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Case report

A fatal case of hemolytic disease of the fetus and newborn associated with Anti-Jk^a

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Abstract. Hemolytic disease of the fetus and newborn (HDFN) is predominantly associated with RhD incompatibility between maternal and fetal blood. However, other blood group systems, including Kidd, Duffy, and MNS, can also cause HDFN. While these cases typically present with mild symptomatology and favorable prognoses, severe and potentially fatal outcomes may occur. This case report delineates a fatal instance of HDFN attributed to anti-Jk^a antibodies. The mother (26 years old) presented with polyhydramnios upon admission and was scheduled for a cesarean section. The neonate was delivered in a hypotonic and flaccid state. Laboratory analyses revealed hemoglobin levels of 13.4 g/dL, total bilirubin of 2 mg/dL, and a strongly positive direct antihuman globulin test (DAT). Anti-Jk^a antibodies were eluted from the neonate's blood. Despite aggressive therapeutic interventions, the infant succumbed within 24 hours post-partum. This case underscores the critical importance of comprehensive prenatal screening protocols for managing pregnancies complicated by alloantibodies to minor blood group systems. (www.actabiomedica.it)

Key words: hemolytic disease of the fetus and newborn, hydrops fetalis, kidd blood group system, prenatal screening screening

Introduction

Hemolytic disease of the fetus and newborn (HDFN) results from maternal alloantibodies against erythrocyte antigens passing the placental barrier during gestation to fetal circulation, causing red cell destruction or anemia (1, 2). The most immunogenic antigens are D, Kell, and c (3). HDFN affects 1/300–1/600 live births, with up to 1 in 80 gravidae harboring clinically significant erythrocyte alloantibodies (4). Both naturally occurring and immune antibodies are implicated, resulting in a spectrum of clinical sequelae ranging from anemia and hyperbilirubinemia to fetal hydrops, kernicterus, and mortality (5). The most frequently reported cases of HDFN is due to anti-D antibodies. However, the incidence of RhD HDFN has dramatically decreased since the introduction of RhD immunoglobulin (RhD IG) in the 1960s (6). Nonetheless, HDFN resulting from sensitisation to other blood group antigens, including Kell, Duffy, and Kidd, has been documented, yet no prophylactic measures have been developed for these cases (7). Managing HDFN caused by non-RhD antibodies involves prenatal interventions to control sensitization severity and postnatal treatment of affected fetuses or neonates (8). Despite their weak immunogenicity and rare allelic frequency, Kidd blood group antigens are detectable as early as 11 weeks of gestation and can cause severe HDFN (9). The Kidd system comprises of two antithetical antigens Jk^a and Jk^b of the SLC14A1 gene (10). Research indicates that anti-Jk^a and anti-Jk^b antibodies could cause mild HDFN (11). Concurrently, the incidence of fetal or neonatal harm from other alloantibodies has increased proportionally,

with most lacking established screening protocols during pregnancy or blood transfusion testing. Recent data from Western countries suggests that the current incidence of alloimmunization due to non-RhD antibodies has reached up to 0.28-0.33% (12). This report presents a fatal case of HDFN to emphasize the importance of prenatal diagnosis and screening for non-RhD antibodies.

Case Report

This case concerns to a male neonate delivered via cesarean section (CS) due to breech presentation to a 26-year-old mother (G2P1+0). Initial ultrasonographic examinations were unremarkable until seven weeks of antepartum, when polyhydramnios, pleural effusion, and abdominal fluid collection were detected. The mother was hospitalized for observation three weeks before parturition, receiving a single dose of dexamethasone and magnesium sulfate. Hematological analysis revealed the mother's blood type as B RhD positive with a positive antibody screen. The antibody identification panel confirmed the presence of anti-Jk^a and anti-E in the maternal serum. The virological screening was negative for cytomegalovirus and toxoplasmosis. The mother was a non-smoker with no history of infections, previous transfusions, radiation exposure, or medication use, including herbal remedies. Family history was negative for inherited or congenital disorders. Upon delivery, the male neonate presented with hypotonia, flaccidity, and bradycardia (heart rate <100), exhibiting a feeble, irregular cry. The infant was positioned under a radiant warmer, and initial resuscitation protocols were implemented. Oxygen desaturation persisted despite room air exposure, necessitating positive pressure ventilation (PPV) without improvement in saturation levels. Subsequently, endotracheal intubation was performed in the operating theatre, followed by umbilical venous catheter (UVC) insertion and intravenous bolus administration, improving cardiac function. APGAR scores were recorded as 5, 6, and 7 at 1, 5, and 10 minutes post-birth, respectively. Initial arterial blood gas (ABG) analysis revealed pH 6.833, pCO_2 107, HCO_3 10.7, and BE 16.1. The neonate was transferred to the neonatal intensive care unit (NICU) and connected to a mechanical ventilator (AC-VG 4ml/kg, PEEP 5, FiO2 100%). Oxygen saturation fluctuated between 50-60%. Radiographic imaging demonstrated a white lung appearance, prompting right lung pleural tapping, which drained 65 ml of fluid. A normal saline bolus was administered for volume replacement. Oxygen saturation improved to 80% with fluctuations. Echocardiography revealed depressed cardiac function, severe pulmonary hypertension, and massive right pleural effusion. Chest tube insertion resulted in partial clinical improvement.

