Case report

Passive transfer of silent red blood cell autoantibodies via the placenta and breast milk: a case report

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INTRODUCTION

Two general types of pathogenic maternal antibodies are recognized. The first are autoimmune antibodies associated with present, past, or potential maternal autoimmune disease[1]. The second are alloimmune antibodies directed at fetal/neonatal antigens that the mother does not carry, causing illness in her neonate but not in herself[1]. When unexpected antibodies recognizing self-red blood cell (RBC) antigens are detected in individuals by a positive direct antiglobulin test (DAT) and with no evidence of hemolytic anemia, they are called "silent red blood cell autoantibodies" (SRBCAA)[2]. SRBCAA have been detected in pregnant women, healthy blood donors, and in patients with autoimmune disorderes[2,3]. Until now, there was no evidence that SRBCAA in pregnant women affects the course of pregnancy or the neonate[2,3].

Maternal antibodies are transferred to the neonate via the placenta and breast milk (BM). While the role of placentally transferred immunoglobulin G (IgG) is well established, less is known about the selection of antibodies transferred via BM[4].

Herein, we describe the case of a neonate born to an SRBCAA-bearing mother.

CASE REPORT

A female neonate was born to a 38-year-old G2P1 at 36 weeks of gestation by C-section. The pregnancy was complicated by maternal hypertension. The neonate weighed 2,690 grams, and Apgar scores were 6 at the 1st and 8 at the 5th minute of life. On the 3rd day of life (DOL), anemia (hemoglobin [Hb] level of 11.1 g/dL) was noted, without signs of infection, hemolysis, or blood loss; therefore, she was transferred to the tertiary neonatal hospital for further investigation. Laboratory analysis confirmed anemia with Hb level of 10.4 (13.4-19.9 g/dL), hematocrit (Hct) 30.4 (42-65%), RBC count 2.84 (3.9-5.5×10^{12}/L), with normal reticulocytes of 1.4 (0.5-2.5%), reactive leukocytosis 22.18, (5.0-21.0×10^{9}/L), normal platelets 373 (150-450×10^{9}/L) and total bilirubin level of 35.5 (17.1-205 μmol/L).

The mother has a past medical history of a pan-reactive autoantibody to RBC antigens since she had her first delivery seven years ago. One RBC transfusion was documented during the first delivery due to blood loss following C-section. She denies any chronic or hereditary diseases. Clinical or laboratory evidence of hemolysis was not noted in the mother.

Initially, the mother and neonate were typed with the same blood group: B RhD-positive, CcDee, K negative. Likewise, both had positive monospecific (IgG) DAT with a strength of 1+ and indirect antiglobulin test (IAT) with a strength of 2+. Antibody identification by an 11-cell panel was performed on maternal and neonatal plasma using a fully

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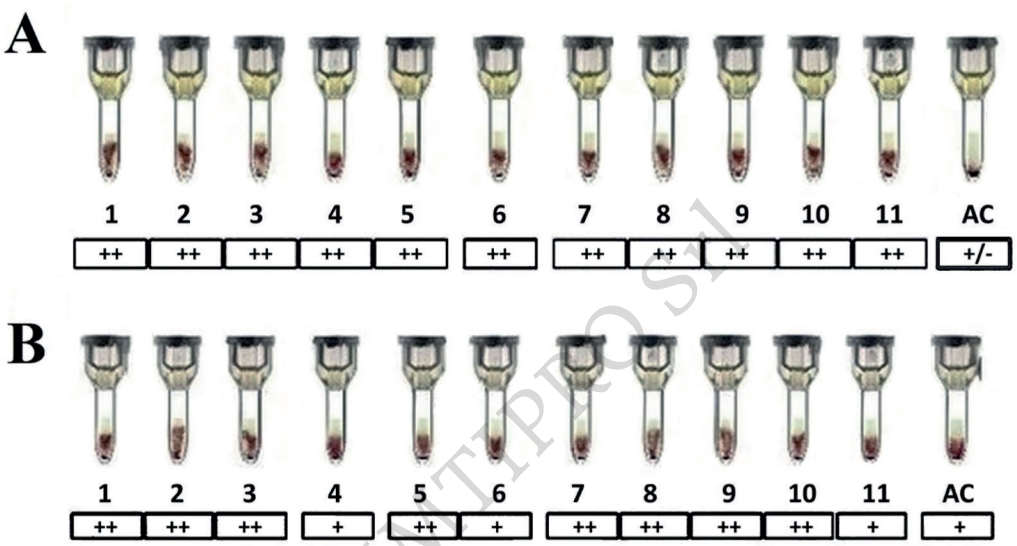
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automated immunohematology analyzer, the IH-500 (Bio-Rad, Cressier FR, Switzerland) (**Figure 1**). An elution was performed on the maternal and neonatal RBCs. Autoantibodies were found in maternal plasma and on RBCs with positive auto-control (1+). A similar reaction pattern was also observed in neonatal plasma with weakly positive auto-control (+/-) but no antibody was detected on RBCs, which may have been below the threshold required to identify low levels of bound antibodies.

