Severe hemolytic disease of the fetus and newborn due to anti-E and anti-Jkα

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Case Report

Red blood cell alloimmunization to antigens other than D, such as C, c, E, e, and antigens in the Kell, MNS, and Duffy blood group systems, has emerged as an important cause of hemolytic disease of the fetus and newborn (HDFN). Antibody screening for these antibodies is not routinely practiced for all antenatal patients in developing countries, mainly because of financial constraints. Here we report a rare case of HDFN due to dual antibodies to Rh and Kidd blood group system antigens: anti-E and anti-Jkα. This case report highlights the importance of routine and regular antenatal screening of all pregnant women for proper monitoring and follow-up. ImmunoHematology 2020;36:60–63.

Key Words: anti-E, anti-Jkα, hemolytic disease of the fetus and newborn, HDFN

Red blood cell (RBC) alloimmunization to antigens other than D, such as C, c, E, e, and antigens in the Kell, MNS, and Duffy blood group systems, has emerged as an important cause of hemolytic disease of the fetus and newborn (HDFN). Antibody screening for these antibodies is not routinely practiced for all antenatal patients in developing countries, mainly because of financial constraints. We report a case of HDFN in a female baby due to maternal alloimmunization against Rh and Kidd blood group antigens. Through this case report, the authors show that regular antenatal screening is highly essential for a safe outcome.

Case Details

A requisition for a packed red blood cell (PRBC) unit was received in the Department of Transfusion Medicine for a 28-year-old antenatal patient at 36 weeks of gestation. She was scheduled for an emergency lower segment cesarean section, with the indication being a complicated pregnancy associated with intrauterine growth retardation (IUGR) and severe oligohydramnios. Blood type was group A, D+ by conventional tube test. Incompatibility of grade 4+ was encountered with a group A, D+ PRBC unit by column agglutination technology (CAT) (Ortho Clinical Diagnostics [USA], Raritan, NJ) at the anti-human globulin (AHG) phase. Further immunohematologic workup revealed an indirect antiglobulin test (IAT) to be positive (4+) by polyspecific (IgG + C3d) cards with pooled group O RBCs. On further crossmatching with 5 more group A, D+ RBC units, 1 unit was found to be compatible and was reserved for the patient. On checking records, it was found that the antibody detection test at 9 weeks of pregnancy was negative.

The patient had a complicated obstetric history: G7A6 with no live births (first pregnancy resulted in a hydatidiform mole, next four ended in abortion, and sixth was complicated with multiple anomalies; karyotype was normal). There was a history of transfusion during her first pregnancy 4 years previously. In this G7 pregnancy, she was diagnosed with antiphospholipid antibody (APLA) syndrome. The early pregnancy abortions may have been related to APLA syndrome. According to a study done by Canti et al.2 in 2018, APLA syndrome is associated with intrauterine growth restriction. There was no family history of phototherapy requirement or jaundice at birth, glucose-6-phosphate dehydrogenase deficiency, hemoglobinopathy, or RBC membranopathy among the parents of the index case or their siblings.

A female preterm baby, weighing 1.1 kg, complicated with respiratory distress (Apgar score 4 and 7 at 1 and 5 minutes of life, respectively), was delivered by lower segment cesarean section. According to the American College of Obstetrics and Gynecologists and American Academy of Pediatrics guidelines, a change in Apgar score to 7 represents the minimum satisfactory response to neonatal resuscitation.3 The baby was shifted to the neonatal intensive care unit for respiratory distress, and the antibiotics ampicillin and amikacin were started in light of suspected sepsis. The baby's blood sample was received for blood typing and a direct antiglobulin test (DAT). The baby's sample typed as group A, D+, and the DAT was positive (3+) by polyspecific AHG card. Routine investigations sent immediately after birth revealed hemoglobin (Hb) 8.7 g/dL (normal range 15.0–24.0 g/dL), hematocrit 36.6 percent (normal range 44–70%), total leukocyte count 16.1 × 10³ cells/mm³ (normal range 9.1–34.0 × 10³ cells/mm³), and platelets 150 × 10³/mm³ (normal range 84–478 × 10³/mm³); the peripheral blood smear showed RBC morphology consistent
with severe hemolysis having numerous nucleated RBCs, a few target RBCs, and polychromatic RBCs.4

The baby appeared icteric up to thigh at 20 hours of birth. As per Kramer’s criteria to assess and track progression of neonatal jaundice, icterus up to thigh is clinically consistent with a total serum bilirubin (TSB) level of 8–16 mg/dL.5 TSB for transcutaneous bilirubin was noted to be 8 mg/dL (normal <5.0 mg/dL). Baby was managed with phototherapy, which continued for 4 days after birth. Blood samples from the mother, father, and baby were sent to the advanced laboratory for further immunohematologic workup.

Anti-E and anti-Jkα were identified in the mother’s sample (IgG CAT cards) with titers of 8 and 2, respectively. RBC phenotyping of the submitted samples showed the mother to be D+C+c+E−e+, Jk(a−b+), the father to be D+C+c+E+e+; Jk(a+b+), and the baby to be D+C+c+E−e+; Jk(a+b+). Anti-E and anti-Jkα were recovered in an eluate (by acid elution) prepared from the baby’s peripheral blood sample.

In view of decreasing Hb level (Hb 7.6 g/dL) and increasing TSB (TSB 8.2 mg/dL) at 28 hours of life, 22 mL of group A, D+ saline-washed, phenotype-matched (E−, Jk(a−)), AHG crossmatch-compatible PRBCs were transfused. After this top-up transfusion, the Hb level rose to 9.9 g/dL measured at 42 hours of life, and the TSB level was 12.3 mg/dL.

