Maternal allo anti-M antibody-induced hemolytic disease of newborn
Ashly Monson Mathew, Sangita Shah, Nidhi Bhatnagar, Mamta Shah, Tarak Patel, Truptee Thakkar

Abstract:
Hemolytic disease of the fetus and newborn is a syndrome associated with immune destruction of the fetal and newborn red cells by maternal red cell alloantibodies. The detection of anti-M in antenatal screening can be responsible for neonatal red cell aplasia. A 32-h-old full-term neonate admitted with inconstant cry and mild fever. Laboratory tests revealed progressive anemia and hyperbilirubinemia on day 3. The peripheral blood smear showed evidence of hemolysis and reticulocyte count was reduced. Intensive phototherapy and antibiotics were started after ruling out other causes of hyperbilirubinemia. Blood group typing and advanced red cell serology workup were done. Antibody screening and identification was suggestive of the presence of anti-M antibody in both mother and baby. Intravenous immunoglobulin and red blood cell transfusions were given. Anti-M is capable of causing hemolytic disease of the fetus and newborn and prolonged anemia. Newborns with anemia should be evaluated for all the possible causes to establish a diagnosis.

Keywords:
Alloantibody, anti-M, hemolytic disease, red cell serology

Introduction
Anemia can present in a newborn as an acute life-threatening event or as an incidental finding of mild severity. In the former case, stabilizing the newborn is the primary objective in management whereas in the latter case, a proper diagnosis has to be made before therapeutic intervention. A detailed obstetrics history along with family history is important in the workup of a newborn with anemia.

Hemolytic disease of the fetus and newborn is a syndrome associated with immune destruction of the fetal and newborn red cells by maternal red cell alloantibodies that are specific for inherited paternal red cell antigens. It is associated with hemolysis either in the fetus in utero and/or after delivery with consequent anemia and hyperbilirubinemia. The early detection and treatment of neonatal hyperbilirubinemia is important in the prevention of kernicterus which is bilirubin-induced encephalopathy.

The MNSs blood group system is considered to be clinically insignificant as it only reacts at temperatures below 37°C. It appears to be more common in infants than in adults. Anti-M’s are naturally occurring antibodies described by Wolff and Johnson in 1933. Anti-M has been rarely associated as cause of diseases with different degrees of severity as intrauterine deaths or hemolytic disease of the newborn (hemolytic disease of the newborn [HDN]).[1,2] Anti-M detection is a rare finding in antenatal screening which can cause neonatal red cell aplasia.[3]

Case Report
A 32-h old full-term female neonate, born vaginally at 38 weeks with an Apgar score of

How to cite this article: Mathew AM, Shah S, Bhatnagar N, Shah M, Patel T, Thakkar T. Maternal allo anti-M antibody-induced hemolytic disease of newborn. Asian J Transfus Sci 2022;16:144-7.
9/10 and birth weight of 2.7 kg developed inconsolable cry and mild fever and mild jaundice. On examination, there was mild pallor and icterus with tachycardia and feeble pulse. A detailed life history was taken, the antenatal period was uneventful. The mother was G1P1 L1A1, who had history of previous first trimester abortion 2 years back.

Laboratory tests showed that infant’s blood hemoglobin and serum total bilirubin concentrations were 11.4 g/dl and 9.4 mg/dl, respectively on day of life 2 and a fall in hemoglobin to 7.6 g/dl and a rise in serum total bilirubin concentration to 19 mg/dl on day 3. The peripheral blood smear demonstrated polychromasia with numerous nucleated RBCs, schistocytes, and prominent spherocytes. Reticulocyte count was 0.5%.

Serological TORCH screening and sepsis screen were negative. There was no evidence of biliary atresia or other obstructive liver diseases in ultrasound scan of the liver. The ECHO study revealed the presence of congenital anacrotic heart disease. Bone marrow examination revealed predominantly normoblasts with the features of dyserythropoiesis such as multinuclearity, nuclear fragments, and cytoplasmic vacuoles. The other cell lines such as megakaryocytes and cells of lymphoid lineage were normal. Thalassemia screening was negative.

