Unexpected Drop in Hemoglobin in a Patient After Undergoing Multiple Surgeries

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A 71-year-old Black man presented to the emergency department (ED) with an upper gastrointestinal tract bleed. He presented with borderline shock with an initial hemoglobin level of 6.8 g/dL prior to fluid resuscitation and transfusion of 4 units of packed red blood cells. He was admitted to the hospital and had a complicated 6-day hospital course characterized by hematemesis and melena.

On the morning of hospital day 3, an endoscopic examination was performed, results of which showed a large 3-cm duodenal ulcer with a large visible vessel and thrombus at its base. The ulcer was treated with endoscopic techniques and proton-pump inhibitor therapy. The patient was monitored over the next few days via twice-daily complete blood cell (CBC) counts, which showed stable hemoglobin levels around the 9.5 g/dL range.

On the morning of hospital day 7, just prior to planned discharge, the patient's vital signs had changed; the patient had new tachycardia (pulse, 110 bpm) with little change in blood pressure and a new fever of 38.3 ˚C. There was no new hematemesis or gross melena, although results of a stool hematest were positive for trace blood. Several observers thought there was a slight yellow tinge to his sclera as well. Results of a repeat CBC test were within normal limits, except the hemoglobin level had again dropped to 7.5 g/dL. Further detailed consultation revealed no history of anemia prior to these events. His only notable history dates to his active duty in the US Army in Vietnam, where he had received a serious extremity gunshot wound that required multiple surgeries to repair and multiple blood transfusions at that time. He has since been tested for sickle cell disease or trait and hepatitis C virus, results of which were all negative.

Which of the following is the most likely explanation for the findings manifested in the hospital?

A. Transmission of blood contaminated by HIV or hepatitis C virus
B. Hemolytic transfusion reaction caused by antibodies in the ABO blood group system
C. Nonimmune hemolysis
D. Delayed hemolytic transfusion reaction caused by antibodies in the Rh blood group system or other minor red cell antigens

Correct Answer: D.

The presented patient is manifesting a drop in hemoglobin roughly a week after an episode of multiple bleeds, surgeries, and transfusions related to peptic ulcer disease. Very appropriately, blood loss was suspected, and the initial and second episodes turned out to be just that. But the third episode was not related to blood loss and introduces us to the blood bank as a hemolytic transfusion reaction, which was eventually confirmed as the cause.

Blood bank issues are yet another seemingly esoteric area of clinical medicine wherein that mysterious corner of the hospital asks for repeated specimens and, in time, publishes a report to the electronic medical record full of notations and a variety of acronyms in lowercase and capital letters. However, the importance of the blood banks can be summarized as follows. Blood transfusion is by far the most common therapeutic procedure experienced by patients in the hospital. About 15% of hospitalized patients will receive a blood product transfusion, and in 1% of these transfusions, an adverse event will occur.[1] About 5% of these adverse reactions will be hemolytic transfusion reactions where the red blood cells are hemolyzed by antibodies of some form.[2]

Before having a more detailed discussion of such hemolytic transfusion reactions, I will briefly mention the interesting history of blood transfusion followed by

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a scheme to classify and remember the aspects of transfusion reactions, which I have used and found very useful. Adventures and misadventures in transfusion of animal and human blood into patients first appears in medical writing in the 17th century.[2] By the 19th century, astute physicians studying transfusion were aware that it was indeed possible and very helpful/lifesaving in about half of cases but catastrophic and often fatal (and very quickly) in the other half. As we will see, this correlates with the evidence of the ABO system of blood types (antigens) and the behaviors the antibodies have to them. Happily for us all, Karl Landsteiner's discovery of the ABO blood group system—for which he received the 1930 Nobel Prize in Medicine—explained a lot of these observations and opened the door to lifesaving blood transfusions.[2,3]

However, hemolytic transfusion reactions are certainly not the only adverse event caused by transfusion of blood products; after all, they only account for 1% of adverse events related to blood transfusions. There are many others, and they can be categorized in the following classification (and if you frequently read my WTTH vignettes, you will know I am a confirmed "lumper" and not a "splitter").

First is the transfusion reaction nonimmune or immune (antibody mediated) reactions. Nonimmune transfusion reactions include volume overload and a variety of infections complications—some acute and others very delayed. Examples of the latter are HIV and hepatitis infections. Acute catastrophes are the transfusions of bacterially contaminated blood and, more commonly, platelets that cannot be refrigerated lower than 22 °C. Infusion of a bolus of bacteria and endotoxin will cause fever, hypotension, renal failure, and vascular collapse easily confused with an ABO reaction. Immune transfusion reactions are much more common, but as stated earlier, very few (5%) are hemolytic. Immune transfusion reactions can be just as lethal and include anaphylaxis due to plasma proteins in the donor being foreign to the recipient such that an Ag/Ab reaction with subsequent release of vasoactive cascades ensues—similar to bee stings or peanut allergies. Again, it is easy to confuse this type of reaction with ABO reactions. A less serious immune reaction is the minor febrile response to transfused product, probably the most frequent adverse reaction reported.[1] The timing of events in the presented case are much too slow for anaphylaxis (Answer C) and much too fast and clinically significant for HIV or hepatitis infections (Answer A), which require an incubation period of significance (eg, weeks) before symptoms.

