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Acute Intravascular Hemolysis Following an ABO Non-Identical Platelet Transfusion: A Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Patient: Female, 61
Final Diagnosis: Acute intravascular hemolysis
Symptoms: Cherry colored urine • chills
Medication: —
Clinical Procedure: —
Specialty: Pathology

Objective: Rare disease
Background:

Platelet transfusion is a common clinical practice required for therapeutic purposes in the setting of symptomatic thrombocytopenia, and, in some cases, prophylactically for asymptomatic thrombocytopenia. Crossmatch compatibility is not routinely done for platelet transfusions, and transfusion of ABO non-identical platelets has been adapted as an acceptable clinical practice. Acute intravascular hemolysis due to ABO non-identical platelets is a rare but clinically significant entity. Our case report reinforces the importance of a vigilant clinical approach in case of ABO non-identical platelet transfusions.

Case Report: We report the case of 61-year-old woman with blood group A, with chemotherapy-induced asymptomatic thrombocytopenia, who developed acute intravascular hemolysis following transfusion of group O single-donor platelets (SDPs). The patient was transfused 1 unit of single-donor platelets for bleeding prophylaxis, as her platelet count dropped to less than $10 \times 10^9/L$ due to chemotherapy that she was receiving for acute myeloid leukemia (AML). Immediately after transfusion, the patient noticed cherry-colored urine; and within 12 h of transfusion, her hemoglobin dropped by more than 2.5 g/dL. A post-transfusion immunohematology work-up showed positive DAT and high titers of anti-A1 isohemagglutinins in the platelet donor, supporting the diagnosis of acute intravascular hemolysis due to ABO non-identical platelets.

Conclusions: The possibility of acute intravascular hemolysis should be kept in mind in cases of transfusion of group O single donor platelets to non-group O recipients. ABO non-identical platelets, even with low isohemagglutinin titers, can cause significant adverse effects, particularly in newborns, children, and immunosuppressed and transfusion-dependent patients; therefore, a cautious clinical approach is recommended.

MeSH Keywords: Blood Component Removal • Hemagglutinins • Hemolysis • Thrombocytopenia

Abbreviations: SDPs – single-donor platelets; LDH – lactate dehydrogenase; FNHTR – febrile non-hemolytic transfusion reactions

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Background

Platelet transfusion is a common clinical practice required for therapeutic purposes in the setting of symptomatic thrombocytopenia, and, in some cases, prophylactically for asymptomatic thrombocytopenia if the platelet count falls below $10 \times 10^9/L$. Platelet transfusions are frequently associated with non-hemolytic reactions such as allergic and febrile non-hemolytic transfusion reactions [1]. In contrast, hemolytic reactions due to ABO non-identical platelet transfusions have been reported to be rare [2]. Mair et al. (1996) performed a study at the Moffitt Cancer Center, reporting that out of 946 ABO non-identical platelet transfusions performed between January 1996 and August 1996, there was only 1 case of hemolytic transfusion reaction, and the estimated overall risk of acute hemolytic reactions due to ABO non-identical platelet transfusions was 1/9000 platelet transfusions over a period of 10 years [2].

Although plasma volume in a platelet unit is almost identical to the plasma unit volume, crossmatch compatibility is not routinely done for platelet transfusions due to logistical and inventory reasons [3,4], and transfusion of ABO non-identical platelets is used as a safe clinical practice [5]. Transfusion of ABO non-identical platelets, however, should not be considered risk free. Acute intravascular hemolysis due to transfusion of ABO non-identical platelets is a relatively rare but clinically significant entity, and fatalities have been reported [6–9]. We report the case of a 61-year-old blood group A female with chemotherapy-induced thrombocytopenia who developed acute intravascular hemolysis after transfusion of 1 unit of group O single-donor platelets (SDPs).

Case Report

The patient was a 61-year-old female, blood group A, with acute myeloid leukemia, who required platelet transfusion

for chemotherapy-induced asymptomatic thrombocytopenia with a platelet count of $6 \times 10^9/L$. One unit of 280 ml irradiated, leuko-reduced group O single-donor platelets was transfused to the patient prophylactically. Immediately after the completion of platelet transfusion, the patient developed chills and body aches and noticed cherry-colored urine. Normal saline infusion was rapidly initiated to avoid hemodynamic instability.

A post-transfusion physical examination of the patient was unremarkable except for pallor. Table 1 shows vital signs of the patient at 15 min pre-transfusion and 30 min post-transfusion. Relevant pre-transfusion and 12-h post-transfusion lab results of the patient are summarized in Table 2. In addition, her post-transfusion haptoglobin level was less than 8 mg/dL (normal range: 40–240 mg/dL) and indirect bilirubin was 1.5 mg/dL (normal range: 0.3–0.9 mg/dL). Urinalysis showed dilute (specific gravity 1.005) red-colored urine with 3+ hemoglobin and 3–10 RBCs per high-power field.

