ANNALS OF CLINICAL AND LABORATORY SCIENCE, Vol. 16, No. 3

Cerebrovascular Accident During a Delayed Hemolytic Transfusion Reaction in a Patient with Sickle Cell Anemia*

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ABSTRACT

A 28-year-old woman with sickle cell anemia suffered a left hemispheric cerebrovascular accident associated with severe right-sided weakness during a delayed hemolytic transfusion reaction owing to anti-rh′ (C) and anti-S. The anti-rh′(C) had been identified four years earlier at a different hospital but neither the patient, her family, nor any member of the staff of the hospital where she was transfused was aware of this information. It is postulated that spherocytes, formed during hemolysis, could slow capillary flow, thereby increasing red cell sickling and producing vaso-occlusion. The patient had no clinically apparent neurologic complications during the preceding 24 years and has had no further neurologic events during the subsequent 20 months. This patient's reaction underscores the compelling need for sensitive pre-transfusion tests as well as the obligation to inform patients and their families of the presence and potential consequences of alloantibodies in the event of future transfusion.

Delayed hemolytic transfusion reactions are a well-known risk of blood transfusion.[2,5,7,10,11,12,13,14] They may occur when routine pretransfusion evaluations fail to detect an alloantibody to a red cell antigen to which the recipient has been immunized previously. The transfusion of red cells possessing this antigen may provoke an anamnestic response that results in immune hemolysis. Although these reactions are usually not threatening to the patient, serious, and even fatal, cases have been recognized.[2,7,8,13] A patient is reported with sickle cell anemia who suffered a cerebrovascular accident during a delayed hemolytic transfusion reaction.

Report of a Case

A 28-year-old woman with sickle cell anemia (Hemoglobin S 90 percent, hemoglobin F 10 percent) was admitted to her local hospital with painful crisis. The hemoglobin was 7.4 g per dl. Four units of red cells were crossmatched without evidence of

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0091-7370/86/0500-0214 $00.90

serologic incompatibility; no alloantibody was detected and the direct antiglobulin test (DAT) of the patient's red cells was negative. Two of these units were transfused with a rise in hemoglobin to 10.4 g per dl. Four days later her symptoms had resolved and the hemoglobin was unchanged. She was discharged but returned ten days after receiving the transfusions with fever of 37.9°C and pain in the back, abdomen and lower extremities. The hemoglobin was 5.6 g per dl and the hematocrit 17.7 percent. Prednisone 60 mg per day was begun. The antibody detection test, DAT, and crossmatch again showed no evidence of red blood cell antibodies. Two units of red cells were transfused and the hematocrit rose to 26.9 percent. The following day she noted the sudden onset of right sided weakness and decreased sensation without associated headache or visual change. Contemporaneously, the hospital's blood bank detected a positive DAT. The patient was transferred to the University of Virginia Hospital the following day.

The past medical history was remarkable for a right hemispheric cerebrovascular accident at age four with residual left hemiparesis and mild mental retardation. Four years prior to admission, a total of 14 units of red cells were administered perioperatively for cholecystectomy. Evaluation of a positive DAT at the time demonstrated alloantibodies rh'(C) and rh"(E) in both serum and red cell eluates. She has never been pregnant. Her only medications were daily folic acid and acetaminophen with codeine as needed.

Physical examination revealed an alert black woman with blood pressure 150/74 mm Hg, pulse 108 per min, respirations 24 per min, and temperature 38.8°C. The examination was remarkable for icteric sclerae, hepatomegaly, and a grade II/VI systolic flow murmur. Neurologic examination showed the previous left hemiplegia with new right upper and lower extremity weakness and a right central seventh cranial nerve deficit. Reflexes were hyperreflexic with a left side predominance, and the left Babinski test was upgoing. Sensation was intact. Mentation was not altered from her baseline.

