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Severe fetal hemolytic disease due to anti-M alloimmunization: A case report and literature review

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ABSTRACT

Fetal hemolysis is caused by maternal antibodies that cross the placenta. Anti-M antibodies can rarely cause severe forms of alloimmunization in the fetus and newborn. We present a case of severe anti-M alloimmunization requiring a total of 8 intrauterine transfusions, in a patient with a prior poor obstetrical history. A 35-year-old Iranian pregnant woman with a prior obstetrical history of one abortion and two stillbirths was found to have had anti-M antibody titers 1:8 and accompanying elevated middle cerebral artery peak systolic velocity (MCA-PSV) of 1.9 MoM suggestive of severe fetal anemia at 17 weeks of gestation. Persistently elevated fetal MCA-PSV was noted despite intraperitoneal transfusion at 17, 19, and 22 weeks. Fetal blood sampling at 27 weeks confirmed severe fetal anemia (3 g/dL), which required additional intravascular and intraperitoneal blood transfusion. At 37 weeks, elective cesarean section was performed. Neonatal hemoglobin immediately after delivery was 10.1 g/dL. In addition to standard supportive care, the neonate required two additional transfusions and remained in the neonatal intensive care unit (NICU) for 23 days.

Anti-M antibodies are a rare cause of severe alloimmunization. We present a case in order to improve management.

1. Introduction

Hemolytic disease of the fetus and newborn (HDFN) or fetal hemolysis is caused by maternal antibodies that cross the placenta, most commonly because of Rhesus alloimmunization. These antibodies (usually created from antigen exposure in prior pregnancies) cross the placenta and can cause fetal hemolysis and anemia. The administration of anti-RhD immune globulin has proven to be instrumental in preventing complications from severe fetal anemia associated with RH alloimmunization, including fetal death [1–3]. Antibody screening and evaluation of antibody titers are non-invasive methods that are utilized during pregnancy for antenatal evaluation of alloimmune fetal disease. A complementary non-invasive method is the Doppler evaluation of the peak systolic velocity of the fetal middle cerebral artery (MCA-PSV) among fetuses whose mothers have tested positive during antibody screening [3,4].

The management of severe fetal anemia associated with alloimmunization is challenging because the underlying pathophysiology continues until the time of delivery. Patients will often require repeated intrauterine transfusions as the pregnancy progresses, which can be accomplished using intraperitoneal or intravascular routes [5].

Rarely, anti-M antibodies are associated with hemolysis in the fetus and newborn [6]. We present the case of a 35-year-old patient with a history of intrauterine fetal demise due to hydrops fetalis and anti-M-positive antibody screen, who presented with elevated fetal MCA PSV at 17 weeks. The fetus was successfully treated with repeated intrauterine transfusions and was delivered at term. The CARE guidelines were used to report this patient [7].

Abbreviations: Hemolytic disease of the fetus and newborn, (HDFN); Intrauterine fetal demise, (IUFD); Intrauterine transfusion, (IUT); The peak systolic velocity of the fetal middle cerebral artery, (MCA-PSV); Packed red blood cells, (pRBC).

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2. Case Presentation

A 35-year-old Iranian woman, G4P2A1 (G: gravidity, P: parity, A: abortion), attended a perinatology clinic at a tertiary care center at 17 weeks of gestation. The patient's first pregnancy had resulted in spontaneous abortion at 8 weeks of gestation. Her second and third pregnancies had resulted in intrauterine fetal demise (IUFD) at 26 and 23 weeks of gestation respectively, in the setting of hydrops fetalis. The patient had no prior blood transfusions or history of trauma. Her blood group was A Rh positive.

