Case Report

Acute Hemolytic Transfusion Reaction in a Pediatric Patient Following Transfusion of Apheresis Platelets

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The practice of transfusing ABO-incompatible platelets, driven primarily by concerns about inventory management, has been considered generally safe because the accompanying plasma is usually diluted in the recipient’s total blood volume. However, if the platelet product contains a large volume of plasma or a high concentration of incompatible isoagglutinin, there may be hemolysis of the recipient’s red cells. Patients with a small blood volume, such as babies and children, are considered to be at particular risk for such a complication. We describe the case of a baby who suffered massive hemolysis of her group A red cells after transfusion of group O Apheresis Platelets containing a high-titered anti-A isoagglutinin. We also offer a review of the literature on this subject and recommendations to avoid acute hemolytic reactions as a result of platelet transfusion. J. Clin. Apheresis 20:225–229, 2005. © 2005 Wiley-Liss, Inc.

Key words: ABO blood groups; platelet transfusion; hemolysis

INTRODUCTION

The transfusion of platelet units having donor plasma that is ABO-incompatible with the patient’s red cells is a minor incompatible transfusion, i.e., it involves the transfusion of antibodies directed against the patient’s red cell ABO antigens. Such a transfusion is believed to be associated with a low risk for hemolytic transfusion reactions [1–3]. This is because the small amount of plasma in the transfused product is diluted in the relatively larger total blood volume of the patient, and soluble blood group substances in the patient’s plasma neutralize the incompatible antibodies [4]. However, patients with a small total blood volume are at risk for intravascular hemolysis because of their limited ability to dilute or neutralize incompatible antibodies. Several instances of hemolysis have been reported as a result of minor incompatible transfusion [1,5–11], and questions regarding the safety of this practice have been raised recently.

Platelet products for transfusion are available in two forms, as whole-blood derived Random Donor Platelets, and as Apheresis Platelets. Individual units of Random Donor Platelets contain only a small amount of plasma (usually 50–60 mL); in addition the pooling of multiple units for transfusion dilutes each donor’s plasma and reduces the chance that a high-titered antibody from any one donor will be transfused to the patient. In contrast, Apheresis Platelets contain 200–400 mL of plasma from a single donor. If the donor has a high concentration of an isoagglutinin against the patient’s red cell ABO antigens (e.g., a group O donor unit, which contains anti-A and anti-A,B antibodies, transfused to a group A patient), transfusion of platelets collected from that donor may be associated with the potential for hemolysis, particularly if the recipient has a small blood volume (e.g., a pediatric patient). We report a case of a baby with severe acute intravascular hemolysis due to a minor incompatible transfusion of Apheresis Platelets.
collected from a donor with high-titered anti-A isoagglutinin.

MATERIALS AND METHODS

Observation for Hemolysis

The patient’s blood sample was collected in a red top serum tube, incubated at 37°C for 60 min, centrifuged for 15 sec at approximately 1,000g, and the supernatant serum observed for hemolysis.

Minor Cross-Match

The patient’s red cells were washed and resuspended to a 3–4% concentration in saline. This red cell suspension was added to a tube containing two drops of plasma from the donor unit. The contents of the tube were centrifuged for 15 sec at approximately 1,000g. Following centrifugation, the tube was examined for hemolysis. The red cell button was gently resuspended and reactivity was graded based upon the macroscopic appearance of the agglutinates [12].

Antibody Titration

Serial dilutions of donor unit plasma and serum from the patient’s post-transfusion sample were incubated with group A and B red cells and the degree of agglutination, titer, and score were noted [13]. The titer is defined as the reciprocal of the highest dilution that causes macroscopic agglutination. The observed strength of agglutination is assigned a number and the sum of these numbers for all tubes represents the score. Strong antibodies are characterized by a high titer and a high score. There are no absolute titers or scores that define a high-titered antibody, but titration studies provide a semi-quantitative measure of the strength of an antibody and may help in determining the potential clinical significance of the antibody.

