Case Study

Hemolytic Disease of the Fetus and Newborn Caused by Maternal Autoantibody with Mimicking Anti-E Specificity

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Laboratory Medicine 2021;52:399-402

DOI: 10.1093/labmed/lmaa096

ABSTRACT

Objective: There are few reports of hemolytic disease of the fetus and newborn (HDFN) caused by maternal autoantibodies.

Methods: We describe the case of a pregnant patient aged 26 years with systemic lupus erythematosus without any transfusion history who developed autoantibody with mimicking anti-E specificity. Her newborn developed HDFN caused by the maternal autoantibody.

Results: The clinical symptoms of the newborn were not serious. After bilirubin light phototherapy and other symptomatic supportive treatment, the baby was discharged with a good prognosis.

Conclusion: This is the first reported case of HDFN caused by maternal autoantibody with mimicking anti-E specificity. However, the real antigenic target of the autoantibody was not clear.

Keywords: hemolytic disease of the fetus and newborn, autoantibodies, mimicking, anti-E

Patient History

Hemolytic disease of the fetus and newborn (HDFN) is a form of immunological hemolytic disease caused by maternal–fetal blood type incompatibility. The common cause involves IgG alloantibodies, which can cross the placental barrier. Only a few patients with cases caused by maternal autoantibodies have been reported. Herein, we report a case of a patient with HDFN caused by maternal autoantibody with mimicking anti-E specificity. On September 30, 2019, a 26 year old, 37 gestational weeks, G3P0Ab2 pregnant patient presented to our emergency department complaining of abdominal pain that had lasted for >3 hours, having had 2 miscarriages of unknown causes but associated with a history of systemic lupus erythematosus (SLE) for >3 years and undergoing treatment using long-term oral administration of prednisone and hydroxychloroquine.

Abbreviations:

HDFN, hemolytic disease of the fetus and newborn; SLE, systemic lupus erythematosus; DAT, direct antiglobulin test; PLT, platelet; RBCs, red blood cells; NT, not tested; W, weak; MC, mother's cell; NC, neonatal cell; TF-History, transfusion history; NM, not mentioned; GA, gestational age; POS, positive; NEG, negative; IAT, indirect antiglobulin test; PT, phototherapy; Hb, hemoglobin; TB, total bilirubin; SA, severe anemia; NP, neonatal pneumonia; RF, respiratory failure; HB, hyperbilirubinemia; Ex-TF, exchange transfusion; IVIG, intravenous immunoglobin; ALB, albumin.

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Clinical and Laboratory Information

During this third pregnancy, the mother had developed thrombocytopenia with a minimum of 35×10^9/L platelets (PLT; normal, $100–450\times10^9$/L), which was considered a complication of her SLE. She had no symptoms or transfusion

history. After admission, her hemoglobin level was 12.9 g/dL (normal, 11–15 g/dL) and her PLT count was 56×10^9/L. Serological results showed that her blood type was AB, her Rh phenotype was DccEE, and her direct antiglobulin test (DAT) was positive (4+); her antibody screening was I (0), II (2+), and III (0). Antibody identification of both the plasma and eluate showed IgG anti-E antibodies plus a positive autocontrol. Repeat serologic testing with the patient's adsorbed plasma showed the removal of apparent anti-E reactivity with either E-antigen-positive or E-antigen-negative red blood cells (RBCs). Adsorption of the plasma was performed based on the method described by Dwyre et al.[1] On the basis of her laboratory results and clinical history, the IgG anti-E was considered to be an autoantibody with mimicking anti-E specificity. Considering her thrombocytopenia, 1 apheresis PLT unit was transfused at the start of the second stage of labor, and the transfusion proceeded smoothly. Then she was transferred to deliver her baby right away. No other treatment was given in the emergency department. Her PLT count recovered to 86×10^9/L before discharge.

A healthy male baby was delivered at 37 weeks of gestation, weighing 2430 g. The Apgar scores were all 10 points for 1, 5, and 10 minutes. The baby was admitted to our neonatology department because of progressive cutaneous jaundice within 24 hours after birth. His hemoglobin level was 16.3 g/dL (normal, 17–21 g/dL), his reticulocyte count was 0.1698×10^{12}/L (normal, $0.024–0.084\times10^{12}$/L), total bilirubin was 16.81 mg/dL (normal, 0.58–11.11 mg/dL), and indirect bilirubin was 16.29 mg/dL (normal, 0.58–10.53 mg/dL). Considering the mimicking antibody detected in the maternal plasma and the potential blood needs of the baby, we collected the baby's umbilical cord blood for serological tests. The results showed that his neonatal blood type was B and the Rh phenotype was DCcEE; the DAT was positive (1+), and the antibody screening was I (0), II (1+), and III (0). Antibody identification of both the plasma and eluate showed IgG anti-E antibodies.