During her previous pregnancy, she had been referred to the clinic for a possible intrauterine transfusion at 23 weeks of gestation. The fetus had ultrasonographic findings suggestive of severe anemia, including severe ascites, pleural and pericardial effusion, skin edema, placentomegaly, and MCA-PSV (middle cerebral artery peak systolic velocity) of >2 MoM in her first referral. The patient underwent cordocentesis with a fetal primary hemoglobin count of 1.2. IUFD occurred shortly before intrauterine blood transfusion (IUT) could be performed.

In the patient's current pregnancy, her medical history was positive for hypothyroidism (TSH: 4.9 mU/L, T4: lower limit of normal), with negative anti-TPO. The determination of the packed red blood cell (pRBC) volume in transfusions is an essential aspect of fetal medicine. In this regard, the calculation involves a formula subtracting 20 from the gestational age in weeks and multiplying the result by 10. For instance, a fetus at 30 weeks would require 100 mL of blood. This approach is commonly employed in clinical practice to ensure that the transfusions are administered in appropriate doses [8].

Sonography of the fetus at 17 weeks revealed MCA-PSV of 1.9 MoM, suggestive of fetal anemia. A blood sample was sent for antibody screening (see Table 1); the anti-M IgG antibody titer was 1:8.

Due to the small caliper of the umbilical vein and posterior placenta, cordocentesis was not attempted. A 20-gauge needle was placed into the fetal abdominal cavity, and 10 cc O negative, anti-M negative washed pRBC were transfused intraperitoneally.

After 24 h, Doppler ultrasonography revealed that MCA-PSV had improved, decreasing to 1.5 MoM. Another intrauterine transfusion was carried out intraperitoneally at 19 weeks of gestation with 15 cc pRBC, followed by a third intraperitoneal transfusion at 22 weeks of gestation with 23 cc of pRBC. MCA-PSV further improved to 1.25 MoM. At 22 weeks of gestation, cordocentesis was tried but due to the posterior lateral position of the placenta and the difficulty of the procedure, the intraperitoneal route was chosen.

Before her 4th IUT, MCA-PSV was 40.6 cm/s (1.3 MoM), and an echocardiogram revealed a somewhat elevated cardiac output. At 27 weeks of gestation, cordocentesis demonstrated fetal hemoglobin of 3 g/dL, and so 70 cc packed RBCs was infused intravenously as well and an additional 70 cc packed RBCs was given intraperitoneally. IUT was thus performed a total of 8 times, with the last at 33 weeks, 1 day of gestation. The interventions performed due to fetal anemia for the patient are shown in Table 2. All transfused packed RBCs were tested M-negative.

Hemoglobin through cordocentesis at 36 weeks of gestation was 11.6 g/dL; therefore, delivery was postponed until the fetus reached term. Cesarean delivery was performed at 37 weeks due to persistent reduced fetal movement. A healthy female neonate was delivered with APGAR scores of 9/9, birth weight of 3050 g, umbilical cord ABG pH of 7.31, and hemoglobin level of 10.1 g/dL. The neonate was hospitalized in the neonatal care unit for 23 days. She required two blood transfusions, on days 2 and 39 of life. At 24 months following the delivery, the infant continued to demonstrate normal development. Evaluations by pediatric cardiology and neurology teams had been normal for two years at the time of writing.

Table 1
Characteristic and clinical information for the patient at first admission.

Age	35 years	
gestational age at first admission	17 weeks	
Obstetrics history	Gravidity: 4, Parity: 2, Abortion:1, Live birth:0, Dead births: 2 1st: aborted 8th weeks, 2nd: IUFD at 26th weeks (intrauterine fetal deaths), 3rd: IUFD at 23rd weeks (hydrops fetalis due to anemia)	
Vital signs at first admission	Blood pressure:110/70, Respiratory rate:14, Temperature:37, Heart rate:78	
Laboratory tests at first admission	CBC	Hemoglobin:11.2 g/dL, WBC: 8200 × 10^9/L, platelet: 254000 per microliter
	Thyroid function tests	TSH:4.9 mU/L, T4: lower limit of normal, Anti-TPO: negative,
	TORCH tests	Toxoplasma: negative, Cytomegalovirus: negative, Rubella: negative, Herpes: negative, and Parvovirus B19: negative
	Antibody screening	, K: negative, E: negative, C: positive, c: positive, e: positive Anti M IgG antibody titer: 1:8

CBC: complete blood count, WBC: white cell count, TORCH: Toxoplasmosis, Other, Rubella, Cytomegalovirus (CMV), and Herpes infections.

