Incompatible crossmatch: First sign of a hemolytic transfusion reaction due to out-of-group platelet transfusion

Debapriya Basu, Sabita Basu, Joydeep Roy, Mahua Reddy, Mammen Chandy¹, Jaydeep Bhaumik²

Abstract:
Platelet (PLT) transfusion is undertaken in a variety of clinical settings with thrombocytopenia, with or without bleeding. Since PLTs are most often stored in donor plasma, group-specific PLT transfusions are preferred to out-of-group transfusions. PLTs adsorb ABO antigens over their surface from the plasma. In major ABO-incompatible PLT transfusions, anti-A/B from the patient plasma react with the ABO antigens on transfused PLTs and can potentially cause adverse reactions or PLT refractoriness. Transfusion of PLTs with major ABO incompatibility, though effective in preventing clinical bleeding, is associated with reduced posttransfusion PLT count increments. In minor incompatible PLT transfusion transfused, anti-A/B can cause hemolytic transfusion reaction (HTR) which is not always related to a high titer of anti-A/B in the donor. Although attempts are made to practice ABO identical PLT transfusion, most centers practice out-of-group random donor platelets (RDPs) as well as single-donor-platelets (SDP) transfusion. The limited PLT shelf life does not always permit ABO identical PLT transfusion. At our center, ABO-specific PLT transfusions are practiced where possible, and in case of minor ABO-incompatible transfusions, antibody titers are not done. Here, we report a case of HTR due to out-of-group SDP transfusion, detected in the laboratory after an incompatible red blood cell (RBC) crossmatch.

Keywords:
Hemolytic transfusion reaction, out-of-group SDP, platelet transfusion

Case Report

A 56-year-old female, a case of carcinoma ovary Stage III C, received chemotherapy treatment of taxane plus carboplatin six cycles. Over 4 years, she had three relapses for which she received cisplatin, gemcitabine, avastin, and abraxane. Subsequently, she developed anemia requiring blood transfusion and thrombocytopenia and carboplatin was stopped. Bone marrow examination revealed hypocellular marrow without evidence of any malignancy. She was started on eltrombopag 50 mg OD, prednisolone 5 mg OD and erythropoietin 40,000/week, granulocyte colony-stimulating factor 300 µg weekly.

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After 1 month, peripheral blood smear showed 10% circulating blasts. Bone marrow aspiration showed 15% blasts, increased monocytes, and dysmyelopoiesis. Bone marrow biopsy revealed an increase in CD34+ immature precursors with increased monocytic component and dysmegakaryopoiesis consistent with myeloid neoplasm. Immunophenotyping results were suggestive of myelodysplastic syndrome (therapy related). She started receiving decitabine and was on transfusion support. The patient received several RBC transfusions (group-specific and crossmatch compatible) and many PLT transfusions, both RDPs and SDPs. PLT transfusions were not always group-specific as it depended on the RDP inventory and availability of group-specific SDP donors.

In this setting, we received a request for two RBC units for this patient. Now, crossmatch with four RBCs was all incompatible. Blood group, antibody screen (Surgiscreen cells, Resolve panel A), and anti-human globulin (AHG) crossmatch (poly-specific card) were done by column agglutination technique (Ortho Biovue Microbead System). Additional tests – heat elution, acid elution (BAG – elution kit, Ab Acid elution, Bag healthcare, Germany) and antibody titration (master dilution method-in tube technique) – were also done. The titration in AHG phase was done using DTT-treated plasma. Standard validated techniques were used. The patient’s blood group was found to be A positive both in forward and reverse. As there was no blood group discrepancy, there was no irregular IgM antibody in the patient. Reaction with Anti-A, lectin was 4+. The antibody screen was negative but crossmatch with four A-positive RBC units were all incompatible. The auto-control and direct antiglobulin test (DAT) (IgG only) were positive, both 3+. The family and medical history of the patient did not suggest any hereditary cause for the hemolysis. The positive DAT test indicated that some acquired immune phenomenon was going on in the patient's body. As DAT showed IgG antibodies and antibody screen was negative, acid elution was done. The eluate did not show any agglutination with panel screen cells. As antibody screening as well as elution results was negative, we concluded that the incompatibility was due to an antibody which was absent in the panel cells. Crossmatch of the eluate with A group RBC was incompatible, implying that the incompatibility was due to anti-A antibody. Heat eluate was also done and antibody screen with eluate was negative, and crossmatch with A group RBC was compatible. Heat eluate showed negative reaction with A, B, and O cells at room temperature. As the acid eluate reacted with A cells and not with O cells, it is unlikely to be a case of drug-induced hemolysis because in that case, the eluate would be nonreactive with any drug nontreated cells and in the absence of the drug. Transfusion history revealed that in the last 48 h, she had received 4 RDP (two A positive and two O positive) and 2 SDP units (both O positive). Hence, it can be concluded that DAT and auto control were positive as a result of sensitization of the patient’s red cells with passively transmitted anti-A (present in RDP and SDP) from donors. And also the incompatibility in crossmatch was caused by this passively transmitted anti A. Both SDP donors were called and fresh blood samples were obtained for anti-A isoagglutinin titration. The anti-A titers were 64 in saline, 512 in AHG in one donor; and 128 in saline, 1024 in AHG in the second donor. Retrospectively, we noted that following the SDP transfusions, hemoglobin dropped from 8.3 to 7.5 g/dl and unconjugated bilirubin increased from 0.8 to 2.2 mg/dl, indicating a hemolytic transfusion reaction. As one O-positive RBC unit was compatible with the patient’s plasma, it was transfused and hemoglobin increased from 7.1 to 8.2 g/dl.

**Discussion**

Hemolysis due to out-of-group SDP transfusions may be mild, delayed in presentation and thus go clinically unrecognized. Contributing factors include small blood volume recipient, exposures to large volumes of incompatible plasma and donors with high-titer anti-A and anti-B.\[^2\] Reports have also shown that ABO antibody titers are not predictive of hemolytic reactions due to plasma incompatible PLT transfusions.\[^3\] In the index case, an unrecognized hemolytic transfusion reaction occurred due to out-of-group PLT transfusion. The SDP donor had high anti-A antibody titer and neither was antibody titer estimated nor was any product modification done pretransfusion. Heat elution technique is routinely used for the elution of ABO antibody. In this case, as IgG was causing a positive DAT, we did acid elution. Subsequently, antibody identified was anti-A. Greco *et al.* reported that acid elution can also be used for ABO antibodies.\[^4\] As antibody titers are not always predictive of hemolysis, anti-A/B titer estimation routinely in all minor incompatible PLT transfusions (RDP and SDP) is not cost-effective and judicious.\[^1\] However, as the “dangerous O group” donors have high titer antibodies, O group SDP donors may be screened for high titers before minor incompatible SDP transfusion. Henceforth, we undertake O-group SDP procedures only if the donor antibody titers are <64. Other preventive measures such as plasma volume reduction and use of PLT additive solution for PLT storage can also be undertaken in minor incompatible SDP transfusion to reduce the chance of hemolysis. This communication also highlights the fact that out-of-group PLT transfusions must be kept in mind when investigating an incompatible crossmatch in a multi-transfused setting.
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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