Additional testing using enzyme-treated 11-cell panel was performed on maternal plasma and indicated the presence of autoantibodies.

The neonate was breastfed with the addition of milk formula.

After obtaining informed consent, a sample of the mother's BM was collected and tested using an anti-human globulin gel cards with IgG specificity (Bio-Rad). The test had been internally validated for BM. The maternal BM agglutinated all panel red blood cells as shown in **Figure 2**.



C

	Rh-hr	Möglicher Genotyp / Probable Genotype / Genotype probable / Probabile genotipo / Genotipo probable / Genótipo provável	Spender / Donor / Donneur / Donatore / Donante / Dador	Rh-hr						Kell						Duffy		Kidd		Lewis		P	MNS				Luth.		Xg	
				D	C	E	c	e	C^w	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^a	♀♂
1	CCC^{w}D.ee	$R_1{}^wR_1$	689856	+	+	0	0	+	+	0	+	0	+	nt	nt	+	0	0	+	0	+	+	+	0	+	+	0	+	+	N/A
2	CCD.ee	R_1R_1	151876	+	+	0	0	+	0	+	+	0	+	nt	nt	0	+	+	+	0	+	+	+	+	+	0	0	+	+	N/A
3	ccD.EE	R_2R_2	767303	+	0	+	+	0	0	0	+	0	+	nt	nt	0	+	+	0	+	0	0	+	0	0	+	0	+	0	N/A
4	Ccddee	r´r	161362	0	+	0	+	+	0	0	+	0	+	nt	nt	+	+	0	+	0	+	+	0	+	0	+	0	+	+	N/A
5	ccddEe	r´´r	662713	0	0	+	+	+	0	0	+	0	+	nt	nt	+	0	0	+	0	+	+	+	+	+	0	0	+	0	N/A
6	ccddee	rr	366012	0	0	0	+	+	0	+	+	0	+	nt	nt	+	0	0	+	+	0	+	0	+	+	+	0	+	+	N/A
7	ccddee	rr	725196	0	0	0	+	+	0	0	+	+	+	nt	nt	0	+	+	0	0	+	0	0	+	0	+	0	+	+	N/A
8	ccD.ee	R_or	485017	+	0	0	+	+	0	0	+	0	+	nt	nt	0	0	+	0	0	+	+	+	+	0	+	0	+	0	N/A
9	ccddee	rr	410185	0	0	0	+	+	0	0	+	0	+	nt	nt	+	0	0	+	0	0	+	+	+	0	+	+	+	+	N/A
10	ccddee	rr	803815	0	0	0	+	+	0	0	+	0	+	nt	nt	0	+	+	0	0	+	0	+	0	+	0	0	+	0	N/A
11	ccddee	rr	000987	0	0	0	+	+	0	0	+	0	+	nt	nt	+	0	+	+	0	0	+	0	+	0	+	0	+	0	N/A

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Figure 1 - Antibody identification patterns in neonatal and maternal samples with RBC antigen profiling
(**A**) Reactivity pattern of neonatal plasma. The antibody identification is positive with a strength of 2+ in all panel cells, and auto-control is +/- weakly positive. (**B**) Reactivity pattern of maternal plasma. The antibody identification panel shows a strength of 1+ to 2+, and auto-control is 1+ positive. (**C**) Red blood cell antigen identification panel.