3. Discussion

This was a rare case of severe fetal anemia associated with anti-M antibodies requiring treatment with 8 intrauterine transfusions starting at 17 weeks of gestation. The patient had a history of one abortion followed by two fetal deaths likely associated with fetal hemolytic disease. In this pregnancy, the patient required 8 IUTs to treat severe fetal anemia.

M is the most common antibody in the MNS system. In rare cases, the anti-M IgG can cross the placenta, leading to fetal hemolysis and severe anemia [6]. The anti-M antibody predominantly manifests as an IgM antibody, albeit it can also present as a composite of IgG and IgM antibodies. The IgM antibody, which is naturally occurring, is deemed clinically inconsequential due to its inability to traverse the placenta and its optimal reactivity at 4 °C. Conversely, the IgG antibody can permeate the placenta and instigate red cell agglutination at 37 °C. In instances where the anti-M antibody has an IgG component, it has the potential to induce a spectrum of hemolysis severity in the fetus [9].

Macpherson et al. and Matsumo et al. were the first to report patients with stillbirths associated with anti-M alloimmunization [10,11]. Subsequent authors have described different interventions for fetal anemia due to anti-M alloimmunization. First, Furukawa et al. performed plasmapheresis for a patient with a suitable outcome in 1993 [12]; then Seo and his colleagues performed fetal intravascular transfusions [13]. Moreover, others use different prenatal therapies, like intrauterine transfusions, intraperitoneal transfusions, and plasma exchanges, with different and suitable outcomes due to the patient's situation [9,14–17]. Table 3 summarizes the reported cases of fetal anemia due to anti-M alloimmunization and their interventions.

Moreover, the benefits of intravenous immunoglobulin transfusion in early hemolytic disease of the fetus and newborn are supported by several pieces of evidence [18]; in particular, the successful management of anti-M alloimmunization in pregnancy with intravenous immunoglobulin transfusion reported by Hubinont et al. is noteworthy [16]. However, this approach was not feasible in the current case due to limited experience and the high cost of intravenous immunoglobulin transfusion in the patient's country.

In Iran, approximately 70–80 pregnant women are referred to the tertiary center for IUT annually [19]; therefore, it enhances the experience of the perinatologists' team in the current center in management, especially for complicated cases like this.

In conclusion, anti-M alloimmunization is very rare among pregnant women in comparison to other etiologies of fetal hemolysis. This case and previous cases mentioned in the literature demonstrate that close follow-up and proactive fetal intervention can result in positive neonatal outcomes. The current state of research on prenatal interventions in cases of anti-M alloimmunization necessitates further investigation for a clearer understanding and development of guidelines in hospitals and

Table 2
The Interventions performed due to fetal anemia for the patients.

No.	Gestational age *weeks + days*	IUT[3] *CC*	MCV- PSV[4] *(MoM)*		Hg[5] *g/dL*		EFW[6] (gr)	AFI[7] (cm)
			Before transfusion	After transfusion	Before transfusion	After transfusion		
1	15 ± 0	–	<1.5	–	–	–	–	–
2	16 ± 0	–	<1.5	–	–	–	190	NL
3	17 + 6	10[1]	1.89	1.44	–	–	243	NL
4	19 + 0	15[1]	1.44	1.31	–	–	439	NL
5	22 + 0	23[1]	1.29	–	–	–	560	15.9
6	24 + 2	50[1]	1.60	1.38	–	–	685	16.7
7	27 + 5	70[1], 70[2]	1.32	–	3	9.7	1205	18.3
8	28 + 6	90[2]	1.38	1.19	5.6	14.8	1339	18
9	31 + 1	110[2]	1.56	1.10	10.9		1603	19.4
10	33 + 1	180[2]	0.95	0.84	9.9	16.8	2294	14,7
11	36 + 0	–	–	–	11.6	–	2989	13.8