The peripheral blood smear showed sickle forms, target cells, and spherocytes as well as many nucleated red blood cells and Howell-Jolly bodies. Laboratory studies revealed a hematocrit 24.5 percent, hemoglobin 8.4 g per dl, reticulocytes 15.7 percent (corrected for siderocytes), serum bilirubin 6.3 mg per dl (2.67 mg per dl conjugated fraction), lactic dehydrogenase (LDH) 2660 U per L (normal 100 to 350 U per L), and haptoglobin less than one mg per dl. Prothrombin time and partial thromboplastin time were normal. Computed tomographic scan of the head showed no acute lesions. A lumbar puncture was normal. An arterial blood gas while breathing room air showed pH 7.44, pCO_2 37 mm Hg, and pO_2 67 mm Hg.

Immunohematologic evaluation demonstrated a positive DAT, with IgG but not C3 detected on the patient's red cells. An eluate of the red cells demonstrated anti-rh' (C). The patient's serum demonstrated anti-rh'(C) and anti-S.

A red blood cell exchange transfusion was performed with the IBM 2997 Blood Cell Processor with the removal of 840 ml of red cells and the infusion of 846 ml of red cells. Hemoglobin electrophoresis showed preexchange hemoglobin S 66 percent, postexchange hemoglobin S 18 percent.

Over the next several days the fever resolved, and the bilirubin and LDH levels fell to normal. She was discharged 24 days after admission having regained complete motor function on the right side. She has remained well over the subsequent 20 months.

Materials and Methods

Local Hospital

The antibody detection test was performed by mixing one drop of the reagent red blood cells* with two drops of patient's serum and two drops of 22 percent albumin* followed by incubation at 37°C for 15 minutes which was followed by centrifugation and specimen examination. The red blood cells were then washed three times with saline followed by the addition of two drops of polyspecific anti-human globulin* and then followed by centrifugation and specimen examination.

The crossmatch was performed by mixing one drop of a five percent saline suspension of donor red blood cells with two drops of the patient's serum and two drops of 22 percent albumin* followed by incubation at 37°C for 15 minutes and then followed by centrifugation and specimen examination. The red blood cells were then washed three times with saline followed by the addition of two drops of polyspecific anti-human globulin* which was followed by centrifugation and specimen examination.

The direct antiglobulin test was completed as part of an autocontrol that was performed by mixing one drop of a five percent saline suspension of the patient's red blood cells with two drops of patient's serum and two drops of 22 percent albumin* followed by incubation at 37°C for 15 minutes which was followed by centrifugation and specimen examina-

* Ortho Diagnostics, Raritan, NJ.

tion. The red blood cells were then washed three times with saline followed by the addition of two drops of polyspecific anti-human globulin* and then followed by centrifugation and specimen examination.

Blood Center

The direct anti-globulin tests were performed by mixing one drop of a three to four percent saline suspension of the patient's red blood cells with two drops of each anti-human globulin reagent. Two polyspecific reagents were used separately†‡. Anti-IgG anti-human globulin (BCA)‡ and anti-C3§ were also tested separately.

The elution was performed by using ELU-KIT II† in direct accord with the manufacturer's printed directions.

Antibody indentification was performed using a panel of reagent red blood cells†. One drop of a three to four percent suspension of each reagent red blood cell was mixed with two drops of the patient's serum and two drops of LO-ION† followed by incubation at 37°C for 30 minutes followed by centrifugation and specimen examination. The red blood cells were then washed three to four times with saline followed by the addition of two drops of anti-IgG anti-human globulin‡ which was followed by centrifugation and specimen examination.

