CASE REPORT

Anti-M Alloimmunization in Pregnancy: An Unusual Cause of Bad Obstetric History

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Received: 3 July 2015 / Accepted: 23 November 2015 / Published online: 26 March 2016
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Introduction

Even 50 years after the advent of Rh D prophylaxis, red cell alloimmunization is still the challenging task for obstetricians [1]. Other red cell antigens, namely C, c, E, e, have now emerged as an important cause of alloimmunization leading to hemolytic disease of fetus and newborn (HDFN) [1].

Alloimmunization rate varies from 0.4 to 2.7 % in pregnant women worldwide [1]. Limited data are available in India on alloimmunization in pregnant women. 1.5–2 % of pregnant females show atypical blood group sensitization [1]. The overall alloantibody prevalence was found to be 1.25 % in a study by Sangeeta et al., but it is 5.5 % in pregnant women with bad obstetric history and 0.5 % in

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those without bad obstetric history [1]. Universal screening of all pregnant women for alloantibodies is controversial, and there are no uniform guidelines in India for the same [1]. According to guidelines by Directorate General of Health Sciences Technical Manual, Government of India, screening for alloantibodies is limited to Rh-negative women or those with adverse obstetric history [1]. At our institute, the routine antenatal screening is done only in Rh (D)-negative women, so there is a paucity of information about such red cell antibodies in Rh (D)-positive women. Anti-M alloimmunization in pregnancy is a rare but an important cause of fetal loss.

Case Report

Thirty-year-old G6P1130 presented to the antenatal clinic of PGIMER, a tertiary institute at 6-week period of gestation (POG) with bad obstetric history. She underwent medical termination of pregnancy at 20-week POG in her first pregnancy for fetal ventriculomegaly. She had missed abortion at 10-week POG in second pregnancy. In her third pregnancy, she had uneventful antenatal period but had sudden intrauterine fetal death at 32-week POG and delivered a stillborn boy by vaginal route. She had sudden intrauterine fetal death at 19-week POG in the fourth pregnancy and aborted the fetus with no gross congenital malformation. In her fifth pregnancy, she had uneventful supervised antenatal period but delivered a stillborn boy at term probably due to intrapartum birth asphyxia. There was no history of hydrops in any of the previous pregnancies. She was evaluated in view of bad obstetric history. Her glucose tolerance test and thyroid function tests were normal. Antiphospholipid antibody tests (lupus anticoagulant, anticardiolipin antibodies and anti- β_2 antiglobulin antibodies) were negative. On routine blood grouping, she was found to be B positive on cell grouping. On serum grouping, she developed 4+ agglutination with pooled O cells indicating ABO discrepancy. Antibody screening and identification were done using a gel technique with 3- and 11-cell panels (BioRad, Morat, Switzerland), respectively. The antibody was identified as anti-M which was reactive at room temperature (RT), at 37 °C and in antihuman globulin (AHG) phase. Subsequently, enzyme treatment was done with 1 % commercial papain (Bio-Rad, Morat, Switzerland), and reactivity was found to be diminished. The titer of anti-M in untreated serum was 128 at RT and 256 in AHG phase, while the titer of dithiothreitol (DTT)-treated serum was 8 at RT and 256 in AHG phase. Subsequently, AHG phase titer remained 256, indicating that it was predominantly IgG type. Her husband's blood group was A positive, and he was typed as M antigen positive (Table 1). Her triple screen and congenital anomaly scan

