

# Hemolytic disease of the fetus and newborn due to antibodies to minor red blood cell groups: two case reports

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## Abstract

This study reports two cases of hemolytic disease of the fetus and newborn (HDFN) associated with antibodies to minor red blood cell (RBC) groups. Case 1 was a 35 week-gestational age (GA) female newborn, diagnosed with fetal anemia and hydrops by prenatal ultrasound. The primigravida mother had been diagnosed with beta-thalassemia/hemoglobin E disease and after being transfused, red cell alloimmunization and autoimmunization were detected during pregnancy. Antibody identification in the mother revealed anti-c, anti-E, anti-Mia and autoantibody. At birth, the patient was severely anemic and required ventilator support due to respiratory failure. Hematocrit was 15.1%. Direct and indirect antiglobulin tests (DAT and IAT) were strongly positive. Case 2 was a 36 week-GA male newborn with early onset of indirect hyperbilirubinemia and anemia. The mother had been diagnosed with systemic lupus erythematosus and transfused several times. At delivery, antibody identification revealed anti-c and anti-Mia in the mother, while DAT and IAT were positive in the newborn. Antibody identification revealed anti-c. The patient was given phototherapy. Maximum bilirubin was 16.9 mg/dL, and the lowest hematocrit was 31% on day 11. **Chiang Mai Medical Journal 2012;51(4):119-123.**

**Keywords:** anti-c, anti-E, anti-Mia, hemolytic disease of the fetus and newborn, alloimmunization

## Introduction

Hemolytic disease of the fetus and newborn (HDFN) is caused by destruction of fetal and neonatal red blood cells (RBCs) through ma-

ternal alloantibody that is specific to paternally-inherited red blood cell antigen. The maternal antibody passes through placenta and binds to fetal RBCs. The red blood cell (RBC) destruc-

tion process begins from in-utero. HDFN presents with a wide variety of severity, from mild anemia, reticulocytosis and neonatal hyperbilirubinemia, to marked fetal anemia and hydropic changes [1].

HDFN causing significant symptoms is due mostly to an antibody to the Rh(D) blood group. Currently, the incidence of Rh(D) HDFN is decreasing, as pregnant women at risk are identified usually and given anti-D immune globulin as a prophylaxis. Other minor blood group antibodies, such as anti-K and anti-c, have been described as causing HDFN [2]. This study reports two cases of HDFN, due to antibodies to minor RBC groups in newborns of previously transfused mothers.

## Case report

The first case was a 35-week-gestational age (GA) female newborn that was diagnosed with fetal anemia and hydrops by prenatal ultrasound. The 23-year-old primigravida mother was anemic and had been diagnosed with beta-thalassemia/hemoglobin (Hb) E disease at 5 years of age. She had had five RBC transfusions during childhood, and two during the pregnancy. The Hb level during pregnancy was 5.9-6.9 g/dL. A thalassemia screen of the father was negative. The first antenatal visit at a primary hospital was at a GA of 26 weeks. Prenatal ultrasound was carried out at 28 weeks to estimate the GA, which showed a normal, single viable fetus. A second ultrasound was performed at 34 weeks of GA because of poor uterine growth. The ultrasound showed fetal ascites and pericardial effusion. Cordocentesis was carried out in order to obtain fetal blood for Hb analysis, which determined the fetus as a carrier of Hb E. At that time, a pre-transfusion test of the mother showed abnormal RBC antibodies. The mother was then referred to Chiang Mai University (CMU) Hospital.

The fetal ultrasound at CMU Hospital showed cardiomegaly (cardio-thoracic ratio 74%), pericardial effusion and ascites. The middle cerebral artery peak systolic velocity (MCA-PSV) was more than 1.5 multiples of the median (MoMs), indicating fetal anemia. The fetus was diagnosed with hydrops fetalis. Antibody screening and identification of the mother showed anti-c, anti-E, anti-Mia and autoantibody. It was postulated that the cause of fetal anemia came from the RBC antibodies. As the GA of the fetus was close to term, an early delivery was planned for the mother. Compatible RBCs, which were crossmatched with maternal serum and had relevant antigen negative to the antibodies, were prepared before delivery. The patient was born at 35

weeks of GA by breech extraction. The birth weight was 1,820 g. The placenta weight was 600 g. The Apgar score was 1 at 1 minute, and 5 at 5 minutes. Physical examination revealed a pale, edematous newborn, with distended abdomen and enlarged liver and spleen. The patient required ventilator support, due to respiratory difficulty. Abdominal paracentesis was performed to release 20 mL of clear straw-colored ascitic fluid.

