Another case of acute cardiopulmonary toxicity with cord blood infusion: is dextran the culprit?

Infusion-related adverse reactions associated with cord blood (CB) transplants are considered to be less frequent and less severe when compared to cryopreserved marrow or peripheral blood stem cells.[1] The true incidence of these reactions is unknown, although it is reported that 30% to 60% of CB recipients are affected by infusion reactions.[1,2] Recently, there have been six published reports of severe, life-threatening cardiopulmonary reactions associated with CB infusions (Table 1).[3,4] A review by the National Marrow Donor Program (NMDP) and the Food and Drug Administration (FDA) of 13 serious CB-associated infusion reactions events showed that the majority of cases (92%; 12/13) involved infusion of at least one red blood cell (RBC)-replete CB unit.[3] As a consequence, the NMDP and FDA provided recommendations for thawing and washing RBC-replete CB units.[3] We report a case of a seventh cardiopulmonary reaction associated with the infusion of a RBC-depleted, CB unit diluted with human serum albumin (HSA)-dextran 40.[2]

The patient was a 16-year-old, 46-kg, group O Caucasian female with acute biphenotypic leukemia. As part of a clinical trial, the patient was randomly assigned to receive a five of six HLA-matched, double-CB transplant (Table 1). Both CB units were RBC-depleted and cryopreserved in a solution containing 10% dimethyl sulfoxide DMSO and 10% dextran 40. After being thawed, both CB units were diluted 1:3 with 5% HSA-8% dextran 40 solution, for a combined final infusion volume of 411 mL and less than 3% DMSO per unit. The total transplant dose was 2.6×10^5 CD34/kg and 5.7×10^7 total nucleated cells/kg recipient weight.

The patient was medicated before transfusion with acetaminophen, diphenhydramine, hydrocortisone, and mannitol per institutional clinical practice guidelines. Less than 5 minutes after starting the first CB unit, the patient experienced a severe anaphylactic reaction characterized by nausea, vomiting, dyspnea, wheezing, chest tightness, tachycardia, and tachypnea. The infusion was immediately stopped and the patient was treated with hydrocortisone, diphenhydramine, lorazepam, ipratropium, and albuterol and placed on 4 L of oxygen by nasal cannula. After 10 minutes, the patient's symptoms improved and the infusion of CB Unit 1 was slowly restarted and subsequently completed within 60 minutes. After additional pretransfusion medication, the patient received the second CB unit over 60 minutes. The second infusion was uneventful except for hypertension and a few hives 2 hours postinfusion. Both were successfully treated with additional antihistamine and antihypertensive medications.

Diagnostic studies at the time of the infusion reaction showed a prolonged QTc (baseline, 0.416-0.514 sec) and elevated troponin (baseline, <0.01-1.7 ng/mL) and B-type natriuretic peptide (baseline, 110-592 pg/mL). An echocardiogram revealed regional hypokinesis of the basal half of the posterior two-thirds of the septum, with overall mildly depressed left ventricular systolic function. The patient had no evidence of electrolyte abnormalities, renal insufficiency, intravascular hemolysis, or acute pulmonary changes. Pertinent EKG and laboratory studies returned to baseline within 48 hours and were attributed to transient myocardial ischemia.

Our patient's symptoms were consistent with a severe, anaphylactic reaction. We believe that the reaction was precipitated by dextran 40. Acute, severe reactions to dextran 40 have a reported incidence of 1 in 2000 and can be associated with cardiac ischemia and pulmonary and renal injury.[4,5] It is noteworthy that the majority (six of seven) of cardiopulmonary infusion reactions reported to date were associated with CB units frozen and/or diluted in HSA-dextran. As observed by Ma and colleagues[4] reports of severe CB infusion reactions "coincide with the introduction of dextran in cryopreservation" and include more recent protocols for dilution or washing CB products in HSA-dextran.[2] Ongoing investigations into severe CB reactions should include the potential role of dextran in such reactions, as well as possible prophylaxis with dextran-1, a hapten known to significantly decrease the risk of dextran reactions.[4,5]

ACKNOWLEDGMENTS

SC was supported by St Baldrick's Foundation and the National Institutes of Health K23 Grant AI091623-01.