Intensive 36 h double surface phototherapy and antibiotics were started. Samples of the mother and baby were received in the blood center for workup for exchange transfusion. Advanced red cell serology workup was done [Table 1]. The baby’s red cells were typed “O” Rh “D” positive and the mother’s red cells were typed “A” Rh “D” positive. Direct Antiglobulin test in the patient was negative using a column agglutination technique at (AHG) Anti human globulin phase using polyspecific antihuman globulin cards whereas indirect antiglobulin test was Grade III positive in both mother and baby. Antibody screening using 3 cell panel (BIO-RAD ID-DiaCell I-II-III) came positive and antibody identification using 11 cell panel (BIO-RAD ID-DiaPanel) was suggestive of the presence of anti-M antibody in both mother and baby. Father was found to have M antigen using Diaclon anti-M monoclonal immunoglobulin G (IgG) antibody (BIO-RAD) suggestive of maternal alloimmunization by paternal M antigen. Type of antibody in the mother was IgG and IgM type whereas in the baby it was IgG type only. Of 14 units (O Rh-positive and O Rh-negative) crossmatched, 2 O Rh-negative units were found compatible with the serum of the baby. The same units were crossmatched with the serum of the mother and found compatible.

Following intensive phototherapy, serum bilirubin concentrations reduced to 17 mg/dl the on 4th day. A single dose of intravenous immunoglobulin (IVIG) was given on the 6th day. As the bilirubin level was reducing with phototherapy and IVIG, exchange transfusion was not required. Two units of crossmatch compatible O Rh-negative packed red blood cells (30 ml each) were transfused on day 6 and 7. Antibiotic medication and supportive therapy were continued. On 8th day of life, the patient’s hemoglobin level raised to 10.4 gm% and serum bilirubin concentrations decreased to 5.7 mg/dl. The changes in hematocrit and bilirubin from day 1 to day 8 are shown in Figure 1.

### Discussion

Anti-M antibodies are naturally occurring, cold reactive saline agglutinins and are mostly IgM type, but 50%–80% have an IgG component. In a study on the prevalence of alloantibodies, only one was anti-M positive among 3,577 multigravidas in India.[4] IgM antibodies with anti-M specificity have been reported to be detected in 10% of pregnant women with a positive antibody screen, but only 0.01%–0.7% of pregnant women would trigger anti-M IgG that can cross the placenta.[2]

Fetomaternal hemorrhage (FMH) occurs spontaneously during pregnancy and its probability increases with gestational age from 3% in the first trimester to 45% in the third trimester.[5] The possibility for FMH is higher in

### Table 1: Advanced red cell serology workup of mother and baby

| Advanced red cell serology workup | Baby | Mother |
|-----------------------------------|------|--------|
| Blood group (EMT)                | O’ Rh positive | ‘A’ Rh positive |
| DAT (AHG phase)                  | Negative | Negative |
| Indirect antiglobulin test (AHG phase) | Grade 3 positive | Grade 3 positive |
| Auto control (AHG phase)         | Negative | Negative |
| Antibody screening               | Positive | Positive |
| Antibody identification          | Suggestive of anti-M antibody | Suggestive of anti-M antibody |
| Crossmatch                       | Out of 14 units (O Rh positive and O Rh negative) crossmatched, 2 O Rh negative units were found compatible | Same units were found compatible with mother’s serum |

EMT=Erythrocyte-magnetized technology; DAT=Direct antiglobulin test; AHG=Antihuman globulin
cases of abdominal trauma, amniocentesis, cordocentesis, and abortions. In this case, the mother has a history of the first trimester abortion 2 years back which has resulted in RBC alloimmunization due to FMH.

Furthermore, reticulocyte count was low in the infant suggestive of decreased erythropoiesis due to the destruction of the erythroid precursor cells by anti-M antibodies. Anti-M causes HDN primarily by destroying erythroid progenitors rather than mature erythrocytes hence can present as prolonged anemia in the neonatal period.

