Case Report

Severe early-onset anemia disproportionate to hyperbilirubinemia in a Rh isoimmunized neonate

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ABSTRACT

Rhesus isoimmunized neonates presenting with hyperbilirubinemia needing exchange transfusion and late-onset anemia is commonly known; however, severe early-onset anemia without significant neonatal jaundice, requiring packed red cell transfusion, is less commonly reported. Index case presented with serial fall in hematocrit levels needing PRBC transfusions and intravenous immunoglobulin infusion to prevent recurrent need for blood transfusion.

Key words: Hyperbilirubinemia, Rh isoimmunization, Neonate

The pathological process of rhesus isoimmunization occurs when a Rh-negative mother is exposed to Rh-positive fetal red blood cells and develops Rh antibodies. Maternal Rh anti-D antibodies cross the placenta into the fetal circulation and attach to Rh antigen on fetal erythrocytes [1]. This results in various pathophysiological manifestations ranging from mild hemolytic anemia to fatal hydrops fetalis or stillbirth [2].

Rhesus isoimmunization in neonates presenting with hyperbilirubinemia needing exchange transfusion is commonly known, but severe early-onset anemia without significant neonatal jaundice, requiring packed red cell transfusion, is less commonly reported. Rh isoimmunization causes bone marrow suppression and ineffective erythropoiesis as evidenced by lack of fetal blood cells in peripheral blood and low reticulocytes count. Further, it is possible that maternally derived alloantibodies in neonates who have undergone intrauterine transfusions or postnatal exchange transfusions may persist longer than one may predict, due to a lack of antigen-positive RBCs to bind the antibodies causing hyporegenerative anemia [3]. Erythropoietin injection can reduce the need of packed red cell volume transfusion by raising reticulocyte count in erythroid hyperplasia [4].

CASE REPORT

A male baby with a birth weight of 2.3 kg, small-for-gestational age was born to a 25-year, fourth gravida ($G_4P_2L_1$) woman at 37^{+2} weeks of gestation through breech vaginal delivery. Baby cried immediately at birth and had Apgar scores of 9 at 1 and 5 min of age. In the history, previous three pregnancies were uneventful, and all the babies were home delivered, but two out of three babies (2nd and 3rd in birth order) died within 1 month after birth. These babies died on day 13th and day 25th of life probably due to anemia as per history of pallor obtained from parents.

The current pregnancy was booked and supervised at a local hospital. Mother had intrahepatic cholestasis of pregnancy, her blood group was AB negative and at 28 weeks of period of gestation, she was referred to higher center in view of rhesus-negative pregnancy with positive Indirect Coombs Test, ICT (1:16 titers). She was advised regular follow-up, but she was lost to follow up and came to our hospital in labor pains. She did not receive intrauterine transfusion or anti-D injection during the pregnancy. The pregnancy was uneventful and there were no feature of hydrops fetalis. Baby's blood group was B positive with positive direct Coombs test (DCT 4+). Kell, Duffy, C, E, and another antibody panel were negative.

Total serum bilirubin (TSB) and packed cell volume (PCV) levels at 0, 2, and 5 h were 4.8 mg/dl, 62%, 5.3 mg/dl, 60%, and 8.1 mg/dl, 55%, respectively. High-intensity phototherapy with flux of 30 μW/cm²/nm was started after birth. TSB and PCV were serially monitored. The baby was neurologically normal on serial assessment by bilirubin-induced neurological dysfunction (BIND) score. Maximum TSB level was 18 mg/dl on day 9th of life. Despite being started on iron and folic acid supplements since day 7th of life, there was progressive decline in hematocrit with minimum level hematocrit of 19% on day 13 and 22% on day 20 of life requiring transfusion twice with PRBC and IVIG. The patient could not afford erythropoietin so the same was not tried as treatment modality.