The complete blood count of the newborn showed an Hb of 4.6 g/dL, hematocrit (Hct) of 15.1%, MCV of 165 fL, MCH of 49.9 pg, MCHC of 30.3 g/dL, RDW of 12%, nucleated RBCs of 872/100 white blood cells (WBCs), corrected WBCs of 11,214/mm<sup>3</sup> (40% neutrophil, 4% band, 54% lymphocyte, 2% atypical lymphocyte), and platelets of 39,000/mm<sup>3</sup>. A peripheral blood smear showed many nucleated RBCs. Both maternal and patient blood groups were B Rh(D) positive. Direct and indirect antiglobulin tests (DAT and IAT) of the mother were positive weakly and 4+, respectively. The newborn's DAT and IAT were positive strongly (4+). Antibody identification from the newborn was not performed, due to limitation in obtaining blood samples. Liver function tests showed albumin of 2.2, globulin of 1.5 g/dL, AST/ALT of 276/44 U/L, and total /indirect bilirubin of 7.0/1.42 mg/dL.

The patient was given ventilator support, fluids, inotropic medications, antibiotics, hydrocortisone, and phototherapy. She received two units of RBC transfusions and a platelet transfusion. Hct increased to 35% and 29% after the first and second transfusion, respectively. Despite the treatment, the patient had intractable metabolic acidosis and progressive hypotension. She died at 18 hours of age.

The second case was a 36 weeks-GA male newborn, who presented with early onset of indirect hyperbilirubinemia and anemia. The mother was 32 years old. She had had systemic lupus erythematosus (SLE) from 12 years old, and had been transfused several times for anemia. One year prior to pregnancy, she was given 5 units of RBCs during surgery for avascular necrosis of the left hip. She had had two previous abortions. During pregnancy, anti-c, anti-Mia and anti-Jka were detected. Infectious markers were all negative. A thalassemia screen was negative.

The patient was born by normal delivery. His birth weight was 2,400 g, and the placenta weight 600 g. He was noted to have jaundice at 12 hours of age. The total bilirubin level was 8.4 mg/dL. He received phototherapy from hour 12 to day 4 and from day 11 to day 18. Maximum bilirubin was 16.9 mg/dL on day 11. Hct on day 1 was 56%, which slowly decreased over several days to a nadir at 31% on day 11. The reticulocyte count was 12.3%. Further investigations revealed that both maternal and patient blood groups were O Rh(D) positive. The maternal DAT was negative, and the IAT positive (3+). Antibody identification from maternal serum showed anti-c and anti-Mia. The DAT and IAT of

the patient were positive strongly (3+ and 3+, respectively). Antibody identification from the patient serum showed anti-c, and the G-6-PD screen was normal. The anemia resolved gradually, and the patient did not require a transfusion.

## Discussion

This study reported two cases of HDFN, due to antibodies to minor RBC antigens. The first case presented a newborn with fetal anemia and hydropic changes, as well as marked anemia, indirect hyperbilirubinemia, disseminated intravascular coagulation and cardiorespiratory failure, and she died shortly after birth. The patient had progressive anemia even after transfusion, indicating an ongoing destruction of RBCs by antibodies. Antibody screening and identification of the mother showed anti-c, anti-E, anti-Mia and autoantibody. Although antibody elution from newborn RBCs and identification was not done, strongly positive DAT and IAT suggested combined maternal alloantibodies and autoantibody as the cause of anemia. The second case had a milder early onset course of neonatal hyperbilirubinemia and anemia that associated with anti-c. Both cases had mothers who were transfused previously and known to have RBC alloimmunization.

Rh(D) blood group incompatibility was the main cause of severe HDFN. After the use of anti-D immunoglobulin, the incidence of Rh(D) HDFN decreased [2]. HDFN has become relatively more important to other minor RBC antigens, such as anti-c and anti-E. In Taiwan, the prevalence of HDFN caused by RBC alloantibodies was 0.01%. The reported antibodies were anti-E, anti-D, anti-c and anti-Mi [3]. The severity of HDFN ranges from mild anemia and neonatal hyperbilirubinemia to severe anemia and fetal hydrops. In Hong Kong, 0.27% of Chinese women had clinically significant antibodies [4]. Interestingly, anti-Mi was the predominant antibody (57.6%) followed by anti-E, anti-S and anti-c. The types of antibodies were different to those seen in the Caucasian population [5, 6].

Anti-c and anti-E alloimmunizations are common in Thai patients, as c and E antigens

are seen in a significant proportion of Thai people (c+ 48.3%, E+ 38.6%) [7]. The incidence of RBC antibodies in patients at Siriraj Hospital, Bangkok, Thailand, was 3.6%. Anti-Lewis, anti-E, anti-c and anti-Mia were the most common antibodies detected [8]. Anti-E and anti-c also are common antibodies detected among multi-transfused thalassemia patients in India and Malaysia [9, 10].

