Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Successful Management of Severe Early-Onset Fetal Hemolytic Anemia Due to Anti-Rh17 Alloimmunization: A Case Report

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Article Info

10.30699/jogcr.8.5.533

Received: 2022/11/05;
Accepted: 2023/01/12;
Published Online: 09 Sep 2023;

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ABSTRACT

As widespread prophylaxis with anti-D Antibodies has dramatically diminished anti-D-associated hemolytic disease of the newborn (HDN), other antibodies-associated HDN has become relatively more significant. Two genes encode Rh proteins: the RhD gene coding for the D and the Rh CcEe gene coding for Cc Ee Antigens. D is a rare Rh phenotype in which RBCs lack Cc/Ee antigens while D antigen is strongly expressed. Anti R17 antibodies are important monomorphic antibodies acting against all previously mentioned antigens. It can pass through the placenta as a G immunoglobulin, leading to fetal or neonatal hemolysis. Here, we reported an immunized pregnant female with D- - phenotype and a history of intrauterine fetal death who had high titer of anti-Rh17 antibodies in her subsequent pregnancy. We would discuss our management strategy which led to good perinatal outcomes. To the best of our knowledge, this is the second case of HDN reported in English written literature in Iran.

Keywords: RH17 Antigen, Fetal Blood, Intrauterine Transfusion, Hemolytic Disease of the Fetal and Newborn, Rh Isoimmunization

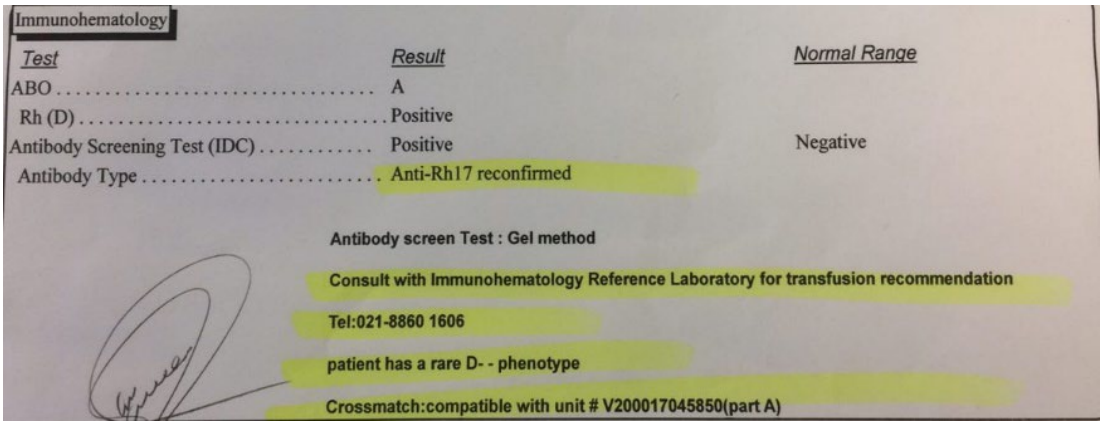
Introduction

Rh antigen is among the most pleomorphic blood group antigen system. There have been identified more than 100 variants of Rh antigen in human beings, which some have extremely rare prevalence **(1, 2)**. Hemolytic disease of the newborn (HDN) secondary to anti -D has dramatically has declined with the widespread prophylactic use of anti–D Antibody immunization especially during pregnancy. Consequently, HDN attributed to other blood groups has become relatively more significant **(3)**. Two similar genes, presented on chromosome 1, encode Rh proteins: the RHD gene coding for the D antigen and the RHCE gene coding for C, c, E, and e Antigens **(4)**. D- - haplotype which was first introduced in the1950s,is a rare Rh phenotype in which RBCs lack C, c, E, and e antigens in their surfaces and instead D antigen is strongly overexpressed **(4)**. It is inherited in a Mendelian pattern and results from homologous deletion of RHCE gene **(5)**. People with D- - phenotype will be immunized via blood component transfusions and or during pregnancy in females **(6-10)**. Anti R17 antibodies are monomorphic antibodies acting against all the previously mentioned RBC antigens. Since these antibodies are IgG subclass they can pass through the placenta to the fetus and result in neonatal or fetal hemolytic diseases **(3, 9-12)**. In fact, anti RH17 antibodies will mainly cause severe hemolytic disease of fetus and neonate (HDFN), although less severe forms have been also reported in literature **(13, 14)**. Severe forms of HDFN could be managed via intrauterine or exchange transfusions **(5)**. As the prevalence of Rh17 negative people has been estimated approximately 1 in 100000 cases, finding an appropriate donor is a main concern, especially among pregnant women **(13)**.