Inotropes were administered to the infant to elevate systemic blood pressure, temporarily maintaining saturation. Subsequently, radiographic imaging revealed bilateral fluid accumulation coupled with poor oxygenation. Consequently, a left chest tube was inserted, resulting in blood loss without evidence of pericardial injury. The patient received a transfusion of 33ml packed red blood cells and a normal saline infusion. However, the patient's condition deteriorated, manifesting frequent desaturation episodes and bradycardia. Upon desaturation, chest compressions were initiated. Despite administration of five epinephrine doses and one normal saline bolus, the patient was pronounced deceased. The infant was B RhD positive with a positive direct antihuman globulin test (DAT) showing +3 agglutination score, and anti-Jk^a was eluted from the erythrocytes. Hematological analysis revealed hemoglobin of 13.4 g/dL and reticulocyte count of 8%. Hepatic function tests indicated total bilirubin of 2, direct bilirubin of 0.3, albumin of 1.9, and LDH 285 (Table 1). The cause of mortality was documented as hydrops fetalis.

Discussion

Anti-Jk^a was initially discovered by Allen et al. in 1951 during serological analysis of an infant diagnosed with HDFN (13). Jk^a antigens develop fully in neonates and are detectable on fetal RBCs as early as 11 weeks gestation but rarely cause severe HDFN due to their low immunogenicity (14). The prevalence among Asian populations was noticed to be in a lower percentage due to reduced Jk^a allelic frequency (14). The majority of HDFN cases identified and reported primarily result from ABO or

Table 1. Laboratory report of the neonate.

Test	Result	Normal ranges
Complete blood count		
Hb g/dl	**13.4**	15-21
RBC (Mil/ul)	**3.84**	4-6
Hct (%)	**45.5**	52-68.5
Reticulocyte count (%)	**8.6**	3-7
WBC (k/ul)	17	10-35
Plt (k/ul)	168	140-450
MCV (fL)	119	105-25
MCH (pg)	**34.9**	24-34
MCHC (g/dL)	**29.5**	32-36
RDW (%)	**18.2**	11.5-14.5
MPV (fL)	**6.4**	7.2-11.1
Renal Function test		
BUN (mg/dL)	**5**	5.1-16.8
Creat (mg/dL)	0.54	0.5-1.2
Na (mEq/L)	138	133-146
K (mEq/L)	4.3	3.7-5.9
Cl (mEq/L)	107	98-107
CO2 (mEq/L)	**19**	20-31
Liver Function test		
T Bili (mg/dL)	**2**	0.3-1
D Bili (mg/dL)	0.3	0.1-0.5
T Protein (g/dL)	**2.9**	4.6-7.0
Albumin (g/dL)	**1.9**	2.8-4.4
Alk Phos (U/L)	178	150-507
SGOT (U/L)	19	5-34
SGPT (U/L)	<5	5-55
LDH (U/L)	**285**	125-220
GGTP (U/L)	**205**	12-64

