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Transfusion Medicine | LETTER TO THE EDITOR

Jk3 antibodies complicated with severe fetal anaemia requiring intrauterine transfusion: a case report

Dear Sir,

Antibodies against Kidd antigens are recognized in delayed haemolytic transfusion reactions and haemolytic disease of the fetus and newborn (HDFN) (Daniels, 2002, pp. 232–267; Dean, 2005, p. 1–5; Kim & Lee, 2006). There are three recognized antigens in Kidd group (Jka, Jkb and Jk3) (Issitt & Anstee, 1998, pp. 655–670; Dean, 2005, p. 1–5; Deelert *et al.,* 2010). Anti-Jk3 is a rare cause of HDFN which often gives rise to less severe HDFN (Dean, 2005, p. 1–5). Also this Jk-null phenotype, Jk(a−b−), is rare in most populations (Dean, 2005, p. 1–5).

The Kidd system of antigens plays a key role in urea transport through cell membrane of red blood cells (RBCs) (Olives *et al.,* 1995; Dean, 2005, p. 1–5). This Jk(a−b−) represents the null phenotype and usually results from homozygosity for a silent gene at the Jk locus (Roback *et al.,* 2008). The Kidd blood group gene locus was found to be linked to two different restriction fragment-length polymorphisms assigned to chromosome 18 in 1987 (Lawicki *et al.,* 2016). Anti-Jk3 can be found in patients with the Jk(a−b−) phenotype, causing acute and delayed haemolytic transfusion reactions and HDFN (Dean, 2005, p. 1–5). The Jk(a−b−) phenotype can be routinely identified by the absence of Jka and Jkb antigens when testing RBCs with specific antiserum using the indirect antiglobulin test (IAT) (Dean, 2005, p. 1–5). The null phenotype has been described in most ethnic groups worldwide (Geitvik *et al.,* 1987; Roback *et al.,* 2008). There is, however, an increased prevalence of this among certain ethnicities including Polynesians/Pacific Islanders and Southeast Asians (Geitvik *et al.,* 1987; Roback *et al.,* 2008; Makroo *et al.,* 2013). Those with the null phenotype may produce an antibody to the high frequency Jk3 antigen necessitating the requirement of rare, antigen negative blood for transfusion (Geitvik *et al.,* 1987). These rare donor blood products can be extremely difficult to find (Geitvik *et al.,* 1987).

Although few case reports with pregnancies complicated by anti-Jk3 have been published, this is the first report with severe HDFN requiring intrauterine transfusion (IUT) treatment. Here, we describe a case complicated with maternal antibodies for Jk3 requiring IUT of maternal blood.

A 42-year-old, Sinhala-ethnic Lankan woman, A blood group Rhesus D positive with Jk(a−b−) (null phenotype), gravida 3, para 1 was referred at 29 (+6 days) weeks of gestation to the Fetal Medicine Unit of University Obstetrics Unit at the North Colombo Teaching Hospital due to rising titre of Jk3 antibody (1 : 128 at 11 weeks of gestation, 1 : 128 at 21 weeks of gestation and 1 : 256 at 28 weeks of gestation, respectively). Her first pregnancy has ended up with a caesarean delivery due to antepartum haemorrhage giving a healthy baby. Her second pregnancy was complicated with a fresh stillbirth at 37 weeks of gestation and hydrops fetalis was confirmed at autopsy. Details regarding the blood group of the stillborn baby are not available. After this fetal demise, mother has been tested for possible alloimmune reaction. Then, she has been found to have positive Jk3 antigen status [Jk(a−b−) phenotype] and also positive serology for anti-Jk3. She has been counselled to seek early obstetric care for her next pregnancy due to this immune status. Her husband's and first child's blood groups are both A Rh D positive with Jk(a−b+). It was the same father for all the pregnancies. There was no history of transfusions of blood, plasma or any blood derivatives to the mother.

Middle cerebral artery peak systolic velocity (MCA-PSV) Doppler screening was performed in order to identify the fetal anaemia. At 30 weeks of gestation, MCA-PSV was 72·8 cm s^{-1}. It also showed above the 1·5 multiples of the median threshold for gestational age. We were unable to find suitable blood from Sri Lankan National Blood Transfusion Service (NBTS) for IUT due to maternal antibody status. Her family screening also could not reveal any individual with negative Jka and Jkb status. According to the Sri Lankan National Blood Transfusion Service, there were no donors who were negative for both Jka and Jkb. This made us to cross match fetal blood with the maternal blood as the only option. Subsequent cordocentesis confirmed fetal blood group, A Rh D positive. In addition, there was severe fetal anaemia with fetal haemoglobin of 3·8 g dL^{-1} (Reference range: 15–20) and a haematocrit of 11·5%. Maternal blood antibody screening was positive in all three panel cells. Further testing showed negative auto-control and antibody identification showed pan-agglutination reaction on all 11 panel cells with enzyme enhancement. The antibody reacted equally with Jk(a+b−), Jk(a+b+), and Jk(a−b+) panel cells. An antibody screen with Jk(a−b−) cells showed no evidence of additional clinically significant red cell alloantibodies.

