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Case Report

A rare presentation of severe alloimmune hemolytic disease of newborn pertaining to minor blood group 'c' incompatibility: a case report and review of literature

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ABSTRACT

Hyperbilirubinemia is one of the most widely seen causes of neonatal morbidity. Haemolytic disease of fetus and newborn is caused by maternal alloantibodies to the fetal RBCs. It is responsible for incompatibility between maternal and fetal blood groups, which results in destruction of fetal red blood cells causing hyperbilirubinemia. ABO and Rh incompatibility are the most common causes of severe indirect hyperbilirubinemia. Besides ABO and Rh isoimmunization, minor blood group incompatibilities such as anti-Kell, anti-C, anti-c, anti-E, anti MNS, Duffy, KIDD, P, Lutheran and Lewis have also been identified as causes of severe neonatal jaundice with an incidence of 385/1,00,000 live births in South-East Asia. We, hereby report a rare case of a full term 2.2 kg newborn presented with severe anemia with reticulocytosis and neonatal hyperbilirubinemia at second hour of life. In view of strongly positive DCT and no Rh negative or ABO setting, minor blood group incompatibility screening test was performed in the mother which revealed presence of multiple alloantibodies; however, the red cell phenotyping confirmed the presence of anti-c antibodies in maternal sera responsible for neonatal alloimmune haemolytic anemia. The baby was offered intensive phototherapy with intravenous immunoglobulin.

Keywords: Neonatal hyperbilirubinemia, Alloimmune hemolytic disease of newborn, Anti C antibody, Minor blood group incompatibility

INTRODUCTION

Hemolytic disease of the newborn occurs when antibodies from the mother crosses to the fetus through the placenta and result into hemolysis and shortening of the life span of the newborn's erythrocytes.[1] Hemolysis of erythrocytes in the fetus and newborn is responsible for pathologic neonatal icterus and is most frequently caused by antibodies produced due to Rh and ABO incompatibilities.[2] In cases with a positive coombs test, where Rh and ABO incompatibilities can not be found, always a possibility of minor blood group incompatibility should be considered.[1,2]

The commonly reported minor blood group antigens that are responsible for blood incompatibility between the mother and baby include C, c, E, e, Kell, Duffy, Diego, Kidd, and MNS antigen systems.[3]Minor blood group incompatibilities are responsible in 3-5% of the cases of neonatal hemolytic jaundice.[4] It has been reported from varied cases that the most severe hemolytic picture is caused by Anti-c antibodies.[1,6] The pathophysiology of isoimmunization in minor blood group incompatibility in the fetus and newborn is similar to the pathophysiology of Rh incompatibility.

Anti-c antibodies may occur due to peripartum exposures, such as feto-maternal hemorrhage, abruptio placentae, spontaneous or therapeutic abortion, cesarean delivery, ectopic pregnancy or prenatal maternal history of transfusion. This incidence can cause acute or delayed hemolytic reactions. As with the D antigen in cases of Rh

incompatibility, here, pregnant women are sensitized to c-antigen during the first pregnancy and complications occur with re-exposure in subsequent pregnancies. The initial maternal antibodies produced as a response to antigenic stimulus are of immunoglobulin subclass IgM antibodies, but they have no significance in the pathogenesis of haemolytic disease of the newborn since they cannot cross the placenta. However, with repeated exposures in subsequent pregnancies, IgG antibodies increase with further antigenic stimuli and in antigen-positive pregnancies which pass trans placentally to the fetus and cause clinical symptoms in the newborn.[5]