Combined with the baby's anemia, jaundice, and laboratory results, the diagnosis of HDFN was confirmed, and the cause was the transfer of the maternal autoantibody with mimicking anti-E specificity. A 16-cell antibody identification panel (Sanquin Reagents B.V., Amsterdam, Netherlands) was used, and the remaining serological determinations were performed using gel testing according to the manufacturer's instructions (Diagnostic Grifols, S.A., Barcelona, Spain). The serological results of the mother and her baby during hospitalization are summarized in **Table 1**.

Patient Follow-Up

Bilirubin light phototherapy and other symptomatic support treatment were given to the baby. Three days later, the jaundice subsided and the total bilirubin concentration decreased to 5.0 mg/dL. The baby was discharged with a good prognosis.

Discussion

Autoantibodies refer to those antibodies that act against one's own tissues, organs, cells, and cell components. When the body experiences immune system dysfunction because of autoimmune or other diseases, it may produce autoantibodies. According to Hoppe et al,[2] the chance of pregnant patients developing autoantibodies is at least 4 times higher than in nonpregnant peers. This process is usually caused by underlying diseases, immune system dysfunction during pregnancy, or other stimuli. In most patients, RBC autoantibodies react with all RBCs (ie, panreactive). Infrequently, in some patients the autoantibodies do have apparent specificity and do not maintain specificity after adsorption with antigen-negative and antigen-positive cells. These autoantibodies are said to be antibodies with mimicking specificity that were first described as "wrong antibodies," usually directed against Rh antigens (e, E, and c) although their true specificity is mostly anti-Hr or anti-Hr0.[3] In our patient, the mimicking specificity was confirmed because (1) antibody reactivity was consistent with anti-E, (2) the patient's RBCs were positive for the E-antigen, and (3) adsorbed serum (with either E-antigen-positive or E-antigen-negative RBCs) did not retain the anti-E activity. However, the real antigenic target of the autoantibody was not clear.

We searched PubMed and three Chinese language databases. To date, there are only 6 reports referring to HDFN caused by maternal autoantibodies. Of these, 3 involved nonspecific autoantibodies alone, 1 concerned a nonspecific autoantibody accompanied with an anti-E alloantibody, and the other 2 involved anti-M and anti-LW autoantibodies, respectively. All the relevant reports are summarized in **Table 2**. Studies have shown that maternal autoantibodies can lead to HDFN with varying

Table 1. Results of Screening Tests and Antibody Identification for Pregnant Patient and Infant in Plasma and Eluate

Cells	Rh-Hr					Kell						Duffy		Kidd		Lewis		P	MNS				Luther		Xg	Experimental Results			
	C	D	E	c	e	K	k	Kp^a	Kpb	Js^a	Jsb	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P1	M	N	S	s	Le^a	Le^b	Xg^a	Pregnant Patient		Infant	
																										Plasma	Eluate	Plasma	Eluate
I	+	+	0	0	+	0	+	0	/	0	/	+	0	+	0	0	+	+	0	+	0	+	+	/	+	0	0	0	0
II	+	0	+	+	0	0	+	0	/	NT	/	+	+	+	+	+	0	0	+	0	+	0	0	/	+	2+	3+	1+	1+
III	0	0	0	+	+	+	+	0	/	0	/	0	+	0	+	0	0	+	0	+	0	+	0	/	+	0	0	0	0
1	+	+	0	0	+	+	+	0	+	/	+	+	+	+	+	+	0	+	+	0	+	0	0	+	0	0	0	0	0
2	+	+	0	0	+	+	+	0	+	/	+	+	…	0	+	+	0	0	+	0	0	+	0	+	+	0	0	0	0
3	0	+	+	+	0	0	+	0	+	0	+	0	+	+	0	+	0	0	0	+	+	+	0	+	0	2+	3+	1+	1+
4	0	+	0	+	+	+	+	0	+	0	+	0	+	0	+	0	+	+	+	+	+	0	0	+	+	0	0	0	0
5	+	0	0	0	+	0	+	0	+	/	+	0	+	+	0	0	+	+	0	+	+	+	0	+	0	0	0	0	0
6	0	0	+	+	0	0	+	0	+	/	+	+	+	0	+	0	+	+	+	+	+	+	0	+	+	2+	3+	1+	1+
7	0	0	0	+	+	+	0	0	+	0	+	+	+	+	0	0	+	+	+	+	+	+	+	+	+	0	0	0	0
8	0	0	0	+	+	+	+	0	+	/	+	0	+	+	0	+	0	+	+	0	0	0	0	+	+	0	0	0	0
9	0	0	0	+	+	0	+	0	+	/	+	+	0	0	+	0	+	+	+	0	0	+	0	+	+	0	0	0	0
10	0	0	0	+	+	0	+	0	+	/	+	+	0	W	0	+	0	+	+	0	0	+	0	+	0	0	0	0	0
11	+	+	+	0	+	0	+	0	+	/	+	+	0	+	+	0	+	0	+	+	+	+	+	+	0	2+	3+	1+	1+
12	W	+	+	+	0	0	+	0	+	/	+	+	0	0	+	0	+	+	+	+	+	+	0	+	0	2+	3+	1+	1+
13	+	0	0	+	+	0	+	0	+	/	+	+	+	0	+	0	+	0	0	+	+	+	0	+	+	0	0	0	0
14	0	0	0	+	+	0	+	+	+	0	+	0	+	+	0	0	0	+	0	+	0	+	+	+	+	0	0	0	0
15	0	+	+	+	0	0	+	0	+	/	+	0	+	+	0	+	0	+	+	+	+	+	0	+	+	2+	3+	1+	1+
16	0	0	0	+	+	0	+	0	+	/	+	0	+	+	0	0	+	+	0	+	0	+	0	+	+	0	0	0	0
MC	0	+	+	+	0	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	2+	3+	/	/
NC	+	+	+	+	0	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	1+	1+

