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Case Report

Prenatal treatment of severe fetal hemolytic disease due to anti-M alloimmunization by serial intrauterine transfusions

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ABSTRACT

Objective: Fetal hemolytic disease is a common cause of fetal hydrops and fetal morbidity and mortality. Despite its relatively low frequency, the anti-M IgG antibody is one of the causes of severe fetal anemia and intrauterine death; only a few cases have been reported.
Case report: This is a case of a pregnant woman with a history of three intrauterine deaths. A diagnosis of severe fetal anemia attributed to anti-M alloimmunization was confirmed in her fifth pregnancy. She came to our center for regular monitoring at the beginning of the pregnancy. Five intrauterine transfusions were performed to correct moderate to severe fetal anemia throughout her pregnancy. A male infant, delivered at the 36th gestational week received two transfusions after birth, and no neurologic abnormalities were observed until the child was 6 months of age.
Conclusion: Anti-M alloimmunization is an important cause of severe fetal hemolytic disease. The characteristics of fetal hemolytic disease due to anti-M alloimmunization may be somewhat different from those of disease due to anti-D alloimmunization.

Introduction

Fetal hemolytic disease results from an incompatibility between maternal and fetal red blood cell antigens. This disorder may lead to fetal anemia, fetal hydrops and stillbirth. Anti-M alloimmunization is an important cause of severe fetal hemolytic disease. Here, we report a case of severe fetal anemia due to anti-M immunization in a pregnant woman with a history of three previous intrauterine deaths. During her fifth pregnancy, fetal anemia due to anti-M alloimmunization was diagnosed and successfully treated by serial intrauterine transfusions (IUTs).

Case report

A 31-year-old pregnant Chinese woman—gravida five, para two, abortus two—with no history of transfusions, had an abortion at 5 weeks gestation during her first pregnancy, when she was 19 years old. During her second pregnancy, an ultrasound revealed that the fetus died in utero due to fetal hydrops at 35 weeks gestation. Her third pregnancy was uneventful until 32 weeks gestation, at which time fetal demise occurred and was found to be accompanied by ascites, a hydrothorax and a pericardial effusion via ultrasound. She was referred to our center 2 years after the pregnancy was terminated.

Blood tests for TORCH (toxoplasma, rubella, cytomegalovirus and herpes) and autoantibodies were negative. Thalassemia screening and the karyotypes of both the patient and her husband were normal. For further investigation, irregular antibody screening was performed. The anti-M IgG antibody titer was 64. No other irregular antibodies were detected. Her blood group was B Rh CCDee M−N+, while that of her husband was O Rh CcDEe M+N+. Two years later, during her fourth pregnancy, a miscarriage occurred at 60 days gestation.

At the beginning of her fifth pregnancy, she came to our center for regular monitoring beginning at 11 weeks gestation. The anti-M IgG antibody titer was 64 during the first trimester. At 17 weeks gestation, the anti-M IgG antibody titer had increased to 256, while the peak systolic velocity in the fetal middle cerebral artery (MCA-PSV) was normal. At 22 weeks and 5 days gestation, a highly elevated MCA-PSV of 1.64 multiples of the median (MoM) indicating moderate to severe fetal anemia was noted. There were no

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signs of fetal hydrops, polyhydramnios or increased placental thickness. Emergent ultrasound-guided cordocentesis was performed to obtain a fetal blood sample (2.5 ml) for analysis. The fetal blood group was B RhD-positive M+N+, the hemoglobin level was 64 g/L and the hematocrit (Hct) was 16.8%. A free antibody test for anti-M IgG and an antibody release test were both positive, while a direct antiglobulin test (DAT) was negative. Viral antibodies (i.e., cytomegalovirus, rubella, etc.) were negative. The fetal karyotype was normal, as were the thalassemia screening and hemoglobin electrophoresis results.

Intrauterine transfusion was performed the following day. Vecuronium at a dose of 0.1 mg per estimated fetal weight was used to ensure fetal quiescence and muscle relaxation. A blood sample (1 ml) obtained prior to transfusion showed that the hemoglobin was 54 g/L and that the hematocrit was 15.5%. The transfusion was performed with freshly prepared, washed and concentrated group O RhD-positive M-negative red blood cells. Twenty-four milliliters of red cells were successfully transfused into the umbilical vein via ultrasound guidance. At the end of the procedure, a blood sample (1 ml) showed that the hemoglobin had increased to 108 g/L, with a hematocrit to 31.6%. Four subsequent IUTs were administered at 24, 27, 30 and 32 weeks gestation (Table 1). A non-stress test was performed to monitor the fetus, beginning at 32 weeks gestation. The anti-M IgG titer was 1:256 during the pregnancy.

An elective caesarean section was scheduled for the 36th gestational week. A male infant weighing 2570 g was delivered, with Apgar scores of five and ten at 1 and 5 min, respectively. The hemoglobin level was 100 g/L, and the hematocrit was 32.1% at the time of birth, so a postnatal transfusion with M-negative red blood cells was immediately performed. A second transfusion was performed on the sixth day after birth when the hemoglobin dropped to 92 g/L. The total bilirubin level was 71.9 μmol/L at the time of birth and then increased to 106.4 μmol/L on day two, accompanied by the development of mild jaundice. The infant received phototherapy for four days. Intravenous immunoglobulin and albumin were administered several times, although an exchange transfusion was not required. He was discharged from the neonatal intensive care unit in good condition on day of life 13. On day of life 43, his hemoglobin decreased to 69 g/L, and his anti-M IgG titer was 1:16. He subsequently received another transfusion. No neurologic abnormalities were observed until 6 months of age.