In Iran, up to 2019, 14 people have been known with D- - phenotype. Here, we report a rare case of early onset severe fetal anemia due to maternal anti Rh17 antibodies who required intrauterine transfusion. As finding a suitable donor was challenging some alternative adjunctive treatment was also done to reduce the transfusion need and finally the mother and healthy baby were discharged home without any significant complications.

Case Presentation

A 24-year-old, Gravid3, Live birth1, Intra uterine fetal death (IUFD)1 Iranian pregnant female was referred to Yas hospital, Tehran university of medical sciences -affiliated hospital, Tehran, Iran in 2019 due to detection of Rh17 antibodies in her antibody screening test at the first prenatal visit. Her first pregnancy had successfully resulted in the birth of a healthy male neonate with a good Apgar score and normal birth weight. Her second pregnancy had been terminated at 36 weeks of gestation upon diagnosis of IUFD. At that time, antiphospholipid antibodies profile, Thyroid Stimulating Hormone and blood sugar tests were all in normal limits. The fetus weighted 2500 grams and no gross anomaly had been detected; however, autopsy had not been performed. At her third pregnancy, she had undergone an indirect coombs test at the age of 13 weeks of gestation and as the result turned positive, she was referred to our hospital which is a referral center for pregnancies complicated with Rh immunization in the country. The patient underwent a full serum antibodies screening at the national blood bank referral laboratory, Tehran, Iran and Anti-Rh17 antibodies at titer of 1:2048 were detected. The mother's blood group antigen was A, D antigen was positive and D- - phenotype was also confirmed (Fig1, and 2). Due to potential risk of fetal anemia, subsequently, middle cerebral artery (MCA) Doppler ultra-sonographic assessment was performed.


Immunohematology

Test	Result	Normal Range
ABO	A	
Rh (D)	Positive	
Antibody Screening Test (IDC)	Positive	Negative
Antibody Type	Anti-Rh17 reconfirmed	

Antibody screen Test : Gel method

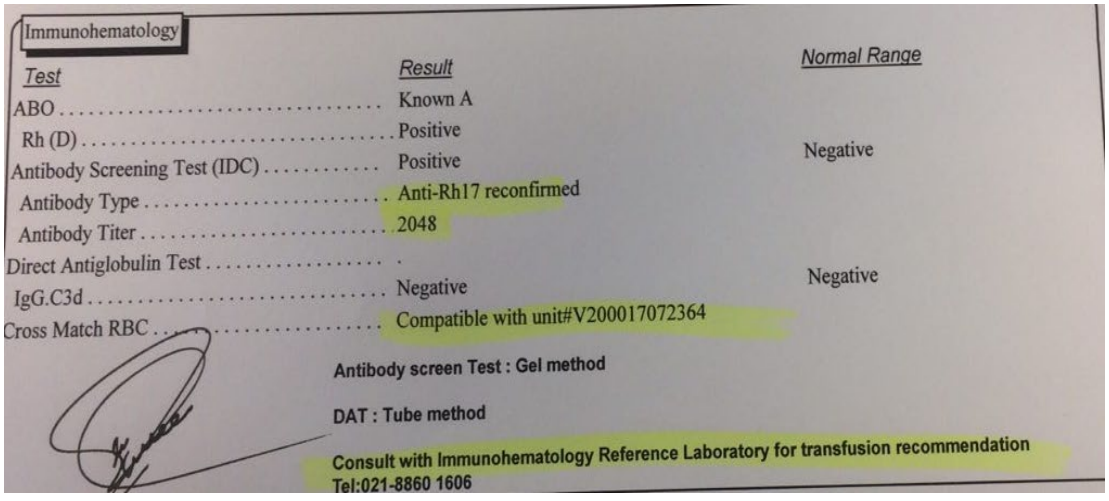
Consult with Immunohematology Reference Laboratory for transfusion recommendation