Discussion

Delayed hemolytic transfusion reactions are a well-recognized hazard of blood transfusion.[2,5,7,10,11,12,13,14] They may occur when pretransfusion testing fails to detect an alloantibody to a red cell antigen to which the recipient has been primarily immunized in response to a prior blood transfusion or pregnancy. Presumably, the inability to find the alloantibody occurs because it is not present in sufficient quantity in the patient's serum to be detectable by routine pretransfusion testing for serologic incompatibility. The transfusion of red blood cells possessing the antigen to which the recipient has been previously sensitized may provoke an anamnestic response. The alloantibody is characteristically first detectable between three and seven days after the transfusion,[9] although longer delays have been reported.[5] The antibody mediates immune hemolysis which characteristically reaches a maximal rate some time between the fourth and thirteenth days after the transfusion.[9] Delayed hemolytic transfusion reactions have been reported at a frequency as high as one in every 1,500 units of blood transfused.[14]

The most common clinical reactions noted during delayed hemolytic transfusion reactions are fever and a reduction in the hemoglobin concentration.[9] The patient reported here had a temperature of 38.8°C on admission to the University of Virginia Hospital. Her fever resolved as the hemolysis abated. Although serious sequelae are uncommon, hemoglobinuria,[5,11] renal failure,[13] and fatalities[2,7,8,13] have been reported. Cerebrovascular accident has not been previously associated with such a reaction.

Painful crises have been reported previously in patients with sickle cell anemia during delayed hemolytic transfusion reactions.[3,4,6] Neurologic manifestations have not been noted in these patients.

Although the stroke and the delayed hemolytic reaction could have been coincidental, they may have been related for the following reasons. The immune hemolysis resulted in the formation of spherocytes. Spherocytic cells are less deformable and can slow capillary flow,

† Gamma Biologicals, Houston, TX.
‡ BCA, West Chester, PA.
§ Accugenics, Garden Grove, CA.

thereby inducing sickling and vaso-occlusion.[1,15] The cycle of vaso-occlusion and sickling can result in ischemic damage and could explain this patient's stroke. While it is impossible to prove this etiologic relationship, it is noteworthy that she had not had any clinically apparent cerebral vaso-occlusion for 24 years prior to the transfusion and has had no further neurologic events during the subsequent 20 months. The fact that this patient was susceptible to cerebral vaso-occlusive crises may have made her particularly vulnerable to developing cerebral vaso-occlusion during a hemolytic transfusion reaction. Diamond et al[6] have postulated that competition between sickle cells and antibody coated transfused cells for reticuloendothelial clearance could exacerbate both processes. Thus, it is believed that a cumulative effect of a damaged cerebral vascular bed, sickle cell disease, and circulating spherocytes caused cerebral ischemia in this patient, with the formation of spherocytes tipping the balance in favor of vaso-occlusion.

The red blood cell exchange transfusion provided large quantities of hemoglobin A, thereby decreasing further sickling and permitting resolution of the process. Thus, in this patient, a delayed hemolytic transfusion reaction appeared to have a devastating effect.

The patient reported here had an alloanti-rh'(C) detected at the University of Virginia Hospital in 1980. She and her family were unaware of the importance of this finding, and the physicians and blood bank staff caring for her at the community hospital had no knowledge of her previous immune sensitization. Thus, when conventional pretransfusion tests detected no alloantibodies or incompatibility, she was provided with two units of red cells. Subsequent investigation has determined that both of these units were positive for rh'(C) and S. Ten days later the hospital again found no alloantibodies or incompatibility, and two additional units were transfused; both of these units were S-negative but were positive for rh'(C). While it is not possible to determine the role played by the rh'(C) red cells transfused the day before the cerebrovascular accident, its infusion (as well as the other rh'(C) units) could have been avoided if the patient or her family had been aware of the need to avoid rh'(C)-positive red cells.

Many patients who receive blood transfusions and who have a primary immune response to a red cell antigen do not have subsequent serologic investigation at a time when the alloantibody is detectable. For example, this patient presumably had made anti-S previously. Although there has been considerable controversy regarding whether or not prospective recipients of blood transfusions need both an antibody detection test and a crossmatch prior to receiving blood, this report of a cerebrovascular accident during a delayed hemolytic transfusion reaction provides compelling evidence of the need for sensitive pretransfusion tests regardless of which tests are performed. Detection of low levels of circulating alloantibody can prevent delayed hemolytic transfusion reactions. The fact that antibodies are often present but at concentrations too low to be detected with routine tests has been demonstrated.[14] Therefore, physicians administering blood products must be alert to detect such transfusion reactions.