CONFLICT OF INTEREST

The authors certify that they have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in this manuscript.

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TABLE 1. Summary of CB infusion reactions with cardiopulmonary symptoms

Patient			CB characteristics				Infusion reaction		
Case	Age	Sex	CB unit	ABO compatible	RBC depleted	CB processing	Final volume (mL)	Onset	Symptoms	Reference
1	16	Female	1	No	Yes	Both diluted 1:3 HSA-dextran 40	169	<5 min	Nausea, vomiting, hypertension, chest pressure, tachycardia, ↑QTc, ↑troponin, septal hypokinesis, ↓ left ventricular function.	This report
			2	Yes	Yes		201	2 hr	Hives.	
2	55	Male	1 + 2	Yes	Yes	None	209	10 min	Chest pain, hypertension, nausea, hypoxia, pulmonary edema, ↑troponin, ARI.	Ma et al.[4]
3	44	Female	1	Yes	No	Both diluted	251	50 min	Chest pain, ↑troponin, hypoxia, ↓EF (69%→15%), pulmonary infiltrates, ARI.	Miller[3]
			2	Yes	NA	HSA-dextran 40	52			
4	65	Male	1	Yes	NA	Both diluted	200	First unit	Chest pain, ↑troponin, ↓EF (25%), ST changes, hypoxia, pulmonary edema, ARI.	Miller[3]
			2	Yes	NA	HSA-dextran 40	50			
5	34	Female	1	No	No	Both diluted 1:4	Total	50 mL	Chest pain, ↓EF (66%→50%).	Miller[3]
			2	Yes	No	HSA-dextran 40	500	During infusion	Hypoxia, nausea, vomiting, chest pain, ↑troponin, ↓EF (50%→40%), pulmonary infiltrates, global myocardial hypokinesis.	
6	20	Female	1	NA	No	None	50	During infusion	Chest pain, hypertension, hypoxia, nausea, vomiting, hemoglobinuria.	Miller[3]
			2	NA	Yes	Diluted HSA-dextran 40	NA			
			3	NA	No	Diluted HSA-dextran 40	114			
7	60	NA	1	NA	No	Centrifuged, resuspended HSA	175	15 min	Nausea, vomiting, abdominal pain, hypertension, hypoxia, ST depression, ↑troponin, mild atrial hypokinesia.	Ma et al.[4]

ARI = acute renal injury; EF = cardiac ejection fraction; HAS = human serum albumin; NA = not available.

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Isoimmune neonatal neutropenia in a North African newborn due to anti-Fcγ RIIIb

Human FcγRIIIb (FcγRIIIb; CD16) is a low-affinity Fc receptor for immunoglobulin (Ig)G1 and IgG3, constitutively expressed with a high density (100,000 to 400,000 copies per cell), only by granulopoietic cells.[1] The human neutrophil antigens HNA-1a, HNA-1b, and HNA-1c, encoded by the FcγRIIIb gene, are polymorphic forms of this receptor.[2] Alloantibodies directed against these antigens can be responsible for neonatal alloimmune neutropenia, transfusion-related acute lung injury, and autoimmune neutropenia. Few people (approx. 1 of 1000 individuals of European origin) lack the FcγRIIIb gene and present the HNA-1 null phenotype (FcγRIIIb deficiency).[3] During pregnancy, women lacking this gene, and subsequently the protein, can produce CD16 isoantibodies able to cross the placenta and cause transient isoimmune neonatal neutropenia (INN).[4,5]

We report a case of INN due to an anti-FcγRIIIb in a mother with FcγRIIIb deficiency. A 25-year-old mother from North Africa prematurely delivered a female newborn at 33 weeks of gestation (body weight, 2300 g), due to early labor. The two previous pregnancies were free of complications and the newborns were healthy. In this case, systematic newborn blood screening showed severe neutropenia (200×10^6 neutrophils/L) and hypocalcemia (1.94 mmol/L) on the first day of life with no other clinical or biologic abnormalities. No complication was observed in the child