During antenatal screening, when an IgG type of anti-M antibody reactive at 37°C is identified in the maternal blood, the paternal blood must be checked for the presence of M antigen. There is no documented evidence for assessing the severity of the disease based on antibody titers. Alloantibody against M antigen mostly IgM type causing blood grouping discrepancy is repeatedly reported. However, very few cases have been reported of anti-M to be IgG type and there are no clinical guidelines for the management of HDN due to anti-M.[7]

A positive direct antiglobulin test DAT is one of the diagnostic criteria for immune hemolytic disease. However, the DAT was negative in our case. Yasuda et al. found that 79% of MN alloantibody-induced cases of hemolytic disease of the fetus and newborn were DAT-negative.[8] The reasons for DAT-negative cases can be due to very rapid intravascular hemolysis or it is possible that the MN antigen is present on the glycoporphins of erythroid progenitor cells.[6,9]

Close monitoring of the bilirubin level is necessary during the 1st days after birth because of the risk of kernicterus. The infant may require phototherapy which oxidizes the elevated unconjugated bilirubin, allowing the oxidation products to be excreted in the urine. IVIG may be given to the infant to control hemolysis. In neonates who are unresponsive to phototherapy and IVIG, a double-volume exchange transfusion removes approximately 90% of the fetal red cells and 50% of the bilirubin. If intrauterine transfusions were administered, then exchange transfusion may be unnecessary. Intrauterine transfusion is considered the most effective method of treating fetal anemia due to anti-M alloimmunization. Wikman et al. described three pregnancies in a single family all resulting in severe anemia. The first fetus died in utero during the 20th week of gestation, the second was delivered at 28 weeks with hydrops fetalis, and the third was treated with intrauterine red cell transfusions before delivery at 28 weeks. The DAT was negative and the anti-M of low titer, but Cr51-labelled M+ red cells in maternal blood were hemolyzed.[6]

### Conclusion

This case was a rare presentation of maternal allo-anti-M antibody-induced hemolytic disease of the newborn. Anti-M is capable of causing HDN and prolonged anemia (red cell aplasia). As anti-M may cause suppression of fetal erythropoiesis, it is recommended that the baby be monitored for symptoms of late-onset anemia up to 2 months of age.[9] Newborns with anemia should be evaluated for all the possible causes to establish a diagnosis and its efficient management. The mother should be closely monitored for future pregnancies as well.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

1. Kanra T, Yüce K, Ozcibe IU. Hydrops fetalis and intrauterine deaths due to anti-M. Acta Obstet Gynecol Scand 1996;75:415-7.
2. Kornstad L. New cases of irregular blood group antibodies other than anti-D in pregnancy. Frequency and clinical significance. Acta Obstet Gynecol Scand 1983;62:431-6.
3. Beal RW. Non-rhesus (D) blood group isoimmunization in obstetrics. Clin Obstet Gynaecol 1979;6:493-508.
4. Pahuja S, Gupta SK, Pujani M, Jain M. The prevalence of irregular erythrocyte antibodies among antenatal women in Delhi. Blood Transfus 2011;9:388-93.
5. Sebring ES, Polesky HF. Fetomaternal hemorrhage: Incidence, risk factors, time of occurrence, and clinical effects. Transfusion 1990;30:344-57.
6. Wikman A, Edner A, Gryfelt G, Jonsson B, Henter JL. Fetal hemolytic anemia and intrauterine death caused by anti-M immunization. Transfusion 2007;47:911-7.
7. Khalid S, Dantes R, Varghese S, Al Hakawati I. Naturally occurring anti M complicating ABO grouping. Indian J Pathol Microbiol 2011;54:170-2.
8. Yasuda H, Ohto H, Nollet KE, Kawabata K, Saito S, Yagi Y, et al. Hemolytic disease of the fetus and newborn with late-onset anemia due to anti-M: A case report and review of the Japanese literature. Transfus Med Rev 2014;28:1-6.
9. Baipayee A, Dubey A, Sonker A, Chaudhary RK. A case of severe foetal anaemia due to anti-M isoimmunisation salvaged by intrauterine transfusions. Blood Transfus 2014;12 Suppl 1:s302-4.