Rh blood group incompatibility, specifically involving the D antigen (15). However, documented cases of HDFN caused by other blood groups, including Kell, Duffy, Kidd, and MNS, exist (7). Despite the availability of RhD prophylaxis for RhD incompatibility prevention, other blood group incompatibilities lack such measures. Generally, HDFN cases related to different blood groups are mild, though moderate and severe cases have been reported (16). Matson et al. documented the first severe HDFN case due to anti-Jk^a. The affected infant developed kernicterus and required exchange transfusion (17). Similarly, Mittal et al. reported another severe case where the mother exhibited a high anti-Jk^a titer of 1:64, and the infant's total serum bilirubin reached 20 mg/dL, necessitating phototherapy as treatment (18). In this instance, the fatal case of HDFN implied that anti-Jk^a was responsible for hydrops fetalis. In order to provide useful information for treatment decisions, fetal genotyping should be evaluated in the context of a diagnostic test (19). Several powerful methods are available for fetal genotyping, including droplet digital PCR (ddPCR), capillary electrophoresis, and massively parallel sequencing. ABO, Rh, Kell, Fy, Jk, and MNS blood group assays have been applied with reliable results (20). An analysis of non-invasive genotyping using fetal cell-free DNA was published by Zhu in 2014 (21). In their analysis, genetic testing for fetal RHD was 99% sensitive and 98% specific. First-trimester samples had better diagnostic accuracy than samples collected in the second or third trimester (99.5%). According to Gutensohn et al., samples collected between 12 and 28 weeks prenatally were genotyped for RHCE alleles and obtained 99% accuracy (22). Implementing plasmapheresis and intravenous immunoglobulin (IVIG) in instances of alloimmunization during pregnancy proves to be efficacious, particularly when severe early-onset fetal anemia is expected (23). Hubinont et al. demonstrated that plasmapheresis treatment for anti-M alloimmunization during pregnancy was effective, resulting in the birth of a healthy infant (24). Intrauterine transfusion becomes a viable option post the 20-week gestation mark. Numerous case reports and series have demonstrated the efficacy of alternative treatments, such as plasmapheresis, IVIG, or their combination, particularly for pregnancies with a history of severe HDFN (25). The newborn exhibited anemia accompanied by elevated lactate dehydrogenase (LDH) levels, a marker commonly associated with hydrops fetalis (26). The key strategy to minimize the consequences of HDFN is effective management of at-risk pregnancies. The primary approach involves careful monitoring during pregnancy. If prenatal screening identifies maternal alloantibodies targeting significant blood group antigens, it is crucial to follow the red cell antibody titer to gauge the degree of sensitization. Hospital blood

banks typically see rising titers as an indication of escalating immune response. Specifically, titers of 1:16 or 1:32 are generally interpreted as markers of fetal anemia, though this is not universally applicable across all blood group antibodies (27). For instance, anti-K antibodies may cause severe anemia even at a titer as low as 1:8 (28, 29). However, in our case, the titres were not estimated in the mother. Therefore, prenatal management was not planned accordingly. Identifying antibodies is essential for diagnosing and monitoring antenatal patients who may deliver infants with HFDN (30). The antibody screening followed by antibody identification is the most efficient and dependable technique for identifying clinically significant antibodies (31). Molecular genotyping has emerged as a pivotal clinical procedure, enabling the determination of blood group antigens, many of which are characterized at the genomic level. Several non-invasive prenatal tests (NIPTs) are available to identify blood group discrepancies between a fetus and a mother. In maternal blood samples, fetal cell-free DNA (cfDNA) is useful for two purposes: first, to diagnose hemolytic disease of the fetus and HDFN, and second, to target antenatal anti-D prophylaxis (RAADP) in women carrying an RHD-positive infant (20). A major issue with Kidd antibodies is that they typically decline or disappears more rapidly than other antibodies, often becoming undetectable within three months following the initial triggering event. Consequently, this poses a diagnostic challenge for serologists (32). Approximately 52% of Kidd antibodies vanish within several months, in contrast to 27% of Rh antibodies (33,34). These common traits of the Kidd alloantibody render it a significant yet challenging antibody in blood bank serology (35). Regrettably, in some nations, there is no routine screening for alloantibodies in pregnant women. This omission can be attributed to various factors, such as the lack of universal healthcare systems and inadequate recognition of immunization-triggering events during pregnancy at various reference centers (36).

Conclusion

Investing in early diagnostic measures is crucial for mitigating risks and complications associated with the progression of Hemolytic Disease of the Fetus and Newborn (HDFN). The utilization of serological and molecular assays proves beneficial for prompt diagnosis. An in-depth comprehension of the pathophysiology of alloantibodies aids in elucidating the development of HDFN. Additionally, given the extensive variability of blood group alleles, it is imperative to investigate maternal alloimmunization and HDFN incidence rates across different demographic groups. Our findings suggest antenatal antibody screening should be conducted in all expectant mothers, regardless of their Jk^a antigen status, to identify and manage red cell alloimmunization against clinically significant blood group antigens.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

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