[1] Intra peritoneal transfusion (into fetal peritoneum).
[2] Intravascular transfusion (into fetal umbilical vein at placental insertion site).
[3] Intrauterine transfusion.
[4] Peak systolic velocity of the fetal middle cerebral artery.
[5] Hemoglobin.
[6] Estimated fetal weight.
[7] Amniotic fluid index.

Table 3
Summary of five fetal anemia case reports and their therapeutic interventions due to anti-M alloimmunization.

No	author	year	country	Interventions	average gestational age at diagnosis	average GA at first intervention	Delivery	outcomes
1	Furukawa et al. [12]	1993	Japan	plasmapheresis 6 times on a biweekly program	–	12 weeks of gestation	–	Intrauterine death
2	Furukawa et al. [12]	1993	Japan	plasmapheresis therapy, 56 Liter	–	2 months of gestation	Normal delivery with induction, 35 weeks	Alive, initiated phototherapy, normal developing
3	Seo et al. [13]	2007	South Korea	Fetal intravascular transfusions, 2 times	32 weeks+2 days	32 weeks+2 days	Normal delivery with induction, 35 weeks	Alive, initiated phototherapy, and one time transfusion for newborn
4	Bajpayee et al. [14]	2014	India	Intrauterine transfusion, 3 times	20 weeks	28 weeks	C-section	Alive, mild jaundice at birth receiving phototherapy for newborn, normal developmental and hematological follow-up after 12 months
5	Li et al. [9]	2017	China	Intrauterine transfusions, 5 times	22 weeks+5 days	22 weeks+6 days	elective cesarean section, 36 weeks	Alive, two blood transfusion for the neonate after birth, normal developmental follow-up until 6 months
6	Hubinont et al. [16]	2017	Belgium	plasma exchange twice a week and daily low molecular weight heparin injection, 1 Intrauterine transfusions	–	–	–	Intrauterine death at 20 weeks
7	Hubinont et al. [16]	2017	Belgium	Plasmapheresis at 7 weeks and twice a week and changed to 3/ week after 12 weeks,	–	7 weeks+5 days	Cesarean, 32 weeks+6 days	Alive, Phototherapy was initiated, discharged after 3 weeks
8	Maki et al. [15]	2020	Japan	Intraperitoneal transfusion due to unsuitable position of umbilical cord for intrauterine transfusion	19 weeks	24 weeks	–	Fetal death
9	Maki et al. [15]	2020	Japan	Plasma Exchange, 25 times; intrauterine transfusion, 1 time	13 weeks	14 weeks	Normal delivery, 31 weeks	Alive, 11 days phototherapy and five transfusion for neonate, discharge at day 46 without abnormal neurological findings

clinics. An approved treatment for the condition would aid obstetricians in providing optimal patient care.

Contributors

Fatemeh Golshahi contributed to patient care and conception of the case report.

Fatemeh Rahimi Sharbaf contributed to patient care, and acquiring and interpreting the data.

Mahboobeh Shirazi contributed to patient care, and acquiring and interpreting the data.

Behrokh Sahebdel contributed to acquiring and interpreting the data.

Jafar Golshahi contributed to undertaking the literature review and revising the article critically for important intellectual content.

Simon Dadoun contributed to undertaking the literature review and revising the article critically for important intellectual content.

Soroush Aalipour: contributed to undertaking the literature review and revising the article critically for important intellectual content.

Mohammad Haddadi contributed to drafting the manuscript and

revising the article critically for important intellectual content.

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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