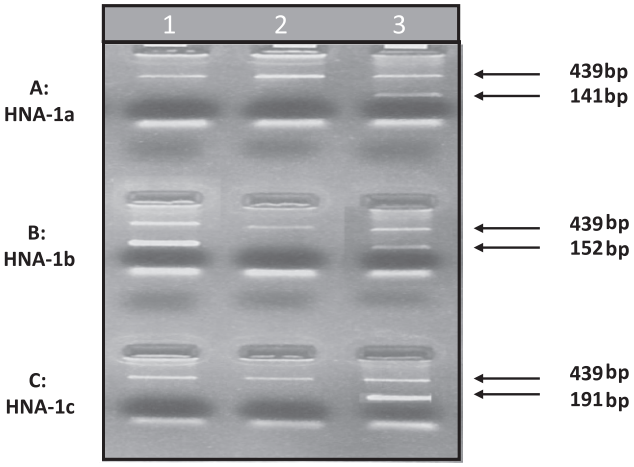

Fig. 1. HNA-1 genotyping by PCR-SSP method. Electrophoresis of HNA-1 allele products were run on 1.5% agarose gel stained with ethidium bromide. HNA-1 alleles -1a, -1b, and -1c are respectively displayed in Lanes A, B, and C. Column 1 = newborn (negative for HNA-1a and HNA-1c and positive for HNA-1b); Column 2 = mother (negative for HNA-1a, -1b, and -1c); Column 3 = individual positive for HNA-1a, -1b, and -1c (positive control). The 439-bp band represents the human growth hormone gene used as internal positive control, and the 141-, 219-, and 191-bp bans represent amplified HNA-1a, HNA-1b, and HNA-1c alleles PCR products.

and, without any treatment, the neutrophil count spontaneously increased to 600×10^6/L on Day 18 and 1800×10^6/L after 1 month, when she was discharged from the hospital. Neonatal alloimmune neutropenia was suspected and laboratory tests were performed on maternal and newborn blood samples obtained immediately after delivery.

IgG anti-granulocyte antibodies were detected in maternal serum by means of a strongly positive granulocyte immunofluorescence test (GIFT), but not by the granulocyte agglutination test (GAT) even after sera dilution (to 1/2 to 1/512). A high level of anti-CD16 was identified by monoclonal antibody immobilization of granulocyte antigen assay. Granulocyte antibodies were also found in the newborn by GIFT. Maternal neutrophils were typed as CD16 negative with the GAT using polyclonal antibodies. HNA-1 genotyping was performed by polymerase chain reaction-sequence specific primers (PCR-SSP). The newborn was found negative for HNA-1a and HNA-1c, but positive for HNA-1b, whereas the mother was negative for HNA-1a, -1b, and -1c, consistent with an FcγRIIIb deficiency (Fig. 1).

Our observation confirms the risk for a mother with FcγRIIIb deficiency to produce CD16 isoantibodies, which can be responsible for INN. To the best of our knowledge, no FcγRIIIb deficiency has been reported in people originating from North Africa. It is known that the HNA-1 null phenotype is more frequent in Africans (1%-2%) than in Caucasians (0.15%) and nearly absent in Asians and Amerindians.[6] Interestingly, this rare null phenotype has been found in 0.8% of Spanish blood donors, which may be related to their berberian origin.[7] Paradoxically, as in our patient, most of the FcγRIIIb-deficient individuals do not suffer from repeated infections or autoimmune or immune complex diseases, while this receptor contributes to the phagocytosis of opsonized microorganisms and the clearance of immune complex from the circulation.[8] Further investigations are required to explain the absence of immune consequences in individuals carrying this rare phenotype.

CONFLICT OF INTEREST

The authors are not aware of any conflicts of interest.

