The Turkish Journal of Pediatrics
Volume 25, No. 2, April-June 1983

HEMOLYTIC DISEASE OF THE NEWBORN DUE TO ALLOIMMUNIZATION AS A CONSEQUENCE OF MULTIPLE TRANSFUSIONS AND A DELAYED HEMOLYTIC TRANSFUSION REACTION IN THE MOTHER*

*Tekin Kanra MD**, Salim Erdoğan MD***, Murat Yurdakök MD****, Gülşen Erdem MD*****

Key words : alloimmunization, blood transfusion, compatibility tests, delayed hemolytic transfusion reaction, hemolytic disease of the newborn (HDNB)

Blood transfusions in women of child bearing age constitute the most important stimulating cause of hemolytic disease in the newborn (HDNB)[1]. In this paper, a typical instance of HDNB due to anti-E, as a consequence of multiple mismatched blood transfusions given to the mother, is presented. In addition, a delayed hemolytic transfusion reaction due to anti-Jk^b is observed in the mother.

Case Report

B.B., a 1750 gram premature girl neonate, was referred to the Hacettepe Children's Hospital on May 16, 1982, 26 hours after delivery to a 42-year-old mother following 37 weeks of gestation. This was the mother's fourth pregnancy, and the third had apparently ended in an abortion. Jaundice started at the end of the first day in this newborn.

Since the mother had been admitted to another hospital, comprehensive data could not be obtained. According, however, to the information received, she had been receiving blood transfusions over the past ten years after being diagnosed as having hypoplastic anemia. She had received 33 units of blood during this last pregnancy and a transfusion of 4 units of blood just prior to delivery. The transfusions had been uneventful.

---

* From the Blood Bank Unit, Hacettepe University Hospital, Ankara.
** Associate Professor of Pediatrics, Blood Bank Unit, Hacettepe University Hospital.
*** Resident in Pediatrics, Hacettepe University Institute of Child Health.
**** Pediatrician, Naval Hospital, Karamürsel.
***** Associate Professor of Pediatrics, Hacettepe University Institute of Child Health.

In the physical examination, the baby was seen to be an icteric premature. Bilirubin was 17.5 mg/dl with 0.8 mg/dl direct fraction. Hb was 15.75 g/dl and 52% normoblasts were seen in the peripheral blood smear. The patient was grouped as O Rh positive (CDe/cDE) and a direct antiglobulin (Coombs') test was (+ + +) positive. O Rh positive red cells reacted slightly with the patient's serum in the crossmatch. An exchange transfusion was performed with one unit of O Rh negative (cde/cde) blood which was compatible. Following exchange transfusion, bilirubin was 5.3 mg/dl and fell to 2.5 mg/dl (0.8 mg direct) after phototherapy.

On the second day after transfusion and delivery, a blood specimen was obtained from the mother. She was grouped as A Rh positive (CDe/cde) and a direct antiglobulin (Coombs') test was (+) positive. Hb was 13.5 g/dl. For antibody identification, panel cells from the Biotest Serum Institute were used. The panel showed the presence of a strong IgG anti-E (1/2048 in titer) with a rather weak IgM fraction, and a weak IgG anti-Jk^b (1/4 in titer) combination in the mother's serum (Table I).

TABLE I

Anti-E + Anti-Jk^b: Antibodies identified in the mother's serum.

Antibody Identification Table			phase I	phase II	phase III	additional tests	Name: M.B. (Mother) 17-5-1982																					
Blood group system			Rh-hr													Kell				Duffy		Luth-eran		Kidd		MNS				Lewis		P
	Rh-Typ		D	C	E	c	e	C^w	Sal. R.T.	37°	Coombs				K	k	Kp^a	Kp^b	Fy^a	Fy^b	Lu^a	Lu^b	Jk^a	Jk^b	M	N	S	s	Le^a	Le^b	P1
	R_1R_1	1	+	+	O	O	+	O	0	0	+				O	+	O	+	+	+	O	+	+	+	+	O	+	O	O	O	O
	R_1R_2	2	+	O	+	+	O	O	+	±	±±±				O	+	O	+	O	+	O	+	O	+	O	+	O	+	+	O	O
	R^zR_1	3	+	+	O	O	+	+	0	0	+				O	+	O	+	+	+	O	+	+	+	+	+	O	+	O	O	+
	R_0r	4	+	O	O	+	+	O	0	0	0				+	+	O	+	O	+	+	+	+	O	+	+	O	+	+	O	O
	r'r	5	O	+	O	+	+	O	0	0	+				O	+	O	+	+	+	O	+	+	+	+	O	O	+	+	O	+
	r''r	6	O	O	+	+	+	O	+	±	±±±				+	O	O	+	+	O	O	+	+	+	+	+	+	+	O	+	O
	rr	7	O	O	O	+	+	O	0	0	+				+	+	O	+	O	+	O	+	O	+	+	O	O	+	O	O	+
	rr	8	O	O	O	+	+	O	0	0	0				O	+	O	+	O	+	O	+	+	O	O	+	O	+	O	+	+
Patient's Cells		9	+	+	O	+	+																	O						

