FEATURED CASE #19-08; ANSWERS;
(Case study by Jim Perkins, © 2019)

Indian Immunohematology Initiative

Questions:

1. What antibody(ies) do you think is present? Is more work needed to prove this hypothesis? What do you think is going on here clinically? What testing would you like to do to investigate this possibility?

   The patient appears to have anti-c (all 8 c-positive cells reacting, 4 c- negative cells including SCI not reacting) and possibly anti-E (note stronger reactions with R2R2 and r" cells) which are new since the previous transfusion. The possibility of anti-E can be proven by testing E-pos, c-neg cells, the most available of which are RzR1 cells. To prove these are alloantibodies we also need to do an extended Rh phenotype to show that the patient lacks c and E.

   The fact that the patient has new antibodies after transfusion as well as evidence of hemolysis in the form of a fall in the hgb level and signs of hemolysis (brown urine, hemoglobinuria on UA, hyperbilirubinemia) suggests a delayed hemolytic transfusion reaction DHTR. Typical workup would include typing of retained segments of the transfused units for c and E antigens, a repeat antibody screen, DAT, and IAT crossmatches with both donor RBCs using both the the pre- and post-transfusion specimens.

2. Is the hypothesis regarding the patient's post-transfusion antibody specificity proved? What about the hypothesis regarding the DHTR? Are there any surprises in this workup? How might this transfusion reaction have been avoided?

   The additional workup confirms the fact that after transfusion the patient had allo-anti-c and anti-E (I.E. 3 or more c-pos/E-neg cells reactive, 3 or more E-pos/c-neg cells reactive, 3 or more c-neg/E-neg cells non-reactive, other antibodies ruled out, patient lacks c and E antigens).

   Transfusion reaction workup also demonstrates that both of the previously transfused RBCs were E-positive and one was c-positive and therefore were capable of stimulating the corresponding antibodies. As we would expect, both units are incompatible with the post-transfusion specimen, but unfortunately they were not crossmatched with the pre-transfusion specimen. Of note however, the repeat antibody screen on the pretransfusion specimen was weakly positive; prior to transfusion it had been resulted as negative, and the units had been crossmatched by an "immediate spin" test only. Note that the rr cell reacts but the RzRz cell does not, so presumably the patient already had a weak anti-c, but the anti-E was not detectable before transfusion. So this DHTR was probably due to an error in reading the manual gel antibody screening test, and was therefore avoidable. Nonetheless, the anti-c was too weak initially to immediately cause overt hemolysis or even a fever. The increase in her pulse rate could have been due to the incompatibility but could equally be due to a degree of volume overload in this small patient. Also note that the anti-c in the pre-transfusion specimen reacted more strongly with PEG enhancement than in the gel test used for routine screening. Finally, DHTRs do not usually cause symptoms or signs other than a fall in hemoglobin in the presence of a new antibody, but this patient had hemoglobinuria.

   To summarize, this patient didn't show evidence of a hemolytic reaction at the time of the transfusion in spite of the fact that the first unit was c-positive, but over the next 13 days she clearly had hemolysis in association with an increase in the strength of the anti-c and a new anti-E. It's interesting to look at the CDC/AABB hemovigilance definition of a DHTR in relation to this case. Note that when the positive antibody screen was discovered the DAT was negative, probably because there were no donor cells left for the stronger anti-c and new anti–E to bind to. However according to the CDC/AABB definition a "Definitive" DHTR requires a positive DAT; this case would only fit the criteria for a "Probable" DHTR. Moreover, whether definitive or probable the criteria would only apply to the anti-E. If the anti-c had been the only antibody present and she had only hemolized after it had become stronger, because it was present at the time of transfusion the criteria for diagnosis of a DHTR would not have been met at all. But could we call this an immediate hemolytic transfusion reaction? Clearly the hemolysis did not occur immediately but was present after some number of days had passed.

   In the author's experience many obvious DHTRs do not fit the CDC/AABB criteria for a "Definitive" DHTR because of the requirement for a positive DAT, and the criteria for IHTRs suffer from a similar problem. Once the donor cells are gone, the DAT cannot be positive!

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This reaction was avoidable in an additional sense that the transfusion appears to have been unnecessary! The pre-transfusion hgb level was 9.0 G/dL and the post-transfusion hgb was near the lower limit of normal at 11.8. At the time of transfusion the physician's notes explicitly identify the patient's ability to fully participate in physical rehabilitation as an indication for the transfusion. This case is over 10 years old at the time of this writing, and the transfusion practices illustrated are out of date. A randomized trial (Carson, FOCUS trial, NEJM 2011) of restrictive (transfusion trigger hgb < 8 G/dL) versus liberal transfusion in patients identical to this one showed no difference in functional outcome and, by inference, ability to undergo rehabilitation.

Take home points

When a DHTR is suspected, repeat testing of a pre-transfusion specimen is an important quality control measure to detect whether the reaction was avoidable.

Weak antibodies present at the time of transfusion may not cause immediate hemolysis, but may only cause hemolysis in a delayed fashion. (This conclusion assumes that hemolysis would still have occurred due to the anti-c without the appearance of anti-E.)

The DAT is often negative at the time of detection of a DHTR, and this fact is not recognized by the CDC/AABB criteria for a DHTR.

One way to avoid negative outcomes to transfusions is to avoid unnecessary transfusion by following restrictive transfusion practices.