FATAL HEMOLYSIS 13 DAYS AFTER CAESARIAN SECTION: Answers

Case study by Jim Perkins M.D. and Elizabeth Clay MT(ASCP)SBB (©2010)

1. What antibody(ies) are present? What is the diagnosis?

This patient has a cefotetan-dependent RBC antibody in her serum and eluate reacting both with cefotetan-coated, washed RBCs as well as with uncoated RBCs in the presence of free drug. The eluted RBCs and serum for these tests were obtained before repeat cefotetan treatment.

Drug-dependent antibody (DDA) testing is performed in two sequences. For drugs such as beta-lactam antibiotics (penicillins and cephalosporins) that bind covalently to the RBCs, the candidate drug is incubated with red cells which are then washed to remove free drug. An indirect antiglobulin test (IAT) is then performed between the patient's serum, plasma, or eluate and the drug-coated RBCs. Results of this testing with the accompanying negative control are given in the first two lines of the drug studies shown.

For drugs that don't bind to RBCs the patient specimen is incubated with RBCs in the presence of drug, and then an antiglobulin test is performed. Lines 3 and 4 of the drug testing table give these results with and without fresh serum added as a source of complement (C'). Of interest, the combination of patient serum and drug was hemolytic in vitro. The negative controls that follow these results demonstrate that: 1) the antibody in the serum and eluate did not bind to the target RBCs in the absence of drug; 2) there is no blood group or drug-dependent antibody in the complement source; 3) the drug alone did not mediate binding of antibodies in the complement source to the RBCs. (Review the constituents of each negative control tube.) Like this one, most cefotetan-dependent-antibody-containing sera react in both formats (Arndt and Garratty, Semin Hematol, 2005).

This cefotetan-dependent antibody appears to be causing drug-induced immune hemolytic anemia (DIIHA). The patient's hemoglobin level was 11.4 g/dL on discharge after delivery. Ten days later it had fallen to 5.1. A large hematoma was demonstrated by ultrasound anterior to the uterus, although it does not seem massive enough (9 x 8 x4 cm = 288 cc) to contain the 750 to 900 mL of RBCs that would cause a 6 g/dL drop in hemoglobin concentration. The slight jaundice noted on the 12th post-op day is consistent with hemolysis, but jaundice can also be seen with resolution of a hematoma. Of note however, the LDH and total bilirubin levels were within normal limits suggesting that rapid hemolysis may have subsided by the time of admission. Her hemoglobin level was not repeated before cefotetan was administered at 22:30.

After the cefotetan was given the patient developed severe hemolysis with a rapidly falling hemoglobin level, as well as hemoglobinuria and hemoglobinemia. She was noted to be oozing blood from her IV catheter sites and had an elevated level of fibrin degradation products suggesting that she had disseminated intravascular coagulation and consumption coagulopathy. As an expected response to the acute anemia she developed severe tachycardia. tachypnea, and a wide pulse pressure, and she died 6 hours after receiving cefotetan.

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2. Why was auto-control, performed with the antibody detection test, positive? Transfusion was delayed because of concern over this finding. Would your laboratory have delayed transfusion because of this result and the positive DAT with a negative eluate? Does your laboratory perform an autocontrol with the antibody screen?

The initial test results performed at the hospital were unremarkable except for the positive auto-control. Since this test is an IAT performed with patient serum or plasma and patient RBCs, it is generally positive whenever the patient's DAT is positive. A positive DAT was confirmed by the hospital laboratory, which demonstrated IgG coating the RBCs, and by the blood center reference laboratory which showed that complement was coating the RBCs as well. In one report of 43 cases of cefotetan-dependant antibodies, all patients had IgG on their RBCs and 37 (86%) had detectable complement binding as well. (Arndt, Leger, and Garratty, Transfusion 1999).