Elution studies showed that of these only anti-E was present in the baby's red cells. The patient was discharged on May 26, 1982. On the same day, i.e. 11 days after transfusion of 4 units to the mother, her hemoglobin was found to be 5.3 g/dl. A direct Coombs' test was negative. There was no jaundice or kidney problem.

Discussion

All the conditions conducive to the birth of a hemolytic infant were present in this case. First, repeated pregnancies, especially involving a fetus carrying incompatible

antigens, increase the risk of hemolytic disease. Secondly, it is well known that a previous abortion induces alloimmunization. Thirdly, when a mother carries a fetus with an incompatible antigen she is far less likely to form alloantibodies than when she is given a transfusion of blood carrying the same antigen. That is, transfusion is a stronger primary stimulus than a small transplacental hemorrhage.

In this case, the neonate showed classical HDNB due to a quite rare antibody (anti-E)[1] that is the result of multiple mismatched transfusions. HDNB was well controlled with a single exchange transfusion. But the mother's condition, as a result of these transfusions, is far from satisfactory.

As a rule, in normal subjects, transfused red cells survive for long periods (110-120 days) in the recipient's circulation, less than 1% of the number transfused being destroyed each day — a fact which goes far to explain the therapeutic success of blood transfusion[2]. Transfused cells are regarded as incompatible if their survival in the recipient's circulation is curtailed by alloantibodies.

According to the findings, the mother in our case had obviously received a transfusion of incompatible red cells. High titer anti-E in the mother's circulation may also have contributed to the destruction of extravascular red cells. Extravascular destruction means the removal of red cells from the blood stream by the cells of the reticuloendothelial system, mainly in the liver and spleen. Antibodies which are non-hemolytic in vitro bring about destruction which is predominantly extravascular. The maximum rate of disappearance of red cells from the blood stream corresponds to the clearance of rather more than one-third of the blood per minute[3].

Since the mother's hemoglobin had fallen from 13.5 g/dl to 5.3 g/dl within eleven days of the transfusion, the main possibility to be considered was a delayed hemolytic transfusion reaction due to low titer anti-Jk^b.

When incompatible red cells are transfused, the amount of antibody in the recipient's serum may be too low to bring about rapid red cell destruction or even one that can be detected, but the transfusion may provoke an anamnestic immune response, so that a few days after transfusion there is a rapid increase in antibody concentration and a rapid destruction of the transfused red cells. In most cases the patient has been primarily immunized by a previous transfusion, although occasionally the only previous stimulus has been pregnancy.

Rarely, signs of extravascular destruction of red cells and of a delayed reaction are combined so that there are only very mild signs of red cell destruction at the time of transfusion and further signs of destruction develop a few days later as the antibody reappears in circulation. There are usually no incompatible red cells left in the recipient's circulation about two weeks after transfusion[2], although in a case described by Mollison and Newlands they could still be detected three weeks after transfusion[4]. The maximal rate of red cell destruction seems to occur between about the

fourth and the thirteenth days after transfusion, although signs of destruction are commonest on about the seventh day.

On reviewing 21 published cases, Howard[5] found that of the 43 antibodies detected in delayed hemolytic transfusion reactions, the majority were within the Rh system and the Kidd system. Sixty-nine percent of the reactions occurred in women.