MC, mother's cell; NC, neonatal cell; NT, not tested; W, weak.

DOI: 10.1093/labmed/lmaa096

Table 2. Review of Published HDFN Literature Caused by Autoantibody

Case	Antibody	Pregnant Woman							GA	Infant						
		Age	Gravida-Para	TF-History	ABO	Rh	DAT	IAT	Titer		ABO	Rh	DAT	IAT	Hb g/dL)	TB mg/dL)	Major Complications	Management	Outcome
1[4]	Auto anti-LW	36	G2P1	NM	A	RhD (+)	POS	POS	NM	Term delivery	AB	RhD (+)	POS	NEG	NM	6.73	Jaundice	PT	Alive
2[5]	Nonspecific IgG autoantibody	25	G2P1	No	O	CcDee	POS (4+)	POS	IgM 4 IgG 256	NM	O	CcDee	POS (4+)	POS	NM	20.53	Jaundice	NM	NM
3[6]	Nonspecific IgG autoantibody	NM	G2P2	NM	B	RhD (+)	POS	POS	16	39+4	O	RhD (+)	POS	POS	14.8	16.41	Jaundice	PT	Alive
4[7]	Auto anti-M	35	G7P1	No	A	NM	NEG	POS	16	NM	NM	NM	NEG	POS	NM	NM	Jaundice	NM	NM
5[8]	Nonspecific IgG autoantibody/ alloantibody-e	21	G2P1	Yes	A	ccDEE	POS (4+)	POS[a]	64[b]	NM	O	CcDEe	POS (3+)	POS[c]	5	12.05	Jaundice/SA/ NP/RF/HB	TF/Ex-TF/PT/ IVIG/ALB	Alive
6[9]	Nonspecific IgG autoantibody	28	G1P0	No	B	RhD (+)	POS (4+)	POS (2+)	NM	NM	B	RhD (+)	POS (1+)	NEG	NM	NM	Jaundice	PT	Alive

ABO, blood type; ALB, albumin; anti-M, anti-M antibody; anti-LW, anti-LW antibody; DAT, direct antiglobulin test; Ex-TF, exchange transfusion; GA, gestational age; Hb, hemoglobin; HB, hyperbilirubinemia; IAT, indirect antiglobulin test; IVIG, intravenous immunoglobulin; NEG, negative; NM, not mentioned; NP, neonatal pneumonia; POS, positive; PT, phototherapy; RF, respiratory failure; Rh, Rh phenotype; SA, severe anemia; TF-History, transfusion history; TB, total bilirubin.

[a] *The autoantibody DAT was positive (4+); the alloantibody-e DAT was positive (2+).*

[b] *The titer was tested at 4°C.*

[c] *The autoantibody IAT was positive (4+); the alloantibody-e IAT was positive (1+).*

degrees. After active treatment, most of the babies born to mothers with these autoantibodies have a good prognosis.

This is the first reported case of a patient with HDFN caused by maternal autoantibody with mimicking anti-E specificity. It reminds clinicians to pay more attention to such a potential cause of HDFN. **LM**

Conflict of interest

The authors declare that there is no conflicts of interest.

Acknowledgments

We extend sincere gratitude and thanks to the staff of the Department of Laboratory Medicine, West China Second University Hospital, Sichuan University, China, and the investigators of the Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education. We also acknowledge with deep gratitude the assistance of James Cummins, PhD, from Liwen Bianji, Edanz Editing China, for editing the English text of a draft of this manuscript.

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