Patients and their families must be informed of the existence and the potential consequences of alloantibodies. They should carry cards or wear bracelets with appropriate serologic information. If these preventive measures are implemented consistently, patients receiving care in hospitals without their serologic records may be assured that the risk of developing a potentially serious delayed hemolytic transfusion reaction has been substantially reduced.

Acknowledgments

Acknowledgment is made of the valuable assistance of Mrs. Beckie Johnson, M.L.T., of the Appalachian Red Cross Blood Services and Mrs. Martha Jo Whaley, M.T. (ASCP), in providing information used in this report. The assistance of Ms. Cathy Murphy and Mrs. Rebecca Fuller in preparing the manuscript is appreciated.

References

1. Bessis, M., Lessin, L. S., and Beutler, E.: Morphology of the erythron. Hematology. Williams, W. J., Beutler, E., Erslev, A. J., and Lichtman, M. A., eds. New York, McGraw-Hill, 1983, pp. 277–278.
2. Bove, J. R.: Delayed complications of transfusion. Conn. Med. *32*:36–39, 1968.
3. Chan-Shu, S. A.: The second example of Anti-Duffy^5. Transfusion *20*:358–360, 1980.
4. Chaplin, H., Jr. and Cassell, M.: The occasional fallibility of in vitro compatibility tests. Transfusion 2:375–384, 1962.
5. Davis, K. G. and Abbot, R. L.: Delayed hemolytic transfusion reactions. Review of three cases. Med. J. Aust. *1*:335–337, 1982.
6. Diamond, W. J., Brown, F. L., Bitterman, P., Klein, H. G., Davey, R. J., and Winslow, R. M.: Delayed hemolytic transfusion reaction presenting as sickle cell crisis. Ann. Int. Med. 93:231–233, 1980.
7. Hillman, N. M.: Fatal delayed hemolytic transfusion reaction due to Anti-c + E. Transfusion *19*:548–551, 1979.
8. Honig, C. L. and Bove, J. R.: Transfusion-associated fatalities: Review of Bureau of Biologics reports 1976–1978. Transfusion *20*:653–661, 1980.
9. Mollison, P. L.: Blood Transfusion in Clinical Medicine. Oxford, Blackwell, 1983, pp. 658–666.
10. Moore, S. B., Taswell, H. F., Pineda, A. A., and Sonnenberg, C. L.: Delayed hemolytic transfusion reactions. Evidence of the need for an improved pretransfusion compatibility test. Am. J. Clin. Pathol. *74*:94–97, 1980.
11. Pickles, M. M., Jones, M. N., Egan, J., Dodsworth, H., and Mollison, P. L.: Delayed hemolytic transfusion reactions due to Anti-C. Vox Sang. 35:32–35, 1978.
12. Pineda, A. A., Brzica, S. M., and Taswell, H. F.: Hemolytic transfusion reaction. Recent experience in a large blood bank. Mayo. Clin. Proc. 53:378–390, 1978.
13. Pineda, A. A., Taswell, H. F., and Brzica, S. M.: Delayed hemolytic transfusion reaction. An immunologic hazard of blood transfusion. Transfusion *18*:1–7, 1978.
14. Taswell, H. F., Pineda, A. A., and Moore, S. B.: Hemolytic transfusion reactions: frequency and clinical laboratory aspects. A Seminar on Immune-mediated Cell Destruction. Bell, C. A., ed. Washington, American Association of Blood Banks, 1981, pp. 71–92.
15. Wintrobe, M. W., Lee, G. R., Boggs, D. R., Bithell, T. C., Foerster, J., Athens, J. W., and Lukens, J. N.: Clinical Hematology. Philadelphia, Lea and Febiger, 1981, pp. 838–840.