RESULTS

Case Report

A 2-year-old female, weighing 12 kg, with a history of medulloblastoma, status post chemotherapy and radiation therapy, hemoglobin 12 g/dL, hematocrit 32.3% and platelet count 11,000/mm³, presented for an outpatient platelet transfusion. Her blood group was A, Rh (D) positive. She received one half (145 mL) of a leukocyte-reduced and irradiated O, Rh (D) positive, Apheresis Platelet unit. Within 30 min of transfusion, she developed symptoms and signs of shock as evidenced by skin pallor, vomiting, decreased blood pressure (116/57 mm Hg → 87/28 mm Hg), decreased temperature (36.6°C → 35.1°C), increased pulse (121 beats per minute → 160 beats minute), and increased respiratory rate (28 breaths per minute → 32 breaths per minute). She had marked intravascular hemolysis, which made measurement of hemoglobin and hematocrit technically impossible for several hours following the reaction. The patient was transfused with two units of group O Red Cells and closely monitored in the pediatric intensive care unit. The first measurable hemoglobin/hematocrit (8.1 g/dL/20.2%) was reported 11 h following the initial transfusion reaction and was obtained after Red Cell transfusion. The patient had grossly discolored urine, and over the next 3 days, she continued to have free hemoglobin in her urine. Her condition improved with supportive treatment and she was discharged 7 days later without any residual effects. Differential diagnoses included hemolytic transfusion reaction versus septic transfusion reaction.

Transfusion Reaction Investigation

No clerical errors were identified upon review of the labels, donor records, and transfusion records. The pre-transfusion blood sample showed no hemolysis but the post transfusion sample was moderately hemolyzed and showed autoagglutination of the red blood cells. Minor crossmatch performed with the pre-transfusion sample showed agglutination, graded 4+, and moderate hemolysis at 37°C, indicating that the donor’s plasma contained anti-A isoagglutinin strongly reactive against the patient’s group A red cells. Gram stain and culture of a sample obtained from the nearly empty platelet bag were negative; a sample obtained from the other half of the Apheresis Platelet unit was also negative. Based upon this investigation, a septic reaction was excluded and the transfusion reaction was attributed to intravascular hemolysis due to passively infused anti-A isoagglutinin from the group O donor.

The donor unit had a high titer of anti-A isoagglutinin, with a comparable high score value (indicating a large quantity of antibody with strong avidity for its corresponding antigen), and the patient’s post-transfusion sample had anti-A isoagglutinin titers and scores comparable with her anti-B titer, most of which may be assumed to be naturally-occurring anti-B isoagglutinin. (See Table I).
TABLE I. Blood Group Isoagglutinin Titer and Score Results in the
Patient's Post Transfusion Sample and in the Donor Plasma From
the Apheresis Platelet Unit*

<table>
<thead>
<tr>
<th>Patient sample</th>
<th>Donor unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titer</td>
<td>Score</td>
</tr>
<tr>
<td>Anti-A</td>
<td>4</td>
</tr>
<tr>
<td>AnthB</td>
<td>4</td>
</tr>
</tbody>
</table>

*Serial twofold dilutions of the sample were tested against red cells
in saline at room temperature. Results are expressed as the
reciprocal of the highest dilution that causes macroscopic aggluti-
nation. The score results represent a measure of the avidity of the
antibody to its antigen with each titration result graded from 0 (no
agglutination) to 12 (+ or maximum agglutination).

2,048; titer in antiglobulin phase 16,384, score 114; titer in antiglobulin phase 156).

The platelet donor was informed about the anti-A
titer result and counseled about its significance. The
donor did not return to donate platelets and was lost
to follow-up. The donor was not deferred from
donation, but a note was made in the chart to tag any
future platelet products collected from this donor for
transfusion exclusively to group O patients.

**DISCUSSION**

Acute hemolytic transfusion reactions usually
present as fever and/or chills, and pain in the back or
abdomen, although pain may occur at other sites,
such as the head or the site of infusion. About 10% of
patients develop hypotensive shock because of mas-
sume complement activation and the release of cyto-
kines such as tumor necrosis factor alpha and
interleukin-1. Intravascular hemolysis is characterized
by hemoglobinemia and hemoglobinuria, with renal
failure developing in about a third of patients and
disseminated intravascular coagulation in approxi-
mately 7% of patients [14].

Acute intravascular hemolysis due to an incom-
patible transfusion is usually the result of ABO
major incompatibility, i.e., the transfusion of anti-
gen-positive red blood cells to a patient who has the
Corresponding isoagglutinin. The most common
cause of such a reaction is a clerical error that results
in transfusion of a unit of blood to the wrong pa-

tient. The risk of a fatal hemolytic reaction is
approximately 1% of all ABO-incompatible trans-

fusions [15], and is thought to be related to the
volume of incompatible component transfused.
Acute intravascular hemolysis, and even overt
hemolytic transfusion reactions, may also occur due
to ABO minor incompatibility, when plasma-con-
taining components, including Platelets, Granulo-
cytes, and Whole Blood, and intravenous

immunoglobulin preparations are transfused [1,5–
11,16,17]. Surprisingly, hemolytic transfusion reac-
tions have also been described following the trans-
fusion of minor-incompatible Red Cell units, which
typically contain only a small amount of plasma
[18,19]. The underlying cause appears to be the
presence in the donor’s plasma of a sufficiently po-
tent isoagglutinin capable of overwhelming the
dilution and neutralization capability of the re-
cipient. Patients with small total blood volume, such
as infants and children, are at particular risk [8,18],
and as the present case illustrates, the problem may
be compounded if the donor unit contains a high-
titered isoagglutinin.