Figure 2 - Reactivity pattern of maternal breast milk
The antibody identification panel shows a strength of 1+ to 2+.

The neonate was discharged after 5 days, clinically well, with a stable Hb level of 10.4 g/dL. Seven days later, she was readmitted due to anemia requiring RBC transfusion (Hb 8.8 g/dL, Hct 25.7%). She received one incompatible cross-matched RBC unit, ABO-compatible, RhD-positive without complication, and was discharged soon afterwards with Hb 13.8 g/dL, Hct 39.1%. Meanwhile, breastfeeding was ceased due to diminished lactation.

DISCUSSION

Data on the clinical course of individuals with SRBCAA are insufficient, and it remains unclear whether disorders commonly associated with autoimmune hemolytic anemia (AIHA) may also occur in these patients[3]. In a retrospective analysis of the long-term outcomes of 60 individuals with SRBCAA conducted by Mauro et al., only 5 (8%) pregnant women were identified during first-trimester screening (3 with IgG, 1 with immunoglobulin M (IgM), and 1 with both IgG and IgM). The autoantibodies persisted during and after pregnancy, but no signs of hemolytic anemia were observed in either the mothers or their neonates[3].

This report describes a premature infant with a mild hemolytic process and a positive DAT and IAT, representing manifestations of maternal autoantibodies. Mother had a history of pan-reactive antibody to RBC antigens, indicating SRBCAA, as AIHA or any other autoimmune diseases had not been confirmed.

The neonate was initially breastfed; however, breastfeeding was ceased because of diminished lactation. We speculate that the neonatal anemia, which was most pronounced on the 17th DOL, was caused by maternal autoantibodies passively transferred via the placenta and potentially exacerbated by continued transfer through breast milk.

Neonates are incapable of making their antibodies until the age of 6 months. IgG transfer from mother to fetus begins at approximately 12 weeks of gestation, however it is not until about the 22nd week of gestation, or mid to late second trimester, that the transfer rate accelerates[5,6].

Preterm infants also experience a decrease in Hb concentration after birth, with a decline that is typically more abrupt and pronounced than in term infants, reaching Hb levels of 7 to 9 g/dL at 3 to 6 weeks of age[7]. The transient leukocytosis observed in our patient may be a consequence of anemia, as it is well known that various non-infectious conditions, such as birth-related stress, physiological adaptation in the immediate postnatal period, and hematologic disturbances, can contribute to elevated white blood cell counts[8].

Bujandrić N *et al.* reported a case of AIHA in a 26-year-old primigravida. The neonate presented with warm autoantibody IgG and a positive DAT of 3+, without jaundice or anemia. The infant was breastfed for nine months after birth. The child's Hb remained stable during the 12-month follow-up[9].

In each infant born to a mother with RBC autoantibodies that have transferred via the placenta and BM, monitoring of Hb and Hct levels is recommended due to the risk of anemia. Careful consideration should be given to providing advice regarding breastfeeding, as the BM is a gold standard for infant nutrition, an irreplaceable source of nutrients and early immunological protection[4,10].

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SRBCAA have been thought to be naturally occurring or part of a homeostatic mechanism for clearing altered self-RBC[1]. Accurate long-term follow-up studies and functional assays are needed to evaluate the innocuous or pathogenic presence of SRBCAA in SRBCAA-bearing "healthy" individuals. This also applies to neonates born to SRBCAA-bearing mothers.

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AUTHORSHIP CONTRIBUTIONS

ZR, JM, and ZR contributed to the concept, wrote, and revised the manuscript. NK performed confirmatory testing and reviewed the manuscript; OŠ revised the manuscript. MB provided administrative support.

The Authors declare no conflict of interest.

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