However, fetal blood direct antiglobulin test (DAT) was negative and elution study was inconclusive. Jk3 antigen was detected in maternal blood. Maternal red cell phenotype was Jk(a−b−). Presence of additional maternal antibodies was excluded. Jk3 antibodies identified in fetal blood sample too which was taken from cordocentsis. It was also negative for both anti-Jka and anti-Jkb. Therefore, it can be concluded that anti-Jk3 as the cause for HDFN in this case. These testing were done at the National Laboratory for Immunohaematology and Transfusion

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Table 1. Change in maternal and fetal haemoglobin concentration with Doppler parameters according to sequential events

Sequential events	Maternal haemoglobin concentration ($g\,dL^{-1}$) [Reference range: 11 – 14]	Fetal haemoglobin concentration ($g\,dL^{-1}$) [Reference range: 15 – 20]	MCV-PSV value ($cm\,s^{-1}$)
1. Initial value	11·0	3·8	72·8
2. After blood donation for IUT (two times, 250 mL in each)	10·0	–	–
3. After first IUT	-	5·9	61·2
4. After second IUT	-	8·3	58·0
5. After third IUT	9·5	10·8	50·4
6. After 250 mL blood donation for autologous transfusion/neonatal use	9·3	–	–
7. At delivery	9·0	–	–

Services in Sri Lanka (Immunohaematology Reference Laboratory of NBTS, Colombo, Sri Lanka).

Maternal blood was processed to get a higher haematocrit (79·1%), then irradiated and also leuco-depleted prior to transfusion. This processing procedure comprised of using IAT to screen for clinically significant alloantibodies (i.e. Jk3 antibodies) and filtering out these antibodies. It also included to get a higher haematocrit (target haematocrit range: 70 – 85%) to minimize the numbers IUT required. Mother's initial haemoglobin was $11{\cdot}3\,g\,dL^{-1}$ (Reference range: 11 – 4) and change in maternal haemoglobin concentration with sequential events has been shown in Table 1. Three IUT (total of 180 mL) were performed within 2 weeks. Mother donated 750 mL blood (250 mL per each donation) for IUT and autologous transfusion/neonatal use. Table 1 also shows change in maternal and fetal haemoglobin concentration with Doppler parameters according to sequential events. Parenteral iron and erythropoietin therapy were given several days before delivery. Maternal blood was preserved for pre-deposit autologous transfusion. At the time of delivery intravenous immunoglobulins were also kept ready. Antenatal corticosteroids were administered for fetal lung maturation in the last week before caesarean delivery. A neonatologist was involved to plan and provide necessary neonatal care. Intravenous magnesium sulphate was given for fetal neuroprotection as recommended by local protocol. Caesarean delivery was done with minimal blood loss at 32 weeks (+3 days) of gestation giving a live baby boy. Birth weight was 1·44 kg.

Newborn's serum total bilirubin value was $60{\cdot}0\,\mu mol\,L^{-1}$ (normal range: $3{\cdot}4 – 18{\cdot}8\,\mu mol\,L^{-1}$) and neonate received 3 days of phototherapy. After that bilirubin became normal. Since baby's haemoglobin was $11{\cdot}0\,g\,dL^{-1}$ (Reference range: 15 – 20), 30 mL of maternal blood top-up transfusion was done for the neonate and post-transfusion haemoglobin concentration was $17{\cdot}0\,g\,dL^{-1}$. Newborn also received two doses of intravenous immunoglobulins against any presumed immune reaction. Mother and her baby were discharged 2 weeks later in a good condition.

The Jk3 antigen is a high-frequency antigen that can make anti-Jk3 only in persons lacking both Jka and Jkb antigens. Sensitization and activation of primary immune response of this patient could have happened in her first pregnancy and resulted a stillbirth in her second pregnancy. However, we do not have details regarding the blood group of stillborn baby. Interestingly, mother was investigated and found to have anti-Jk3 with null phenotype. Since anti-Jk3 is rare and incidence of fetal anaemia following sensitization is varied, early detection of anti-Jk3 prior to this pregnancy is important. Previously reported cases on anti-Jk3 showed mild HDFN fetuses (Pierce *et al.,* 1980; Kuczmarski *et al.,* 1982; Marshall *et al.,* 1999; Jator, 2014). In contrast, this fetus was severely affected due to anti-Jk3 with haemoglobin of $3{\cdot}8\,g\,dL^{-1}$ in the first cordocentesis sample. Management of this patient made a challenge as there were no compatible donors negative for both a and b Kidd antigens in Sri Lanka. Therefore, her own blood was used for IUT despite of low level of maternal haemoglobin concentration. In literature, this method of maternal blood IUT as a therapy has been used in three difficult cases of erythroblastosis fetalis in 2014 (Kucińska-Chahwan *et al.,* 2014). Low maternal haemoglobin reserve and IUT dependent fetal anaemia resulted in the decision of delivery at 32 weeks (+3 days).

However, early detection of these Jk3 antibodies and timely interventions by specialists in Fetal Medicine, Transfusion Medicine and Neonatology, resulted a good outcome in this high risk case. Educating ethnic populations with rare phenotypes and organizing targeted blood drives may increase inventories of these rare blood phenotypes. This is the first case report with severe HDFN in need of IUT treatment using maternal blood.

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CONFLICT OF INTEREST

The authors have no competing interests.

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