CASE REPORT

Full term male child with a birth weight of 2200 gm born out of non-consanguineous marriage with spontaneous onset of labour at 39 weeks of gestation with meconium-stained liquor was admitted at our NICU at second hour of life with severe pallor and icterus up to soles with severe respiratory failure requiring mechanical ventilatory support. The mother aged 24 years had taken adequate antenatal care with iron supplements and had significant obstetric history of two neonatal deaths in previous two appropriate for age male babies conceived at 21 and 22 years of age respectively. Both had severe anemia and icterus with history of perinatal asphyxia each requiring blood transfusions but expired at second and fifth day of life respectively. However exact cause of death was not known. Mother had history of one PCV transfusion in the first pregnancy for anemia. In the current pregnancy, the mother had documented antenatal scans with no evidence of hydrops fetalis. However, MCA Doppler was not available. On investigating the baby at second hour of life, complete blood count revealed 4.3 mg/dl, MCV 142.7 FL, MCH 39.1 pg, MCHC 27.04 g/dl, total leukocyte counts of 17,580, platelet counts of 52000/mm^3. The reticulocyte count was 29.77% with an absolute retic count being 330.45×109 /l. There were macrocytic normochromic RBCS with anisocytosis, presence of target cells and elliptocytes with polychromatic and nRBCS constituting 80%. Inferring the presence of active severe hemolytic anemia with thrombocytopenia, hemolytic workup was sent which revealed presence of neonatal indirect hyperbilirubinemia with total bilirubin levels of 10.4 with indirect bilirubin of 7.7 with serum ferritin levels of 882, LDH 550 and with presence of normal glucose-6-phoshate dehydrogenase activity. Maternal and baby blood types were both found to be A Rh (+) direct Coombs test was positive (+4) and indirect Coombs test of mother was also positive (+3). Cardiomegaly and hepatomegaly were present but there was no evidence of splenomegaly or post-natal hydrops fetalis. Cranial and abdominal ultrasonography was normal. Mother was further evaluated but had normal complete blood counts with normal hemoglobin electrophoresis along with a normal liver function assay. Also, complete ANA profile was evaluated which turned out normal. For further investigation regarding the etiology of immune hemolytic hyperbilirubinemia with a positive Coombs test, screening was done by a 3 cell and 11 cell testing which tests for Rh, Kell, Duffy, Kidd, Lewis, P, MNS Luth, xg types and was found positive for multiple antigens. Hence a confirmatory Red Cell Antigen Phenotyping and Antibody Identification was done which revealed maternal Rh and Kell phenotyping as (C+ c- E- e+ K-). Paternal Rh and Kell phenotyping suggested (C+ c+ E- e+ K-). A complete match for anti-"c" antibodies was found in the maternal sample with indirect Coombs test positive which hence confirmed minor blood group c incompatibility between mother and baby responsible for severe hemolysis in fetus and the newborn.

Management and outcomes

The patient was treated with Intensive phototherapy along with intravenous immunoglobulin with maximal ventilatory support. However, we couldn't offer exchange transfusion to baby on account of hemodynamic instability. The baby succumbed to death at 36 hours of life.

DISCUSSION

Our case suggested that the mother was sensitized in her first pregnancy and had a history of both previous pregnancies presenting with anemia and icterus in the newborn at birth leading to further increase in the maternal IgG titers and fetal red cell sensitization in the present pregnancy These antibodies can cross the placenta and may lead to a positive indirect Coombs test in the mother. Thus, they cause hemolytic disease in the fetus and newborn with varying severity.[1,2] In the case presented in this article, the direct Coombs test, Indirect Coombs test in the mother, and anti-c antibody levels were positive and the diagnosis of hyperbilirubinemia caused by minor blood group incompatibility secondary to Anti-c antibody was was confirmed.

Cases of hemolytic disease due to minor blood group incompatibility, may vary from subclinical hemolysis to active hemolysis and hyperbilirubinemia, which require exchange transfusion.[1-3] Early and severe cases present as hydrops fetalis and later and mild cases present as prolonged icterus.[1,7] However, hemolysis due to anti-c antibodies has been reported to be of a very severe variety, though, in our case, there was no evidence of hydrops fetalis.

Minor blood group incompatibilities share the same treatment modalities with any other blood group incompatibilities. Jaundice caused by hemolysis is treated with phototherapy. Hemolytic anemia with hydrops may need exchange transfusion with subgroup matched RBCs. Few reports are available for usage of IVIg for hemolytic Anemia caused by minor blood group incompatibilities.[8] We administered 1 gm/kg IVIg to our patient. However, due to active severe hemolysis patient succumbed to death at 36 hours of life.

