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Inappropriate Blood Transfusion in Neonatal Hemolytic Anemia Due to Anti-c

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Abstract For transfusion in premature infants and newborns red blood cell (RBC) units of blood group 0, D–, and haplotype ccddee are often falsely regarded as universal compatible since they are suitable for all AB0 constellations between mother and child. In case of maternal diaplacental immunization with antibodies directed against RBC surface antigen Rhc (rare) or Rhe (very rare) these concentrates should be retained due to the risk of hemolytic disease. We report a case of immune mediated hemolytic anemia of a newborn due to anti-c and anti-E where this restriction was not considered.

Keywords: *anti-c, blood transfusion, hemolytic disease of the fetus and newborn, hemolytic anemia*

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1. Introduction

Hemolytic disease of the fetus and newborn (HDFN) due to blood group incompatibility between mother and child is a potentially fatal disorder [1]. It results from the destruction of fetal and newborn red blood cells by maternal antibodies that are capable of crossing the placenta into the fetal circulation, targeting inherited paternal antigens located on the erythrocyte surface. Their binding causes cellular breakdown, hemolysis and anemia, affecting fetal or neonatal morbidity and mortality. This fetomaternal transfusion occurs in up to 75 % of all pregnancies. With Rhesus D hemolytic disease being the prototype of maternal isoimmunization, sensitization to antigens in the Rhesus system other than D (c, C, e, E,) as well as Kell and Duffy is rare [2]. Anti-c is one of the clinically most important ones, as the symptoms of HDFN caused by anti-c may range from a mild to a severe disease [3].

2. Case Presentation

A four-week old female newborn was admitted to the pediatric unit with symptoms of anemia, including pale appearance and weakness but no jaundice. A blood sample was sent to our laboratory for a complete blood count and preventive blood group typing. The baby's full blood count revealed microcytic anemia with a hemoglobin level of 6.4 g/dL (10.0 – 18.0 g/dL) and a hematocrit of 19.0 % (39 – 50 %), thus confirming the initial diagnosis of an anemia. Bilirubin and LDH were within their normal ranges, while haptoglobin was found to be slightly decreased to 0.02 g/L (0.03 - 3.00 g/L).

The baby's blood group was serologically typed as blood group 0, showing prominent mixed-field reactions (two distinct erythrocyte populations, Figure 1) for D, C, E and Kell. The direct antiglobulin test (DAT) turned out to be negative.

Figure 1. Blood group typing cards (Grifols, Germany) from the baby's blood, showing mixed-field reactions in the lanes for D, C, E and Kell. No reaction with the A_1 cells and B cells is visible

Meanwhile, our blood bank received an urgent request for two unmatched RBC units group 0, D–, and haplotype ccddee. Now, we contacted the attending physician due to the remarkable mixed-field reactions, which are usually a hint for recent blood transfusion.

According to the physician the infant was transfused in a medical emergency at a university hospital ten days ago with an unmatched RBC concentrate group 0, D–, haplotype ccddee. With this information, we could elucidate the observed mixed-field reactions and fix the baby's blood group as 0, D–, haplotype CcD.Ee, Kell positive.

Moreover, referring to previous findings from the university's medical report the infant had a history of hemolytic disease of the fetus and newborn (HDFN) as a consequence to detected maternal alloantibodies. Since the DAT in our laboratory was negative, our lab staff asked for the medical records. In addition, a blood sample of the mother was requested.

The subsequent indirect antiglobulin test (IAT) from the baby's plasma was positive (Figure 2). Serologic workup identified clinically relevant alloantibodies of specifity anti-c and anti-E.

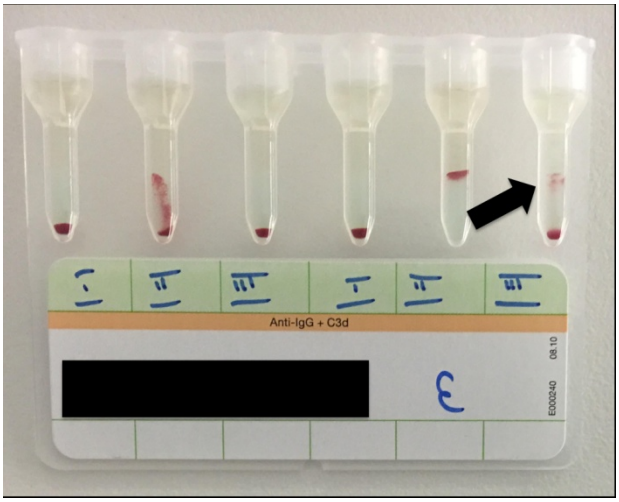

Figure 2. Indirect antiglobulin test of the baby's blood. Cell II is positive for antigen E. Black arrow indicates additional weak reaction in enzyme treated cell III. Cells I and II are positive for antigen c

The blood group typing from the mother's blood revealed group A, RH positive, haplotype CCD.ee, Kell positive. The IAT was likewise positive. Consistent with the results from the infant's plasma the subsequent serologic characterization of the antibodies resulted in anti-c and anti-E. In view of the presence of anti-c and anti-E in both the maternal and the baby's blood and clinical presentation of hemolytic anemia, a diagnosis of hemolytic disease of the fetus and newborn secondary to these antibodies was made.