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Syncope after whole blood donation: factors associated with increased donor injury

Syncope occurs in 0.13% (American Red Cross [ARC] whole-blood donation database, unpublished data, July 1, 2005-June 30, 2010) to 0.27%[1,2] of all allogeneic whole blood donations and in approximately 4% to 5% (same ARC database) of vasovagal reactions. Sixty percent[1] of syncopal reactions occur after the donor leaves the donor bed, with 10% to 12%[1,3] of reactions occurring after the donor leaves the donation site. Syncope after donors stand up is an issue because approximately 4% to 9% of donors who fall sustain an injury (same ARC database).[1] The donor injury rate for allogeneic whole blood donations is 0.011% (same ARC database) to 0.014%.[1] Overwhelmingly, the injuries are minor, but there can be severe injuries such as fractures, lacerations, and closed head injuries.

It seems intuitive that the risk of donor injury would be the same for all donors who progress to syncope. This hypothesis was tested by analyzing 30.2 million allogeneic whole blood donations to the American Red Cross over a 5-year period (same ARC database). The syncope and donor injury rates at the collection sites were evaluated. The overall donor syncope and injury rates were 0.13% (39,392/30,190,815) and 0.011% (3462/30,190,815), respectively, and a donor injury occurred in 8.8% of the syncopal episodes.

The proportion of syncopal episodes associated with donor injuries was evaluated by age interval for donations by all donors, first-time female donors, repeat female donors, first-time male donors, and repeat male donors (Table 1). For each of these donor groups, the baseline interval was defined as the interval, among all intervals with at least 40 donor injuries, that had the lowest proportion. The ratio of the proportion for each interval to the proportion for the baseline—that is, the relative risk—was calculated. The proportions and relative risks were also evaluated for all donors grouped by sex and donation status (first-time vs. repeat donation).

Table 1 shows that for all donations, the proportion of syncopal episodes associated with injuries is highest in 16-year-old donors, decreases with increasing age, and begins to plateau in the 29- to 42-year-old age group. Relative risks are increased in 16-, 17-, 18-, and 19-year-olds by 125, 96, 72, and 39%, respectively. The same pattern is observed in first-time and repeat female donors and also in first-time male donors but not in repeat male donors. Donor injury rates after syncope were 17% higher in females (9.3% [2222/23,855]) than in males (8.0% [1240/15,537]; 95% confidence interval [CI], 1.09-1.25) and 12% higher in first-time donors (9.3% [1887/20,354]) than in repeat donors (8.3% [1575/19,038]; 95% CI, 1.05-1.19).

These findings show that donor injury rates after syncope are greatly increased in very young donors and also increased, but to a much lesser degree, in females and first-time donors. A study of the character of syncopal reactions in very young donors and older donors might explain why the rates of donor injuries after syncope differ with age. A better understanding of syncope could potentially help us to improve safety for donors.

CONFLICT OF INTEREST

None.

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TABLE 1. Relationship between donor syncope and donor injury: influence of age, sex, and donation history

Age group (years)	All donors: Incidence of syncope (per 10,000)	All donors: Incidence of injury (per 10,000)	All donors: Injury/syncope (%)	Injury/syncope (%): Females: First-time	Injury/syncope (%): Females: Repeat	Injury/syncope (%): Males: First-time	Injury/syncope (%): Males: Repeat
16	48.1	6.5	13.6*	13.5*	14.1*	14.4*	8.7
17	43.5	5.2	11.9*	13.1*	11.4*	10.4*	10.9*
18	35.6	3.7	10.4*	11.1*	12.1*	8.7*	8.2
19	32.2	2.7	8.4*	7.6*	10.3*	6.3	8.2
20-22	24.5	1.8	7.5*	5.9	9.1*	7.7*	6.8
23-28	17.0	1.3	7.9*	7.8*	8.0*	7.4*	8.5
29-42	9.3	0.6	6.2	6.2	7.0	4.4†	6.8†
43-57	5.2	0.3	6.0†	5.1†	6.0†	5.5	7.0
58-96	4.7	0.3	6.1	5.0	6.8	3.3	5.8
Total	13.0	1.1	8.8	9.9	8.7	8.3	7.6

* Risk is greater than baseline's risk (lower 95% confidence limit for relative risk >1.0).
† Baseline for group.

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