Several cases of HDFN due to anti-E and anti-c have been reported. Clinical presentation of affected newborns ranges from mild anemia and neonatal hyperbilirubinemia to severe fetal anemia and hydrops [11-18]. As anti-E and anti-c can cause clinically significant HDFN, close monitoring of fetuses that indicate maternal alloimmunization and treatment with intrauterine transfusion is recommended, as per the guideline for Rh(D) alloimmunization [19, 20]. After birth, a prolonged period of anemia has been noted, and periodic follow up of infants with maternal alloimmunization is suggested.

Prevalence of the Mia+ phenotype among Chinese blood donors in Taiwan is 7.3%. Anti-Mia is the most common alloantibody to the RBC minor blood group seen in Taiwan, with a frequency of 0.28% [21]. A case of severe HDFN, presenting with hydrops fetalis, was reported in a newborn from a nulliparous mother, who had no history of transfusions [22]. HDFN due to anti-Mia (anti-Mur) also was reported in a newborn from Hong Kong [23]. In Thailand, prevalence of the Mia+ phenotype is 9.1% [7], while in northern Thailand, its incidence is higher at 20.4% [24]. This report underscores the clinical importance of anti-Mia.

In summary, RBC alloantibodies to the minor RBC antigen can cause clinically significant HDFN. Positive DAT and IAT in newborns, who had compatible ABO and Rh(D) blood groups, indicate alloimmunization to other RBC antigens. Screening for alloantibodies to minor RBC antigens should be considered in mothers with a history of transfusion. If antibodies are detected, the fetus should be monitored closely for signs of anemia, and postnatally for anemia

and indirect hyperbilirubinemia. Preparation before delivery of a negative crossmatch antigen compatible with RBCs is important.

## Conflicts of interest

The authors declare no conflicts of interest.

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## ภาวะเม็ดเลือดแดงแตกในพีตัสและทารกแรกเกิดจากแอนติบอดีต่อเม็ดเลือดแดงหมู่ไมเนอร์: รายงานผู้ป่วยสองราย

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### บทคัดย่อ

รายงานผู้ป่วยสองรายที่มีภาวะเม็ดเลือดแดงแตกในพีตัสและทารกแรกเกิดจากแอนติบอดีต่อเม็ดเลือดแดงหมู่ไมเนอร์ รายที่ 1 เป็นทารกแรกเกิดเพศหญิง อายุครรภ์ 35 สัปดาห์ ได้รับการวินิจฉัยจากอัลตราซาวด์ว่ามีภาวะซีดและทารกบวมน้ำตั้งแต่อยู่ในครรภ์ มารดาตั้งครรภ์ครั้งแรก เคยได้รับการวินิจฉัยว่าเป็นโรคโลหิตจางเบต้า-ธาลัสซีเมีย/ฮีโมโกลบิน อี และเคยได้รับเลือดมาก่อน ระหว่างการตั้งครรภ์ เคยตรวจพบว่ามีแอนติบอดีต่อเม็ดเลือดแดงชนิด anti-c, anti-E, anti-Mia และ autoantibody หลังคลอด ผู้ป่วยมีอาการซีดมาก มีภาวะการหายใจล้มเหลวจำเป็นต้องใช้เครื่องช่วยหายใจ ค่าฮีมาโทคริตแรกคลอดร้อยละ 15.1 การตรวจ direct และ indirect antiglobulin tests ให้ผลบวก รายที่ 2 เป็นทารกแรกเกิดเพศชาย อายุครรภ์ 36 สัปดาห์ มีอาการตัวเหลืองและซีดเมื่อแรกเกิด มารดามีประวัติเป็นโรค systemic lupus erythematosus และเคยได้รับเลือดหลายครั้ง หลังคลอด ตรวจเลือดของมารดาพบ anti-c และ anti-Mia การตรวจ direct และ indirect antiglobulin tests ในทารกให้ผลบวก และตรวจพบ anti-c ทารกได้รับการรักษาด้วยการส่องไฟ ค่าบิลิรูบินสูงสุด 16.9 มก./ดล. และค่าฮีมาโทคริตต่ำสุดร้อยละ 31 เมื่ออายุ 11 วัน **เชียงใหม่เวชสาร 2555;51(4):119-123.**

**คำสำคัญ:** หมู่เลือดแดงไมเนอร์ ภาวะเม็ดเลือดแดงแตกในพีตัสและทารกแรกเกิด แอนติบอดีต่อเม็ดเลือดแดง