The patient's post-transfusion specimen was positive for visible hemolysis. ABO and RhD testing performed on pre and post-transfusion samples was congruent. The pre-transfusion sample was negative for tube DAT. A post-transfusion immunohematology work-up showed positive tube DAT, negative reactivity with anti-IgG, and 4+ reactivity with anti-C3. The patient's red blood cell antibody screen was negative for non-ABO allo-antibodies, and the patient's serum was negative for anti-A. An elution test performed on the patient's RBCs demonstrated anti-A1 antibodies. The donor's specimen testing for anti-A1 antibodies in saline revealed a titer of 1: 512 at room temperature. These laboratory investigations, along with the overall clinical picture, supported the diagnosis of acute intravascular hemolysis due to high anti-A1 titers in the transfused group O platelets. The patient's hemoglobin dropped further to 4.5 g/dL 18 h after platelet transfusion, prompting red blood cell transfusions. She received a total of 4 ABO-compatible group A

Table 1. Pre- and post-transfusion vital signs.

	Pulse	BP (mmHg)	Resp. rate	Temperature	O2 sat*
15 min pre-transfusion	74/min	140/68	17/min	37.1°C	97%
30 min post-transfusion	81/min	135/66	18/min	37.3°C	95%

BP – blood pressure; sat* – saturation on room air.

Table 2. Pre- and post-transfusion laboratory values.

	Hb (g/dL)	Total bilirubin	LDH	Platelet count
Normal lab range	12.1–15.0	0.3–1.2 mg/dL	100–238 U/L	150–400 $\times 10^9/L$
Pre-transfusion	8.1	0.8	369	6
12 h post-transfusion	5.5	2.4	1125	56

Table 3. Data of patients with hemolytic reaction following ABO non-identical platelet transfusion.

Reference	Year	Patient/recipient			Donor's ABO	Donor's antibody titer (in saline)
		Age (years)	Sex	ABO		
Jain et al.	2011	49	F	B	Multiple	Not reported
Sadani et al.	2006	65	F	A	O	Anti-A=1: 128
Sapatnekar et al.	2005	2	F	A	O	Anti-A1=1: 1024
Zubair et al.	2004	67	M	A	O	Anti-A=1: 512
Angiolillo et al.	2004	8 m*	M	A	O	Anti-A=1: 128
Oztürk et al.	2003	21	M	A	O	Not reported
Valbonesi et al.	2000	51	F	A	O	Anti-A >1: 8000
Valbonesi et al.	2000	16	F	A	O	Anti-A >1: 8000
McManigal et al.	1999	72	F	AB	O	Not done
Larsson et al.	1999	44	F	A	O	Anti-A=1: 16,384
Mair et al.	1998	28	M	A	O	Anti-A=1: 128

m* – months.

packed red blood cell units during her hospital stay and 1 unit of ABO-identical group A single-donor platelets on the day of her discharge. On day 5, the patient was discharged home in stable condition. Two months after her discharge, she underwent a successful allogeneic bone marrow transplant for acute myeloid leukemia.

Discussion

Platelet transfusion is a common clinical practice carried out for therapeutic purposes in the setting of symptomatic thrombocytopenia, and, in some cases, prophylactically for asymptomatic thrombocytopenia. Platelet transfusions in comparison to red blood cells and fresh frozen plasma are associated with a higher rate of non-hemolytic reactions, including FNHTR and allergic reactions [1]. Volker Kiefel (2008) reviewed the incidence of different transfusion reactions encountered with platelet transfusions. Based on his literature review, febrile and allergic reactions can be expected in up to 20–30% of patients in case of platelet transfusions [10]. In contrast, hemolytic reactions due to ABO non-identical platelet transfusions have been reported to be rare [2]. This is due to dilution of the small volume of donor's plasma (present in platelet units) by the relatively larger plasma volume of the recipient. Transfusion of ABO non-identical platelets, however, should not be considered risk free. Major and minor ABO-incompatibilities can be encountered in case of transfusion of different blood products, including platelets. Major ABO incompatibility involves transfusion of a foreign antigen (for example, group A or B platelets being transfused to a group O recipient), whereas minor ABO incompatibility involves transfusion of a foreign antibody

to a recipient having the corresponding antigen (for example, group O platelets having anti-A/B antibodies being transfused to a group A or B recipient). Reduced post-transfusion platelet amounts can be seen with major ABO incompatibility [3], whereas transfusion of minor ABO-incompatible platelets can lead to acute intravascular hemolysis [3,11], particularly in case of transfusion of SDPs from group O donors, who may have high titers of anti-A or anti-B isohemagglutinins [4].

Our patient developed acute intravascular hemolysis due to transfusion of single-donor platelets from a group O donor, having an anti-A1 titer of 1: 512 when tested in saline. We reviewed the cases of acute hemolytic reactions due to ABO non-identical platelet transfusions that have been reported in literature over the last 20 years. In all of these cases, single-donor platelets, mostly from group O donors, were suspected to be the cause of intravascular hemolysis. Table 3 summarizes some of these reported cases.

