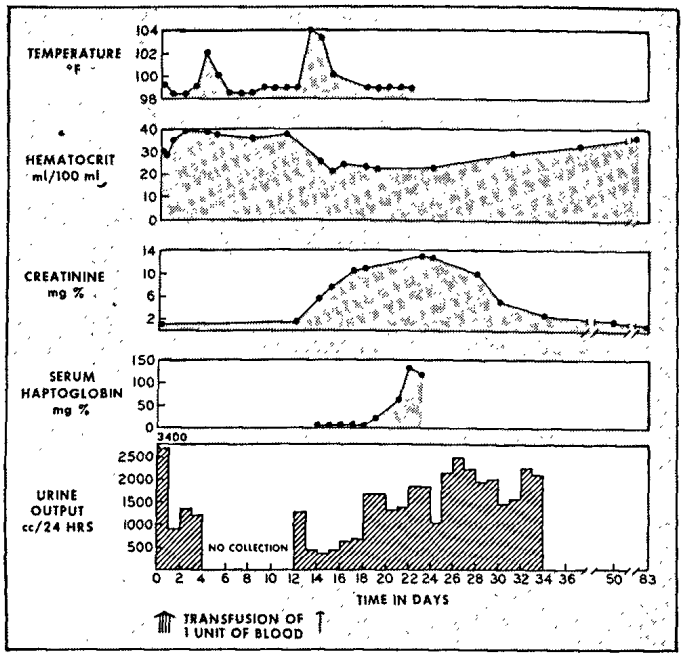

Hospital course of patient.

Physical examination revealed a pale Chinese man in no distress. The pulse rate was 112; temperature, 98 F (36.7 C); and blood pressure was 95/60 mm Hg. Neither jaundice nor stigmata of liver disease were evident. The stool was mahogany colored with a 4-+ reaction to guaiac resin, and the hematocrit value was 28%.

After the transfusion of 4 units of blood (compatible by high protein and indirect Coombs' cross match) without incident, the hematocrit value was 36% (Figure). A transient febrile episode four days later was not associated with symptoms and blood and urine cultures were negative. Hospital treatment consisted only of a bland diet and frequent antacids. On the 13th hospital day the patient's temperature was 104 F (40 C); he complained of headache but denied chills, pain, and difficulty breathing. "Grossly bloody" urine was noted twice that day but microscopic examination showed only a few red blood cells per high-power field. Over the next two days the fever continued, urine output fell below 500 ml/day, and the hematocrit value fell to 20.5%, despite transfusion of 1 unit of blood, while the stools consistently showed no evidence of blood when tested with guaiac resin. Since no source of blood loss could be found, acute hemolytic anemia, possibly due to sepsis, was suspected. Hemoglobinemia, methemalbuminemia, absent haptoglobins, hemosiderinuria, and a reticulocyte count of 4.9% were noted. The platelet count was 124,000/cu mm, and the serum lactic acid dehydrogenase value was 495 units (normal, 110 units), but the bilirubin level never increased above 1.0 mg/100 ml on four consecutive days. Test values for the following were normal or within normal limits: prothrombin time, fibrinogen (by Fi-Test), partial thromboplastin time, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, uric acid, white blood cell count and differential, blood and urine cultures, red blood cell glucose 6-phosphate dehydrogenase, and lupus erythematosus preparations. Oliguria continued and the patient became rapidly uremic and hyperkalemic, necessitating fluid restriction and polystyrene sodium sulfonate enemas. The level of serum creatinine reached a peak of 13.2 mg/100 ml (Figure) after which clinical and hematologic recovery occurred gradually; on the 36th hospital day the creatinine level was 3 mg/100 ml and the patient was discharged.

