To the Editor:

There have been a number of reports of immune hemolytic anemia after organ transplantation despite the use of immunosuppressive therapy. In all these reports, the recipients have been transplanted from ABO-mismatched donors. Anti-recipient's red blood cell (RBC) antibodies could be detected by positive direct antiglobulin test (DAT) and evidence that these antibodies were of donor origin could be obtained by allotyping of the IgG eluated from the patient's RBCs. So, these cases could be considered as a graft-versus-host (GVH) antibody reaction. This report presents a case in which an immune hemolysis developed after ABO-matched liver transplantation, suggesting the possibility of GVH antibody reaction associated with blood transfusion.

The patient was a young male who had developed jaundice at birth caused by congenital biliary atresia and had been treated twice with the portoenterostomy. However, this treatment had not been successful and he had suffered from persistent jaundice, recurrent cholangitis, and progressive biliary cirrhosis. Therefore, at the age of 11 months, the patient underwent liver transplantation from a living donor who was his 26-year-old, healthy father. Blood type of the donor and recipient matched with group A and RhD-positive. During the surgery and postoperative course, the patient had been multiply transfused, including fresh whole blood, packed RBCs, fresh frozen plasma, and platelets. The immunosuppressive therapy was achieved with the use of cyclosporine, azathioprine, and prednisolone. When signs of graft rejection appeared, prednisolone pulse therapy and/or administration of FK506 was performed. On postoperative day 198, the patient had massive bleeding from the portal vein and became severely anemic. At this time, he presented positive DAT for the first time after transplantation (33 days after the last blood transfusion of RBCs). The antibody eluated from the patient's RBCs showed panagglutination including panel cells (Ortho Diagnostic Systems Inc, Raritan, NJ), cord cells, Rh null, and -D- cells. Because the patient had a life-threatening anemia with hypovolemic shock, we tested a large number of donor blood samples and selected those units that had given the weakest reactions in vitro, and then transfused them into the patient. Although we could obtain recovery from the shock with this treatment, severe hemolytic reaction with progressive anemia (Hgb, 4.0 g/dL), hyperbilirubinemia (direct, 16.6 mg/dL; indirect, 6.2 mg/dL), hemoglobinuria, high LDH (2,546 IU/L), and increase of nuclear red blood cells in the peripheral blood (191.5/100 WBC) ensued 2 days later. Plasmapheresis and whole blood exchange were performed. Cyclophosphamide pulse therapy (500 mg/m²) to suppress the antibody production and high-dose γ-globulin to block the reticuloendothelial activity were also added. Fulminant hemolysis was well controlled with these treatments and DAT became negative 31 days later. Further serologic analysis of the eluate from the DAT-positive RBCs showed that the antibodies had a titer of 1:32 in the dilution test and that IgG subclass with the ability to bind complements was predominant. As panagglutination is a characteristic type of reactivity of autoantibodies, we analyzed the IgG heavy chain allotypes (Gm) of the eluate and compared them with those of the Ig in the serum of donor and recipient to determine the origin of the antibody. Gm allotypes were exactly the same between recipient and donor (axgb°b°b°b°) before transplantation. However, Gm typing of the eluate from the DAT-positive RBCs showed that the antibodies had all kinds of allotypes tested (axgb°b°b°b° b°b°). This means that these antibodies are multiple alloantibodies derived from two or more persons other than the donor and recipient. The possible source of passenger lymphocytes evoking such a situation may be the multiple transfusion. Thus, the observed delayed hemolytic anemia might be the manifestation of a GVH antibody reaction after blood transfusion, whereas T-cell–mediated transfusion-associated GVH disease is well established. There are several anecdotal cases of delayed hemolysis after multiple blood transfusion by antibodies showing panagglutination. The investigators have explained that this was caused by autoantibody production by the recipient of blood transfusion. However, nobody has presented enough evi-
ence that these antibodies were of recipient origin. So, we hypothesize that similar mechanisms as our case might have occurred in some of these cases, although it is not certain whether these patients were under an immunosuppressive state or not. Thus, it should be noted that GVH antibody reaction causing a delayed hemolytic anemia after blood transfusion is a distinct possibility.

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Graft-versus-host antibody reaction causing a delayed hemolytic anemia after blood transfusion [letter]

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