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Workup done for anemia showed hemolysis (anisopoikilocytosis, microcytes, tear drop cells, and fragmented cells) with raised plasma hemoglobin of 143.8 mg/L. Parvovirus serology (IgM and IgG level) was negative and liver function tests were normal. Serial reticulocyte count was 1.2, 1.6, and 0.92% on day 2, 7, and 22 of life. The baby was started on oral corticosteroids at 2 mg/kg/day due to poor bone marrow response of reticulocyte production which was tapered and stopped after 2 weeks of therapy. At discharge on day 25 of life, TSB and hematocrit were 7.5 mg/dl and 33% with normal neurological status.

Follow-up was advised on day 28 and then after weekly till 6 weeks of postnatal age. PCV at 5 weeks of postnatal age fell to 19%, hence, the baby was again admitted on day 36 of life for PRBC transfusion. Serial measurement of PCV done at 6, 12, and 16 mg/dl weeks of postnatal life was 38, 36, and 34%, respectively. DCT became negative at 6 weeks.

DISCUSSION

Rh isoimmunization causes IgG antibodies production which crosses placental barrier and causes destruction of fetal RBCs with 50% of the affected neonates being mildly anemic at birth; never develop severe hyperbilirubinemia; do well without the need for immunoglobulin therapy or transfusions. About 25–30% will require intervention with phototherapy and/or exchange transfusion and another 20–25% are severely affected and develop hydrops *in utero* with severe anemia and jaundice needing intervention in postnatal life [1].

Most of the neonates with Rh isoimmunization develop late anemia between the 2nd and 6th week of life. The pathogenesis of which is hypothesized to be persistent hemolysis secondary to anti-D antibodies, erythroid hyporegeneration caused by the presence of anti-D antibodies in the bone marrow which destroy erythroid precursors, and erythroid hypoplasia due to high concentrations of hemoglobin A introduced during intrauterine transfusions [2].

However, early-onset anemia in such babies is not commonly known. In this case, we have observed that an Rh isoimmunized neonate presented with severe anemia as early as within the first 13 days of life. Persistently, low reticulocyte count has been possibly due to low to moderate grade hemolysis with the bilirubin production finely balanced by an enhanced hepatic capacity to conjugate and excrete, leaving behind anemia as predominant manifestation [3]. Intensive phototherapy prevented the need for exchange transfusion but the serial falling trend of hematocrit led to PRBC transfusion and administration of IVIG to prevent the further hemolysis [2].

A case report by Louis *et al*. concluded that early-onset anemia can present as sole manifestation of Rh isoimmunization and IVIG administration has a major role in preventing further hemolysis. All the neonates in this series were born to multigravida mother, had early-onset anemia manifesting in the first 5–7 days of life with hemoglobin in the range of 5–6 g/dl, and responded to packed red cell transfusion and intravenous immunoglobulin therapy [5].

Roda *et al*. reported early anemia as sole manifestation of Rh isoimmunization, where the baby never had neonatal jaundice but had anemia needing blood transfusions in the first 3 weeks of life [6]. Anemia may be the sole manifestation of Rh incompatibility as late as 2–3 weeks of postnatal life. Haider *et al*. reported a case of late-onset anemia needing multiple blood transfusions. In this case, neonate was born to a multigravida mother with uneventful previous pregnancy outcome and asymptomatic neonate in the first 2 weeks of postnatal life [7].

In another case report of late-onset anemia manifesting at 3 weeks of postnatal life, whereby neonate was born to multigravida mother who had received IUTs in her third trimester of pregnancy. Anemia in this case hypothesized to be due to transient marrow suppression as reticulocyte count was disproportionately low till 8 weeks of life [8].

Recombinant human erythropoietin increases reticulocyte count in hyporegenerative anemia hematocrit is raised and need for packed red cell transfusions is reduced. Another study conducted by Erduran *et al*., has shown that the role of erythropoietin can decrease the need for PRBC transfusion in late-onset anemia of Rh isoimmunization [9].

CONCLUSION

Severe anemia in Rh isoimmunized neonates is not common in early neonatal period and if present, is a lesser known fact and the use of packed cell transfusion, IVIG, and erythropoietin prevents the need for further blood transfusions.

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