Tel:021-8860 1606

patient has a rare D- - phenotype

Crossmatch:compatible with unit # V200017045850(part A)

Figure 1. The patient's blood group and antibodies screening results


Immunohematology

Test	Result	Normal Range
ABO	Known A	
Rh (D)	Positive	
Antibody Screening Test (IDC)	Positive	Negative
Antibody Type	Anti-Rh17 reconfirmed	
Antibody Titer	2048	
Direct Antiglobulin Test	.	
IgG.C3d	Negative	Negative
Cross Match RBC	Compatible with unit#V200017072364	

Antibody screen Test : Gel method

DAT : Tube method

Consult with Immunohematology Reference Laboratory for transfusion recommendation

Tel:021-8860 1606

Figure 2. The patient's blood group and antibodies screening results

Fetal anemia was confirmed by the presence of MCA Peak Systolic Velocity of 42 cm/second, which was over1.5MOM for that specific gestational age. Consequently, Intra uterine transfusion (IUT) was planned. So, group A positive, D- - phenotype Packed cells were required. According to our national blood bank declaration at that time, only 14 people had been recognized with D - - phenotype in our country.

Unfortunately, because of ABO incompatibility with the patient or the presence of medical comorbidities in some others, we could not find a compatible donor among these 14 people. Comprehensive consult was done with the patient regarding rarity of this blood group type, unavailability of compatible blood for IUT and also the possibility of intrapartum or postpartum hemorrhage and chance for transfusion need. Pregnancy termination was proposed but the couple decided to continue pregnancy. While all efforts were done to find a suitable donor, the fetus was under serial sonographic follow-up exams, although the fetus was anemic, no ascites, pericardial and or pleural effusion was evident. Finally, antibody screening of all her family members revealed that the patient's sister had the same ABO and Rh phenotype. Hence, the first IUT was done at the age of 27 weeks of gestation. At first, Cord synthesis was done which confirmed severe fetal anemia as the fetal cord blood hemoglobin was 3.9 ng/dL. 100 cc packed RBCs were transfused and hemoglobin reached to 14.1 ng/dL. After the first IUT, serial MCA Doppler sonographic exams were performed weekly. Eventually, 37 days later, the fetus presented again with severe anemia but as no other compatible donor was available except the fetus's aunt, IUT was not performed. Instead, the patient was followed one week later and as ascites was newly developed, after consultation with blood bank, they convinced the fetal aunt to give another bag of packed cell. The next IUT was performed in 2 sessions, 24-hours apart each other. This IUT resulted in Hb increase from 3.5 to 8.8 ng/dL and then from 8.8 to 14.1 ng/dL. After the third IUT serial sonographies were done and finally labor induction was done at the age of 37-38weeks of gestation and a male neonate weighting 2710gr with good Apgar scores was born. The cord blood sampling showed: blood group A, Rh D positive, Hb: 9.6 ng/dl, platelet count: 57000/mm^3, retic 1%, total bilirubin: 2.5 and direct: 1. To treat neonatal anemia we had no compatible donor yet, so Prophylactic phototherapy was done and IVIG was administered in hope to prevent ongoing hemolysis. Doing all these procedures the neonate was discharged after 6 days while his Hb was 9.7 ng/dL at the time of discharge.

Discussion

D- - phenotype is an extremely rare phenotype in which RBCs lack CcEe antigens in their surfaces and instead strongly express D antigen **(4)**. After immunization via pregnancy or blood component transfusion, these people will be immunized and in case of passing of these antibodies through the placenta, fetal hemolytic anemia can happen **(6-10)**.

Anti Rh17 is one of the most important of these antibodies which can act against all Rh antigens **(3, 9-12)**.

Very few similar cases due to anti Rh17 antibodies have been reported **(3, 9-12)**. For example, K. Aref and et al. in 2002 reported the successful management of a case of hemolytic disease and hydrops fetalis secondary to anti–Rh 17 antibodies in a woman with the rare D- - phenotype **(3)**.