The range of blood group isoagglutinin titers re-
ported among normal group O individuals is 8–2,048
for anti-A isoagglutinin and 8–256 for anti-B iso-
agglutinin. High titers are believed to result from
previous antigen exposure, such as vaccination or
pregnancy. Group O blood donors with high isoag-
glutinin titers have been described as “dangerous
universal donors,” but the range of titers that would
characterize a donor as “dangerous” has not been
clearly defined [20]. The lack of uniformity in testing
and reporting isoagglutinin titers of implicated do-
nor units makes it difficult to determine the signifi-
cant titer, but a recent publication accepts an
arbitrary IgG titer of 256 and IgM titer of 64 for the
anti-A isoagglutinin [21]. Most hemolytic reactions
following minor incompatible transfusion were
attributed to anti-A isoagglutinin, but a few cases
due to anti-B isoagglutinin have also been described
[6,18].

Platelets are often transfused without regard for
ABO compatibility, primarily to permit efficient
management of the blood product inventory. Most
such transfusions have no clinically significant ill
effects, as evidenced by the fact that information
about hemolysis due to incompatible transfusions is
limited to isolated case reports in the literature,
suggesting that this is an unusual event. Moreover, a
small study of paired transfusions, ABO-identical
and ABO minor incompatible, showed no significant
changes in post-transfusion hemoglobin levels after
the administration of the incompatible transfusions
[1]. Nevertheless, it is important to recognize that
hemolysis does occur, and that its consequences can
be devastating. Blood bank laboratories that are
accredited by the College of American Pathologists
are required to have a policy to prevent the ad-
administration of ABO-incompatible donor plasma
in platelets given to infants [22]. However, there may
be other circumstances under which incompatible
transfusions may be unsafe, and it may be necessary
to extend such a policy to cover additional patients
and clinical situations. The increasing use of
Apheresis Platelets, which are associated with the potential for transfusion of a large volume of high-titered isoagglutinin to the recipient, may be associated with an increased risk of hemolysis due to incompatible transfusion. This concern for the risk of hemolysis is not restricted to Apheresis Platelets but also applies to Random Donor Platelets, when a single-unit transfusion is used for a baby.

In order to avoid the risk of hemolytic transfusion reactions due to minor incompatible transfusion, a number of different approaches can be adopted [23]. Some investigators have proposed the use of a rapid antibody titer and a hemolysin screen on all group O Platelets, or prior to each transfusion of group O platelets to a non-group O patient. Unfortunately, there is no practical or cost-effective means to screen donors and no consensus on the definition of high titters. Such screening is national policy in some countries and has been adopted by a few centers in this country; however, the value of the practice is not yet fully established [21,24]. An alternative approach is to transfuse only group-specific platelets, particularly to pediatric patients. If this is not feasible because of an inventory shortage, the volume of incompatible plasma in the unit may be reduced before transfusion. It should be noted that volume reduction may cause the loss of a significant number of donor platelets and delays in providing units for transfusion. Furthermore, there is some evidence that the transfusion of even small volumes of incompatible plasma may cause hemolysis [25]. If incompatible transfusion is unavoidable, group A or group B Platelets are preferred over group O Platelets because of the generally lower levels of isoagglutinin titers in group A and group B individuals. Also, the use of pooled Random Donor Platelets rather than Apheresis Platelets can minimize the risk of transfusing a large volume of plasma that may contain high concentration of incompatible isoagglutinins. Patients with passively-acquired isoagglutinin should be transfused with group O Red Cells, rather than group-specific Red Cells, until the isoagglutinin is no longer detectable [4]. The development of platelet preservative solutions in the future may permit the use of platelet products that are devoid of plasma and, therefore, have no risk of causing hemolysis due to minor incompatibility.

In conclusion, minor ABO-incompatibility in platelet transfusion has the potential for severe, life-threatening hemolysis. Pediatric patients with small blood volumes are at high risk for such a complication. To avoid this risk, we recommend the use of group-specific platelet transfusion whenever possible, especially if an Apheresis Platelet unit or a single Random Donor Platelet unit is used. This policy would also avoid other potential extravascular complications of minor ABO incompatibility in certain subgroups of pediatric patients [26].

REFERENCES