Discussion

Fetal hemolytic disease results from an incompatibility between maternal and fetal red blood cell antigens. The most frequent cause of red-cell alloimmunization is RhD negativity (80%) [1]. In recent years, universal antenatal screening for RhD-negative pregnancies and the use of RhD immunoglobulin have significantly reduced the incidence of severe hemolytic disease of the fetus and newborn (HDFN). However, non-RhD antigens still contribute to perinatal morbidity and mortality.

The MNS system consists of 46 antigens including M, N, S, s antigens. These antigens are fully developed on fetal red cells and can be detected as early as nine weeks gestation. The anti-M antibody is primarily an IgM antibody, although it may also be a combination of IgG and IgM antibodies. IgM occurs naturally and is considered to be clinically insignificant because it cannot cross the placenta and reacts optimally at 4 °C. However, IgG can cross the placenta and causes red cell agglutination at 37 °C. When the anti-M antibody has an IgG component, it may cause varying degrees of hemolysis in the fetus. Anti-M IgM can be detected in 10% of pregnant women with a positive antibody screen, while 0.01%–0.7% of pregnant women are found to have clinically significant levels of anti-M IgG, the production of which is always induced during the first pregnancy [2,3].

A positive DAT is one of the diagnostic criteria for immune hemolytic disease because fetal red blood cells are coated with maternal antibodies. However, the DAT was negative in our case, as previously reported [4–6]. Yasuda et al. found that 79% of cases of HDFN resulting from MN incompatibility were DAT-negative [7]. One hypothesis explaining this phenomenon may be very rapid intravascular hemolysis. Another hypothesis is that the MN antigen is present on the glycophorins of erythroid progenitor cells, unlike the antigens of the Rh system [4,8]. These two scenarios may explain the low detection rate of nonagglutinating antibodies on red blood cells.

There have been sporadic case reports of fetal hemolytic disease due to anti-M alloimmunization, mainly in Asian populations. Most intrauterine deaths associated with anti-M alloimmunization reportedly occur between 10 and 35 weeks gestation, and the majority of pregnancies are affected at approximately six months gestation [4,9]. Anti-M IgG may cause HDFN in the first fetus due to placental transfer of the antibody into the fetal circulation. Approximately 72% of cases of MN-incompatible HDFN manifest as severe hemolytic anemia and/or hydrops fetalis [7].

Doppler ultrasound measurements of MCA-PSV are highly reliable predictors of fetal anemia secondary to red cell alloimmunization. An MCA-PSV of 1.5 MoM was established as the threshold to predict moderate to severe fetal anemia. However, MCA-PSV seems to be less helpful for predicting the timing of subsequent IUTs, despite a good correlation between MCA-PSV and fetal hemoglobin levels [10]. In a previous study, the positive predictive value of MCA-PSV was 75.3% for the first IUT but decreased to 46.7% and 48.8% for the second and third IUTs, respectively [11]. Thus, subsequent IUTs should be carried out at intervals based on estimated decreases in fetal hemoglobin.

Table 1
Clinical characteristics of the five IUTs.

IUT No.	GA (weeks + days)	IUT interval (days)	MCA-PSV (MoM)	Freshness of donor blood (days)	Transfusion volume (ml)	Hb (g/L)			Hct (%)	
						Pre-transfusion	Post-transfusion	Decline rate (per day)	Pre-transfusion	Post-transfusion
1	22 + 6	–	1.58	2	24	54	108	–	15.5	31.6
2	24	8	1.03	6	35	95	131	1.6	27.1	38.3
3	26 + 5	19	1.34	4	45	89	151	2.2	25.2	42.7
4	30	23	1.56	6	85	70	#	3.5	19.9	#
5	32 + 2	16	1.50	8	100	84	197	#	24.4	59.5
Birth	36	26	–	–	–	100[a]	–	3.7	32.1[a]	–

IUT No. = number of intrauterine transfusions; GA = gestational age; Hb = hemoglobin; Hct = hematocrit; MCA-PSV = peak systolic velocity of the middle cerebral artery; MoM = multiples of the median.
#Blood sample could not be obtained for a complete blood count after the fourth IUT because the puncture needle slipped off.
[a] Evaluated at the time of birth.

Theoretically, the rate of hemoglobin decline should decrease after repeated transfusions due to replacement of antigen-positive fetal red blood cells with antigen-negative red blood cells, which have a longer life span. Friszer et al. reported that the rate of decrease in fetal hemoglobin was approximately 4.5 g/L per day between the first and second transfusions and 3.5 g/L and 3.2 g/L between the second and third transfusions and following the third transfusion, respectively [11]. And Scheier et al. reported that the mean rates of decrease in hemoglobin were 4, 3, and 2 g/L per day, respectively, after the first, second and third transfusions [12]. However, the rates of decrease were 1.6, 2.2, 3.5 and 3.7 g/L per day after the first, second, third and fifth IUTs, respectively, in our case. These results are very different from those of IUTs administered to treat anti-D alloimmunization, as reported in the literature. One hypothesis is that the antigens present on the membrane glycoproteins of immature erythroid precursors cause inhibition of precursor cell growth due to maternal anti-M alloimmunization [13]. It has been suggested that neither the freshness of red cells nor the use of different donor blood samples has an impact on the rate of consumption of transfused red blood cells [14].

Our observations show that the characteristics of fetal hemolytic disease secondary to anti-M alloimmunization may be somewhat different from those of disease secondary to anti-D alloimmunization, as shown by the increased rate of hemoglobin decline and the negative DAT result observed in this study. As soon as fetal hydrops or intrauterine death due to anti-M alloimmunization is diagnosed, intensive surveillance involving both antibody titers and Doppler ultrasound measurements should be carried out. IUT is the most effective method of treating fetal anemia due to anti-M alloimmunization.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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