At 48 hours of life, because of the prematurity of the baby and persistent hemolysis (falling Hb, high rate of increase in bilirubin level), a double-volume exchange transfusion (DVET) was done with 160 mL phenotype-matched (E−, Jk(a−)), crossmatch-compatible group A, D+ PRBCs and 90 mL group AB, D+ fresh frozen plasma. After that, intravenous immune globulin (IVIG) was administered at a dose of 1 g/kg. Feeding was started via a nasogastric tube with expressed breast milk and intermittent formula supplementation.

After DVET on the third day of life, Hb was 13.5 g/dL and TSB was 7.6 mg/dL. Phototherapy was continued for the next 48 hours after DVET. On the fourth day of life, the TSB level decreased to 6.4 mg/dL, Hb level rose to 16.4 g/dL, platelet count was 50,000/mm³, and reticulocyte count was 8 percent (normal range 0.1–1.3%). In view of the low platelet count, 1 unit of random donor platelets was transfused on day 4, after which the platelet count improved to 67,000/mm³. On day 16, as blood culture was found negative, antibiotics were stopped, and spoon-feeding of only expressed breast milk with supplements (vitamin D, calcium, iron, etc.) was started. Testing showed Hb of 10.2 g/dL, total leukocyte count of 13,000/mm³, and platelet count of 359 × 10³/mm³.

On day 30, Hb estimation showed 7.6 g/dL, reticulocyte count was 5 percent (normal range 1–1.2%), and top-up PRBC transfusion was performed with phenotype-matched (E−, Jk(a−)), group O, D+ saline-washed PRBCs compatible with both mother and baby. The baby improved gradually, started accepting feedings well, gained weight (weight 1.65 kg), and was discharged on day 42 of life. Figure 1 shows the sequential changes in Hb and TSB levels of the neonate.

Discussion

A neonate’s hyperbilirubinemia within 24 hours of birth may be due to low birth weight and prematurity of liver, preterm birth, early-onset neonatal sepsis, or cephalohematoma.6 In the index patient, since there was no history of birth injury or significant history of hemoglobinopathy or RBC membranopathy in the family and the association of hyperbilirubinemia with anemia and stressed bone marrow indicated ongoing hemolysis, severe HDFN of the newborn was suspected.

Fetal IUGR may be attributed to APLA syndrome in the mother. Severe ongoing hemolysis and IUGR of neonate both played a significant role in development of perinatal asphyxia.

Anti-E is frequently encountered as a cause of RBC alloimmunization in antenatal mothers.7 Usually, HDFN due to anti-E is mild to moderate in severity.8,9 Moran et al.10 showed that anti-E titers are an insensitive and poor predictor of HDFN severity and recommended that all infants born to mothers with anti-E alloimmunization should be considered potentially at risk of HDFN irrespective of the titer. In our case, the anti-E titer of 8 in mother’s serum caused severe HDFN. Exposure in a previous pregnancy or transfusion could not be ruled out.
Jk² antigens are well developed on RBCs of neonates and have been detected on fetal RBCs as early as 11 weeks. To date, few cases of HDFN related to anti-Jk² have been reported in the literature—especially from Eastern Asia, since there is a higher frequency of the JK*²A (JK*01) allele in the Eastern Asian population (particularly Indian populations [81.4%]); therefore, more individuals are Jk(a+) and would not make the antibody.¹¹ Cases of HDFN due to anti-Jk² (titer 4, CAT) have been reported that were managed with phototherapy only.¹² In our case, phototherapy, exchange transfusion, and IVIG were required because of the severe hemolysis.

The mother at the time of her first pregnancy received a PRBC transfusion, during which she presumably received Jk(a+) RBCs, given the high prevalence (81.4%) of Jk² in the donor population; later she developed anti-Jk², since Jk² is significantly immunogenic. Alternatively, exposure may have happened through pregnancy, since her husband was Jk(a+).¹³ Kidd (Jk) antibodies are notorious for being associated with delayed hemolytic transfusion reactions because of their tendency to become undetectable after first sensitization.¹⁴ In our case, IAT done at 9 weeks' gestation was negative probably because of this phenomenon. On re-exposure, however, a strong anamnestic response was observed.

Baek et al.¹⁵ reported that there is a longer duration of antibody presence and persistent low hemoglobin in infants with HDFN due to anti-Jk². In the index case, there was a persistent fall in Hb level, and a top-up PRBC transfusion was needed even after DVET. Therefore, longer duration of follow-up of Hb level is essential.

On the other hand, a case report published by Leonard et al.¹⁶ showed prolongation of HDFN with known maternal alloimmunization to Jk² due to continuous exposure of antibody via breast milk. In this case, the titer of anti-Jk² in breast milk was not estimated, but it may have been a reason for the prolonged anemia in the neonate, as breastfeeding improved significantly after day 16.

**Conclusion**

This case not only illustrates the importance of performing an IAT in all antenatal women irrespective of D status, but also emphasizes the need for a policy of repeating the IAT at regular intervals at least twice in the gestational period, especially with high-risk pregnancies. The British Committee for Standards in Haematology guidelines recommend that pregnant women should have ABO and D typing and antibody detection testing at 10–16 weeks and at 28 weeks of pregnancy.¹⁷ In India, because of lack of awareness and inadequate resources, IAT is only performed on D− antenatal mothers, usually once or twice in pregnancy, for Rh immunoprophylaxis and mainly at tertiary care centers.

These alloimmunized mothers should have regular follow-up. A high-risk approach to manage these neonates should be adopted as well. They should be monitored closely for any signs of hyperbilirubinemia irrespective of the titers of implicated antibodies.

### References


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