As in our case, when a large amount of blood has been transfused, the majority of the red cells in the patient's circulation are involved in a subsequent delayed hemolytic reaction and a positive direct Coombs' test; a picture closely resembling acquired hemolytic anemia, may result[6]. The onset of jaundice, if present, most commonly occurs 5-7 days after transfusion[7-9]. Hemoglobinuria associated with delayed hemolytic transfusion reactions is not very common[2]. Renal failure is also very rare[2] but not unknown[10,11]. Cases of disseminated intravascular coagulation and even death due to delayed hemolytic transfusion reactions have been reported[11].

In fact, it is from an immunohematological point of view that this case is important for it points to the serious nature of the outcome of malpractices in the conduct of blood transfusions in Turkey. Actually, almost all blood banks are satisfied with a primitive saline crossmatch on a slide. In saline crossmatching, particularly when a slide is used, only ABO incompatibilities can be detected, while incompatibilities due to immune (IgG) or weak (IgM) antibodies as in our case, go undetected.

The compatibility test, as routinely performed in most blood banks today, needs to be a multiphase test done in several tubes and in several stages, each stage being designed to provide optimal conditions for the reactions of specific antibodies. Hemolysis and/or agglutinations in any tube at any phase is evidence of incompatibility, and that unit of blood must not be given to the patient. It should be apparent that great care must constantly be exercised during the performance of these tests. There are no shortcuts in the cross matching procedure.

Although the compatibility test, when performed properly, does not prevent primary isoimmunization of the recipient, it does prevent repeated immune stimuli and the elevation of antibody titration if the recipient's serum contains immune antibodies. If an incompatibility is detected, recipient or donor serum must be tested with standard reagent cells for antibody identification, and compatible blood must accordingly be selected for transfusion.

Like almost all other things in medicine, blood transfusion is a calculated risk, a big risk, and the physician in charge must be aware of the size of the risk. It is an enormous physiologic experience in transfusion that, several times a day large transfers of complex biologic materials, including viable cells, are made between unrelated humans. Responsible physicians should know at least that, beside the known serious ill effects, there is a 1% chance that the patient will produce an antibody which will constitute a threat in the event of a transfusion at some future date.

Summary

Hemolytic disease of a newborn due to a quite rare antibody, anti-E, is presented. The situation of the mother, who had been subjected to unnecessary blood transfusions which produced anti-E and anti-Jk^b and who developed a delayed hemolytic transfusion reaction due to anti-Jk^b, is discussed with respect to the abuse of, and the inadequacy of compatibility tests for, blood transfusions.

REFERENCES

1. Giblett ER. Blood group antibodies causing hemolytic disease of the newborn. *Clin Obstet Gynec* **7**: 1044, 1964.
2. Mollison PL. *Blood Transfusion in Clinical Medicine* (4th ed). Oxford: Blackwell Scientific Publ, 1979.
3. Mollison PL. Destruction of incompatible red cells in vivo in relation to antibody characteristics. In *Mechanism of Cell and Tissue Damage Produced by Immune Reactions* (2nd International Symposium on Immunopathology, Brook Lodge, Michigan, USA, 1961). Basel: Schwabe, 1962, p 267.
4. Mollison PL, Newlands M. Unusual delayed haemolytic transfusion reaction characterised by slow destruction of red cells. *Vox Sang* **31**: 54, 1976.
5. Howard, PL. Delayed hemolytic transfusion reactions. *Ann Clin Lab Sci* **3**: 13, 1973.
6. Croucher BEE, Crookston MC, Crookston JH. Delayed haemolytic transfusion reactions simulating auto-immune haemolytic anemia. *Vox Sang* **12**: 32, 1967.
7. Stuckey MA, Osoba D, Thomas JW. Hemolytic transfusion reactions. *Canad Med Ass J* **90**: 739, 1964.
8. Rauner TA, Tanaka KR. Hemolytic transfusion reactions associated with the Kidd antibody (Jk). *N Engl J Med* **276**: 1486, 1967.
9. Morgan P, Wheeler CB Jr, Bossom EL. Delayed transfusion reaction attributed to anti-Jkb. *Transfusion* **7**: 307, 1967.
10. Meltz DJ, David DS, Bertles JF, DeCiutiis AC. Delayed haemolytic transfusion reaction with renal failure. *Lancet* **2**: 1348, 1971.
11. Pineda AA, Taswell HF, Brzica SM Jr. Transfusion reaction. An immunologic hazard of blood transfusion. *Transfusion* **18**: 1, 1978.