Interestingly, almost all of the ABO non-identical platelet transfusion-associated acute hemolytic reaction cases found in our literature review occurred in group A recipients, except for 2 recipients, one with blood group B [9] and the other with blood group AB [12]. Among the case reports mentioning isohemagglutinin titers from the donors, anti-A titer was found to be 1: 128 or higher when tested in saline. Isohemagglutinin titers were not reported in cases by Jain et al. [9], McManigal et al. [12], and Oztürk et al. [13]. Sapatnekar et al. described a case in which transfusion of half a unit of group O single-donor platelets was enough to cause severe but non-fatal intravascular hemolysis in a 2-year-old child with medulloblastoma [14]. Jain et al. (2011) reported the case of a blood group B positive female who

Table 4. Summary of recommendations to reduce the risk of intravascular hemolysis due to platelet transfusions.

No.	Proposals/recommendations
1.	Screening of all single-donor group O platelet units for anti-A titers/anti-B titers
2.	Transfusion of ABO-identical platelet units, if possible
3.	Transfusion of ABO-compatible platelets if ABO-identical platelet unit is not available
4.	If ABO mismatch is unavoidable in case of non-group O recipients, then prefer transfusion of group A or group B platelets over group O platelets
5.	If group O platelet transfusion is unavoidable for group A, B, or AB recipients, then transfuse group O platelets from donors with undetectable or low titers (preferably less than 1: 128) of anti-A/anti-B antibodies
6.	Plasma volume reduction of ABO mismatched single-donor platelet units for non-group O recipients [3,9]
7.	Washing non-identical ABO platelets to reduce the supernatant plasma volume and replacing it with normal saline
8.	Implementing the use of platelet additive solutions (PASs) for single-donor platelet storage to reduce isohemagglutinin titers

developed acute intravascular hemolysis with fatal outcome after she was transfused 8 units of ABO non-identical platelet rich plasma for thrombocytopenia over a period of 2 days [9].

Although the risk of hemolytic reactions due to ABO non-identical platelet transfusions has been reported to be very rare [2], in future, the actual risk of hemolytic reactions due to minor ABO-incompatible/non-identical platelet transfusions is expected to increase due to increasing use of single-donor platelets and limited availability of random-pooled platelets [5]. This is due to the fact that a single-donor platelet unit contains undiluted plasma from a single donor who may have unusually high titers of anti-A or anti-B antibodies, thereby increasing the recipient's risk of acute hemolysis in case of minor ABO-incompatible/non-identical platelet transfusions [4]. In contrast, random-pooled platelets are much less likely to cause hemolysis because of the smaller amount of plasma from each donor, and dilution of any potent high-titer isohemagglutinins due to pooling of plasma from multiple donors [11].

Transfusion of ABO-identical platelets is the safest therapeutic strategy; however, it is not always feasible due to logistical and inventory reasons, including: (i) limited availability of ABO-identical platelets, especially in emergent situations, (ii) limited shelf life of platelets (about 5 days after collection) [4], and (iii) increased workload and cost involved in overcoming ABO barrier in platelet transfusions [3]. Some authors suggest that group A and B recipients should be transfused single-donor group O platelets only if the anti-A or anti-B isohemagglutinin titer in the donor platelets is low (typically ranging between 1: 50 and 1: 250). However, there have been reported cases of acute hemolysis after transfusion of single-donor group O platelets, even with anti-A titers as low as 1: 128 [2,6,7], and there is still a lack of consensus in the literature regarding the critical isohemagglutinin titer. Reis et al. recommended

plasma volume reduction of platelet units from group O donors in case of isohemagglutinin titers of 1: 64 or higher [15]. Washing the platelet units to reduce the volume of supernatant plasma and replacing it with normal saline helps to reduce the isohemagglutinin titers, thereby allowing the use of plasma-depleted/plasma-reduced ABO non-identical platelet units and decreasing the risk of intravascular red cell hemolysis [16]. Another technique to help reduce the risk of hemolysis due to ABO non-identical and incompatible platelet transfusions is the use of platelet additive solutions (PASs) instead of 100% plasma for platelet storage. Single-donor platelets stored in PAS contain almost 65% less plasma (and therefore lower titer of isohemagglutinins) compared to single-donor platelets stored in 100% plasma [17]. In addition to reducing allergic and febrile transfusion reactions, enabling pathogen inactivation, and making more plasma available for fractionation, suspension of platelets in PAS as compared to 100% plasma provides the advantage of greater removal of ABO-incompatible plasma, thus reducing the risk of hemolysis [18].

Based on our case report and literature review, we propose a more vigilant approach towards patients who are at risk of hemolysis due to transfusion of ABO non-identical and minor incompatible platelets. Some proposals to help reduce the risk of hemolytic reactions due to platelet transfusions are summarized in Table 4.

Conclusions

Transfusion of ABO non-identical platelets should not be considered risk free, and the possibility of acute intravascular hemolysis should always be kept in mind, particularly in the case of transfusion of single-donor group O platelets to non-group O recipients. ABO non-identical platelets, even with low

isohe magglutinin titers, can cause significant adverse effects, particularly in newborns, children, immunosuppressed patients, and transfusion-dependent patients; therefore, a cautious clinical approach is recommended.

Conflict of interest

None.

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