And finally, we arrive at immune-mediated hemolytic reactions as described by Lansteiner and Ottenburg.[3] We now know that these clinically most often manifest acutely and catastrophically as "acute" (almost always related to ABO reactions) or "delayed" (essentially the rest of the RBC antigens). This clinical behavior is predicated upon the behavior of these antigens and that of the antibodies that arise from exposure to them. Acute reactions, usually defined as occurring within 24 hours of transfusion, arise because the antibodies to the ABO antigens are pre-existing in the recipient. This is because ABO antigen carbohydrate antigens are not unique to RBC but are rather ubiquitous in nature in food stuffs and other substances. By 6 to 12 months of age, an individual has typically been exposed to these antigens and has made antibodies—unless, for example, the individual is blood type B so that B antigen is "self," not foreign, and no antibody is made. However, antibody to A substances will be made and ready to react immediately with blood type A if transfused. Further, antibodies created against ABO blood group system antigens are immunoglobulin M (IgM), large molecules that can fix complement and cannot cross the placenta. The complement fixation then triggers a complex set of pathways, which results in the life-threatening manifestations of an ABO hemolytic transfusion reaction (ie, acute hemolysis with intravascular lysis of RBC, hemoglobinemia, hemoglobinuria, renal failure, vasodilation, hypotension and death).[2] Happily, the timing and severity of our patient's reaction was not compatible with this pathophysiology, and Answer B is not correct.

Delayed hemolytic transfusion reactions are much more subtle. There are many "minor" RBC antigens—including the Rh system of CDE and other names that can confuse us all, such as Kidd, Kell, and Duffy—and they are essentially red-cell unique and not ubiquitous in nature. One needs to have been exposed to them by RBC transfusion in the past, as was the case in our presented patient. Further, these antigens most commonly elicit an IgG response. This takes about a week to titer up a significant Ab level (eg, anamnestic response). And these IgG antibodies do not usually fix complement such that the reaction is much milder than ABO reactions and are rarely life-threatening resulting in macrophage hemolysis (rather than intravascular), a decrease in hemoglobin and/or haptoglobin levels, a rise in lactate dehydrogenase and bilirubin levels, and fever,[2,4] as was seen in our presented patient, making Answer D correct. It needs to be noted also that these IgG antibodies are smaller molecules than IgM ABO forms and can cross the placenta such that the Rh system is responsible for most cases of hemolytic disease in neonates.

Finally, here are my comments on prevention and management of any form of hemolytic transfusion reaction. Essentially all—and I use that frequently too-inclusive medical term purposely—ABO reactions are due to "clerical error," where there was a labeling or human error in handling the specimens or blood product, and the wrong blood was given to the wrong patient. This is becoming less common with the advent of barcode labeling and electronic verification systems, but we must not forget about care in handling specimens and blood products. Investing a few seconds of attention to clinical detail can also reduce ABO reactions, even when we clinicians are being rushed

TAKE-HOME MESSAGE

Blood and blood product transfusions, the most frequent therapeutic procedure in hospitalized patients, can be associated with a variety of adverse events, which occur in 1% of transfused products. Adverse reactions can be nonimmune (eg, volume overload, bacterial or viral contaminations) or immune mediated in pathophysiology. Very common immune-mediated reactions include febrile and anaphylaxis transfusion reactions. Finally, about 5% of adverse transfusion reactions result in hemolysis. The most serious and life threatening are ABO reactions related to preform IgM complement fixing antibodies. Less serious are delayed hemolytic transfusion reactions mediated by anamnestic response of IgG antibodies due to prior exposure to blood transfusion of units with incompatible minor RBC antigens such as Rh and Duffy. Many transfusion reactions have the potential to be quite serious and even fatal such that, with any significant finding in a patient receiving blood product, the transfusions must be stopped immediately and investigated by the transfusion service technicians.

by the blood bank technicians while we urgently require blood product for a trauma patient or other seriously ill patients.[5] To prevent delayed reactions, working closely with the blood bank technicians is extremely helpful. We must provide them with an accurate patient history, including ethnicity (eg, Duffy negative is very common in Black patients, while blood supply is common in White patients) and history of prior transfusions, as well as logs of prior workups for transfused patients and results in medical alert cards and bracelets when indicated.[2,6]

Managing any suspected transfusion reaction—be it immediate or delayed, suspected immune or nonimmune, hemolytic or nonhemolytic—requires all transfusion of product in all patients be stopped, as we do not know what the precise reaction is and how far it may go. One death per about 2 million red cell units transfused have been reported, yet that is still more than the combined risks of infection with hepatitis or HIV viruses.[1,2] The blood bank technicians can then quickly perform their diagnostics such that appropriate support can be given, and specifics about what product can be safely obtained and administered can be communicated.

Patient Follow-Up

Laboratory studies were conducted in our presented patient. Results of blood cultures and a serologic gram stain of the specimens from the patient and transfused blood were negative. The patient's clinical status had remained stable. Within hours, a repeat hemoglobin test showed that the patient's level had dropped one more gram. A repeat stool test again returned positive results for trace blood. The patient's lactate dehydrogenase level was 497 u/dL, haptoglobin level was 0 mg/dL, and bilirubin level was 2.2 mg/dL mainly indirect. Thus, hemolysis was suspected rather than blood loss. Shortly thereafter, the blood bank technicians reported a positive antiglobulin test with antibodies to C and Duffy present in the patient's serum, while 2 of the transfused blood units were also positive for C and Duffy.

Over the next several days, the patient's fever resolved, and the hemolysis parameters normalized. It was clinically judged that further transfusion was not required, but several units of negative C/Duffy blood were obtained by the blood bank technicians as a precautionary measure. The patient was discharged after hospital day 6. At his 3-week follow-up, the patient's hemoglobin level had risen 3 g, and he was doing well. He has a medical alert card to carry in his wallet.

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