The patient's blood was group B, Rh positive, type Rh_1 Rh_2 (CDe/cDE). His Kidd blood groups were Jk(a+b−). During the acute hemolytic episode, the direct Coombs' test was repeatedly negative as were high protein and indirect antiglobin cross-matching tests of the patient's serum with a pool of red cells of donors who have most of the antigens which are implicated in transfusion reactions, including Jk^a and Jk^b. When the same serum was tested by the Irwin Memorial Blood Bank against the cells of individuals known to be Jk(b+), no reaction occurred after incubation with albumin at 37 C for 30 minutes or in the indirect Coombs' test, unless the cells were first treated with trypsin in the latter test. Similarly, when the red blood cells from the original four donors were retested, three turned out to be Jk(b+) as were those from the fifth unit transfused during the hemolytic episode; all Jk(b+) units transfused were incompatible with enzyme plus antiglobin. No serum remained from the patient's sample prior to his transfusions for similar testing. The serologic studies were repeated on the 40th day at which time anti-Jk^b could be demonstrated with the standard indirect Coombs' test as well as with cells treated with trypsin and combined with antiglobin, but the antibody was no longer demonstrable by either method two months after the patient was discharged.

Comment

Delayed transfusion reactions are recognized and reported only infrequently; and posttransfusion anemia is usually blamed on continued external or internal blood loss, "autoimmune" hemolytic anemia,[1] or acute hemolytic anemia caused by sepsis or induced by drugs. To implicate a delayed hemolytic transfusion reaction, demonstration of an isoantibody in the patient's serum and of the appropriate incompatible antigen on the donor cells are essential for correct diagnosis. Such reactions due to Kidd antibodies are well known but are characterized by difficulty in detecting the antibody before transfusion or even at the time of the hemoglobinemia. In addition, antibodies which rapidly become potent enough to destroy red blood cells may be barely detectable several months after transfusion.[1] This type of reaction, though famous for the Kidd group,[1,3-5,7,8,10] has also been reported in the Lutheran,[1,2] the Duffy[1] and the Rh groups.[1,6]

Hemoglobinemia and hemoglobinuria are conclusive evidence of intravascular hemolysis. Bilirubinemia, methemalbuminemia, and loss of haptoglobin are strongly suggestive of hemolysis, but on occasion may be observed following intraperitoneal bleeding with reabsorption of breakdown products of red blood cells into the blood stream.[11] The appearance of spherocytosis probably indicates hemolysis, but reticulocytosis is not diagnostically helpful.

When a clinician therefore suspects that a patient has undergone a delayed hemolytic transfusion reaction, further serological investigation is necessary. Repeated cross matching of both pretransfusion and acute serum from the patient should be performed by both the standard techniques of the high protein and indirect Coombs' tests and also by a proven enzyme method. The use of a panel of donors whose red blood cell antigens are known will then facilitate identification. It may be that only by serial testing will the etiology be ascertained since many antibodies are only potent enough transiently to be documented; only on the 40th day posttransfusion was our patient's anti-Jk^b demonstrable by the indirect Coombs' test.

Delayed transfusion reactions may be due to a primary or an anamnestic response, after variable delay and with or without serologic evidence of incompatibility.[1-9] Usually primary responses are so mild that they go virtually unnoticed and occur 10 to 20 days after transfusion. A secondary or anamnestic response more commonly appears from three to ten days posttransfusion with more rapid destruction of red blood cells when the antibody level in the patient's blood is sufficiently raised from its previously undetected level. The current case represents apparent in vitro compatibility before transfusion with a very severe reaction with renal failure 13 days later. It is likely that the patient was exposed to Jk^b with his prior transfusions and that the reaction represented an anamnestic response, but it could have been due to a primary immunization. It is also possible that the anti-Jk^b in this patient was entirely incidental and not the causative agent.

The occurrence of actue renal failure followed quite closely the severe, delayed transfusion reaction. While it cannot be proven that the renal insufficiency was due to the hemolytic transfusion reaction, the temporal relationship is certainly suggestive; and no other overt etiologic causes were apparent. Acute renal failure can result even without hemoglobinemia and hemoglobinuria when incompatible red blood cell antigens, eg, stroma, are transfused.[12]

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