In consequence to the proved incompatibility of a RBC unit showing haplotype ccddee based on the maternal anti-c we declined provision of the requested RBC unit. Instead, a stocked adult RBC concentrate group 0, D–, haplotype CCD.ee (matching the maternal haplotype) was provided. After transfusion of 20 mL, hemoglobin level increased to 10.5 g/dL and remained stable without further hemolysis.

3. Discussion & Conclusion

Our case report emphasizes the importance to evaluate the complete patient's medical history.

Due to the determined blood group 0, D–, haplotype CcD.Ee Kell positive the therapeutic transfusion of every RBC unit 0, D–, without regard to the Rh haplotype was possible. Corresponding to Table 1 the presence of maternal alloantibodies anti-c and anti-E reduced the potential tolerable haplotypes to CCD.ee and Ccddee. In patients with haplotype CCD.ee anti-c shows high incidence in combination with anti-E and is the most frequent cause for HDFN within the Rhesus system directly behind anti-D [4]. Anti-c alone as well as together with anti-E was described to be responsible for severe hemolytic episodes [5,6,7].

Table 1. Compatible Rhesus haplotypes for the newborn and relative their relative prevalence in Germany (modified from [12])

Haplotype of newborn's blood (%)		Compatible haplotypes (%)		Compatible haplotype due to IAT (%)	
CcD.Ee	12.5	CcD.ee	35.6	CCD.ee	19.5
		CCD.ee	19.5	Ccddee	0.8
		CcD.Ee	12.5		
		ccD.Ee	11.3		
		ccddee	15.8		
		ccD.EE	2.0		
		ccD.ee	1.7		
		Ccddee	0.8		
		ccddEe	0.4		
		CCD.Ee	<0.4		
		CCD.EE	0.0005		

The previous findings from the university hospital laboratory that we got at a later time reported the emergency transfusion of a RBC unit without cross-matching. The observed stagnating hemoglobin level was soon cleared by the determination of anti-c and anti-E in the maternal and infant plasma, matching our obtained antibody differentiation results. These foregoing results, as well as an explicit cautionary advice to not transfuse RBC units of haplotype ccddee in future due to the risk of repetitive hemolysis, were not considered by the attending pediatric unit staff.

We sometimes make the experience that physicians misinterpret the fact that till the end of the fourth week of life, no final blood group typing is made due to the physiological absence of regular antibodies. This leads to the fatal misbelief that within this short lifespan, no Rhesus incompatibility can occur and thus a RBC unit 0, D– with haplotype ccddee can be regarded as universal compatible for transfusion in premature infants and newborns. Given the very low incidence of anti-c and anti-e this procedure might be valid for the vast majority of patients but can be dangerous in case of rare fetomaternal immunization against those antigens.

This misunderstanding might be a consequence of the German legislation which allows limited pre-transfusion testing with renouncement of cross-matching till the end of the fourth week of life if the RBC unit is haplotype ccddee, the absence of irregular antibodies in the plasma of both mother and child is confirmed and the DAT on the

baby's erythrocytes is likewise negative. This implicates that at least prior to an initial transfusion cross-matching has to be performed. In our case report, no initial cross-matching was done. Since antibodies found in a newborn's blood derive from the maternal isoimmunization, serologic cross-matching can be made from the maternal blood sample, not least to save the small infantile circulation volume. In this context McAdams *et al.* underscore the importance of the DAT and IAT regardless of the mother's blood type or prior antibody screen to rule out a potential isoimmunization from a minor blood group antigen [8].

In the present case, the intervening laboratory staff prevented repetitive transfusion of an incompatible RBC unit even though the initial workup was misled by the negative DAT.

Reports of clinically manifest HDFN with the infant's red cells showing a weak or negative DAT are rare [9]. Heddle *et al.* described several examples of HDFN in infants whose red cells had a negative DAT [10]. In one case, the infant was admitted to hospital at the age of three weeks with severe anemia and cardiac failure. While the DAT on the infant's red cells was negative, both maternal and infant sera were positive for anti-C. The etiology was cleared retrospectively, since the baby subsequently died. In a second fatal case presenting a hydropic stillborn, anti-c was implicated as provoking HDFN as other causes of non-immune hydrops could be excluded. However, even in this severely affected patient, DAT was likewise found negative.

Despite the high sensitivity of the gel centrifugation method, a negative DAT during HDFN could be caused by a low antibody load on the erythrocytes. It is known that even small amounts of antigen-positive erythrocytes are able to eliminate reactivity from the plasma by absorbing significant amounts of alloantibodies [11]. Probably as a consequence of the initial transfusion the number of antigen E positive erythrocytes has markedly fallen. Since erythrocytes loaded with antibodies are rapidly eliminated from the circulation, the antibody titer could have decreased, turning the DAT negative. The IAT was still capable to detect unbound circulating antibodies in the plasma. Anti-c was only detected with enzyme treated cells.

This case report illustrates an immune mediated hemolytic anemia detected in a neonate, which was caused by a combination of maternal anti-c and anti-E. The accurate treatment would have covered transfusion of an antigen c and E negative RBC unit. Instead, medical history was missed and the neonate received a concentrate group 0, D–, haplotype ccddee. We thus emphasize not to consider a RBC unit of group 0, D–, haplotype ccddee as universal compatible. Every clinician should have a heightened level of suspicion and carefully question all given information before transfusion, especially in case of premature infants and newborns.

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