On other hand, N. Salamat and et al reported a pregnant lady with anemia, mitral valve disease and anti Rh17 alloantibodies who required blood for operation and her baby suffered from hydrops fetalis and unfortunately the fetus died **(14)**.

In Iran, Choobdar et al. reported the first case of severe hemolytic disease of the newborn due to anti-Rh17 antibodies with maternal blood group B RHD- - **(15)**.

Our patient was sensitized via her previous pregnancies, probably after her second one which had resulted in IUFD, and as previously mentioned, during her subsequent pregnancy, maternal sensitization was detected at 13 weeks of gestation at her first prenatal visit in antibody screening high level of anti RH17 antibodies were identified

In our case, despite the presence of high level of antibodies, fetal blood level of bilirubin and reticulocyte count before all IUTs and their level in cord blood sample, all showed mild hemolysis and this can rationalize why intrauterine fetal death did not happen although IUTs were done with delay. This result was parallel to what Hirose and et al. found **(10)**. They suggested that the preexisting antibody had a low hemolytic potential. These authors concluded that the IgG1 subclass of the antibody, or a long-time interval between sensitization and pregnancy, or both, may have contributed to the severity of the disease. The antibody newly produced by the second immune response has a high hemolytic potential that caused a striking and rapid decrease of fetal hematocrit. It is possible that an appropriate assessment of the interval between sensitization and pregnancy, as well as antibody titer, IgG subclass determination, and fetal Doppler ultrasonography findings, might have helped to avoid some of the invasive interventions and prevented the second immune response, resulting in pregnancy prolongation **(10)**.

Due to unavailability of compatible blood for our patient, early term vaginal delivery was scheduled and labor was induced at the age of 37 weeks of gestation. Several methods for treatment of newborns with hemolytic anemia have been reported, as an example, exchange transfusions with maternal blood (frozen previously or freshly donated) have been used with successful outcomes (**16**). Some authors have reported good neonatal outcome even with repeated incompatible Rh D negative exchange transfusions **(15, 17, 18)**.

High dose of IVIG has been shown beneficial in the management of fetal-neonatal hemolytic anemia since many years ago and it seems to be effective in decreasing the chance for blood transfusion without any significant side effects **(17, 18)**. But the therapeutic

response depends on IVIG dose and the disease severity **(17, 18)**.

As no compatible donor was available, we transfused IVIG to our neonate in hope to decrease further hemolysis and prophylactic phototherapy was done too. Hopefully, our management led to the birth of a healthy male neonate who discharged on the day 6th without any blood transfusion.

Our patient was a rare case of severe early-onset fetal anemia due to maternal anti Rh17 antibodies who required intrauterine transfusion. Successful management during pregnancy caused good outcomes for the mother and her neonate. However, at first we were worried because we did not have accessed to compatible blood, and intrapartum or postpartum hemorrhage were our main concerns and this led to proposal of pregnancy termination. But refusal of our patient and good cooperation of the national blood bank and prophylactic use of IVIG and phototherapy all resulted in good perinatal outcomes.

As a final recommendation, considering the rarity of this blood group phenotype in the Iranian population and much more prevalence of this phenotype among Japanese, it seems that international blood bank cooperation will make management of patients much easier.

Conclusion

None.

Acknowledgments

We would like to thank our colleagues in the Iranian Blood Transfusion Organization for good cooperation specially Mr.Mostafa Moghadam, MA, MT (ASCP). We also appreciate our patient and her husband who let us share their data in hope to provide more evidence in this regard.

Disclosure

All authors have not any financial relation with any organization.

Conflict of Interest

The authors have no conflict of interest.

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How to Cite This Article:

Ghalandarpoor-Attar, S. N., Rahimi-Sharbaf, F., Ghalandarpoor-Attar, S. M. Successful Management of Severe Early-Onset Fetal Hemolytic Anemia Due to Anti-Rh17 Alloimmunization: A Case Report. J Obstet Gynecol Cancer Res. 2023; 8(5):533-7.

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