were normal. She was monitored with middle cerebral artery peak systolic velocity (MCA PSV) since 20-week POG. She was diagnosed to have anemia at 25+ 4-week POG in view of increased MCA PSV more than 1.5 MOM. Cordocentesis was done and confirmed fetal anemia with a PCV of 23.3 %. Intrauterine transfusion (IUT) was given at cord insertion. Baby's blood group was AB positive, and red cells were found to be M antigen positive. O-negative, M antigen-negative packed red cells with a PCV of 70–75 %, collected within last 5–7 days, were used for IUTs. The amount of blood transfused was calculated by the formula: estimated fetal weight (in g) $\times$ 0.02 = amount of blood to increase PCV by 10 %. She was subsequently monitored by ultrasonography for fetal growth, liquor and MCA PSV and received three further IUTs in the cord, last IUT being given at 34 weeks with last post-transfusion PCV of 39.8 %. Her fetal growth and liquor were within normal limits. She was induced at 36-week POG and delivered a live-born boy weighing 2.7 kg with Apgar's score of 8 and 9 by vaginal route. Baby's cord blood PCV was 40 %, and total serum bilirubin was 1.8 mg/dl. Baby did not require any exchange or top-up transfusion but kept under phototherapy for 96 h. Both mother and baby were discharged in satisfactory condition after 4 days.

Discussion

Usually, antenatal screening for antibody detection which leads to HDFN is limited to anti-D detection, but non-D alloimmunization does contribute to perinatal morbidity and mortality in good number of cases [2]. Anti-M is a naturally occurring IgM antibody presenting as cold agglutinin. Its conversion to IgG is rare and is associated with HDFN [2]. The transmembrane protein glycophorin A carries MN determinants and can be detected in the fetus as early as 9-week POG [2]. The incidence of HDFN due to anti-M antibody is very low although the prevalence of anti-M antibodies in pregnant females ranges from 10 to 15 % [2, 3]. The severity of anti-M varies from asymptomatic to severe HDFN. It can present as recurrent hydrops or intrauterine fetal death [2]. The statistically significant correlation was found between alloimmunization and adverse pregnancy outcome [1]. The anti-M titer is not the reliable predictor of severity of HDFN as determination of antibody titer depends on various factors such as technique and suspension medium used, incubation temperature and homozygous or heterozygous expression of M antigen on reagent red cells [2]. There are only a few case reports of anti-M alloimmunization so far. Archana et al. reported a case where pregnancy was successfully salvaged by multiple intrauterine transfusions in a pregnant

Table 1 Extended red cell phenotyping in mother (patient) and her husband

	C	E	c	e	M	N	K
Antenatal mother	+	–	+	+	–	+	–
Husband	+	+	+	+	+	–	–

woman with anti-M alloimmunization with previous six intrauterine deaths between 11 and 32 weeks of gestation [2]. Our patient was also successfully managed with repeated intrauterine transfusions.

HDFN is caused by maternal IgG antibodies transferred transplacentally against paternal antigens on fetal red cells leading to lysis of cells and hence anemia [2]. De Owens studied 115 pregnancies with anti-M antibodies. None of the patients developed hemolytic disease of newborn [2].

Furukuwa et al. reported a patient with multiple intrauterine deaths with anti-M antibodies where intensive plasmapheresis was done reducing anti-M titer to 256 from 4096 giving birth to live-born baby requiring phototherapy [2]. Plasmapheresis with intrauterine transfusions (intraperitoneal and intracardiac) once hydrops developed was used as a treatment for anti-M alloimmunization in a gravida 3 para 1, but baby could not be salvaged [2].

Although extensive studies are required, successful outcome with the use of direct injection of human immunoglobulins into the fetal abdominal cavity to treat anti-M alloimmunization has been reported [4].

Our patient was monitored with MCA PSV and detected to have anemia by increased MCA PSV for which she received multiple intrauterine transfusions resulting in live birth.

Hence to conclude, anti-M alloimmunization in pregnancy is rare and presentation can vary from asymptomatic to hydrops to intrauterine fetal death. Alloimmunization

should always be considered as a cause of bad obstetric history. Hence, indirect Coombs' test and an antibody screen should be done in such patients and can save a life of a newborn. It can be effectively managed by MCA PSV monitoring and intrauterine transfusions if MCA PSV is more than 1.5 MOM, suggesting anemia with a good neonatal outcome.

Compliance with Ethical Standards

Conflict of interest The authors report no declaration of interest.

Informed Consent Informed consent was obtained from the patient for publication.

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