However, to prevent further feto-infantile mortalities in future pregnancies, antenatal serial ICT monitoring should be undertaken. With serially increasing trend of ICT titers, plasmapheresis of maternal blood could be planned. Also, intrauterine fetal blood transfusion with c negative whole blood could be executed with advancing fetal medicinal interventions keeping its complications in mind. However, once the baby delivers and presents with severe hemolysis, exchange transfusion with c negative whole blood from phenotypically compatible donors can also be planned.

Review of literature with prior reported cases of minor blood group incompatibility

There being paucity of cases reported for minor blood group incompatibility, a few with variety of presentations have been discussed below:

Indirect hyperbilirubinemia caused by minor blood group incompatibilities (P1, M, N, s and Duffy) reported by The Pan African Medical Journal by Tugcu et al.[9] A 32 gestational week preterm male baby, weighing 1815 gm was born by cesarean section, to a 32 year old mother whose blood group was O Rh (+) and the baby's blood group was found out to be O Rh(-). Bilirubin levels on postnatal day five were 14.6 mg/dl. direct Coombs test was negative with no parameters of hemolysis. Phototherapy was initiated then. The baby became icteric again on day 11, with a total bilirubin level of 14.66 mg/dl and hematological parameters revealed active hemolysis. Antibody screening and defining tests revealed incompatibility on different minor groups (P1, M, N, s and Duffy (Fya ve Fyb)). Baby was stabilized with IVIG therapy, red cell transfusion and three day long-phototherapy. The baby was discharged with full recovery. Our case had an earlier presentation of severe hemolytic anemia with severe indirect hyperbilirubinemia at birth, not resolving with intravenous immunoglobulin therapy, thus inferring greater severity of hemolysis when caused by minor blood group “c” incompatibility.

Minor blood group E antibody incompatibility reported by intractable and rare disease research by Agrawal et al.[10] A term 40-week gestation, female baby with birth weight 2,860 g was born to a 29-year-old mother. Investigations showed baby's total serum bilirubin of 23.8 mg/dL. Blood group was O Rh (+), and direct Coombs test was positive (3+). Mother and father blood groups were B Rh (+) and O Rh (+) respectively. Indirect Coombs test was positive in the mother. Phenotype analysis for minor blood group antigens in mother and father was done. Antibody screening showed anti-E antibody in the mother and baby and a diagnosis of indirect hyperbilirubinemia due to minor blood group incompatibility as a result of anti-E antibody was established. The patient received phototherapy for 48 hours and serum bilirubin declined. Herein, the patient did not require exchange transfusion or intravenous immunoglobulin therapy.

A case with anti-c antibody incompatibility, was reported by the medical bulletin of Sisli Etfal hospital by Odabasi et al.[11] A term 38-week baby, was born to a 23-year-old mother at 38 weeks of gestation, with a weight of 2650 grams, with severe pallor. Hematological parameters were supportive of hemolytic anemia without any lab parameters of jaundice. Mother and baby blood types were A Rh (+) and direct Coombs test was (-). When the mother and baby minor blood groups were evaluated, Kell (-) E (+) e (+) C (+) c (-) and Kell (-) E (+) e (+) C (+) c (+) were determined, respectively. Thus, diagnosed to have the hemolytic disease due to c minor blood group incompatibility transfused with a subgroup-compatible erythrocyte suspension on the postnatal first day and was discharged after stabilization this patient, however, did not develop hyperbilirubinemia and need for transfusion, was discharged on postnatal fifth day for outpatient care.

Lessons learnt

Severe neonatal Allo immune hemolytic anemia should always be investigated for minor blood group incompatibility, if Rh and ABO incompatibilities have been ruled out.

Minor blood group incompatibilities share the same treatment modalities with any other blood group incompatibilities.

Timely management with exchange transfusion on following the crash cart approach, can prevent grave complications like kernicterus as a “never event” for newborn safety.

To prevent further feto-infantile mortalities in future pregnancies, antenatal serial ICT monitoring should be undertaken and maternal plasmapheresis could be planned timely.

With availability of newer investigations, timely diagnosis could be made and intervention with the help of fetal medicine can help treat such cases.

CONCLUSION

In conclusion, neonatologists should consider possibility of minor blood group incompatibilities involved in the etiology of newborns who present with icterus and have a positive direct Coombs test. They have same treatment algorithm as other types of hemolytic anemia. This includes phototherapy, IVIg and exchange transfusion.

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