A positive DAT is a common, incidental finding in hospitalized patients and would not have been a reason for delaying transfusion once the eluate was prepared and tested. Typically, preparation of an eluate from the RBCs of patients and donors with an incidental finding of a positive DAT yields a clinically insignificant, warm-reactive autoantibody. One would expect the combination seen in this patient, namely a positive DAT with a non-reactive eluate, to be the typical finding in DIIHA since eluates are only investigated for presence of a DDA when the diagnosis is suspected. In fact it is not rare for there to be a transient pan-agglutinin (antibody reactive with all RBC samples in the absence of added drug) in cases of DIIHA (Johnson, Fueger, and Gottschall, Transfusion 2007; Ahrens et al, Am J Hematol 2006) as illustrated in the accompanying case "Hemolysis after Chemotherapy".

Many laboratories have stopped performing an autocontrol in routine pre-transfusion testing. A study in our laboratory (Perkins et al, Transfusion 1990) looked at 56,090 patient pre-transfusion test cases performed over 56 months in which an autocontrol was performed. In 902 cases (1.6%) the autocontrol was positive with a negative antibody screen as in this case, prompting a complete investigation including testing of the serum with enzyme-treated RBCs in 684. Investigation yielded nothing or only a cold-reactive autoantibody in 457 cases and a warm-reactive autoantibody in 131. Only 17 of the investigations (10 patients) led to identification of a potentially hemolytic alloantibody, 9 of which reacted only with enzyme-treated RBCs. The overall yield of potentially hemolytic antibodies on first workup was 8 cases, most of which would have experienced only a delayed hemolytic reaction based on the weak nature of the antibody. Thus the autocontrol generated a large amount of effort (902 investigations) but relatively few marginally improved transfusion outcomes. Because of this relatively low yield we stopped doing the test routinely as part of the antibody detection test.

Ironically, had the autocontrol not been performed a compatibility problem would not have suspected, and this patient might simply have been transfused early in her course without incident. Unfortunately, it appears that once the positive DAT was detected the complete differential diagnosis of this finding was not considered, and DIIHA was never suspected.

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3. The patient first noted symptoms 11 days after treatment with cefotetan, in spite of the fact that the plasma half-life of cefotetan is 3 to 5 hours. How could this happen?

   Delayed hemolysis after cefotetan given as prophylaxis for surgical infections is, in fact, a common occurrence among cases of DIIHA, constituting 10 of 43 DDA cases (35 cefotetan-dependent) encountered over 8 years by one prominent laboratory (Garratty, Leger, and Arndt, Am J Obstet Gynecol 1999). In the 8 cases reported in detail the patients presented with hemolysis 9 to 16 days after discharge. Seven had received only 1 or 2 doses of the drug, and all were DAT-positive/eluate-negative. Presumably the drug binds to the RBCs in vivo and continues to circulate bound to the RBCs as the primary or secondary immune response occurs directed against the drug-membrane complex. In fact, Davenport and coworkers (Transfusion, 2004) demonstrated that cefotetan can be detected bound to RBCs for weeks after administration.

4. Why did the antibody detection test and crossmatch results change from negative to positive after the patient received cefotetan?

   All of the indirect antiglobulin tests were positive which used patient blood specimens drawn after the 2 gm dose of cefotetan, including reactions with the 3 screening cells and with 6 donor RBC samples. Soon after administration one would expect there to be a small amount of cefotetan in the patient's blood samples. This appears to have been sufficient to mediate binding of the cefotetan-dependant antibody to the RBCs. This mechanism was demonstrated in 5 cases in a recent series of 71 patients with DDAs (Johnson, ibid). In these cases the patients' sera were initially reactive in the IAT in the absence of added drug, but became non-reactive after the drug was dialyzed out of the specimen. Addition of drug restored the reactivity of the serum.

5. What was the root cause of this patient's death?

   Similar to the current case, 2 of the 8 patients reported by Garratty and coworkers (1999, ibid) received additional doses of cefotetan after readmission with hemolysis. In this case such repeat administration had tragic results. Had all of the causes of a positive DAT been considered, followed by a careful review of her medication history, drugs she had received before could have been avoided and her death averted. The root cause was a failure to understand the differential diagnosis of a positive direct antiglobulin test.