Acute pancreatitis associated with massive hemolysis due to a delayed hemolytic transfusion reaction

We present the following case report of acute pancreatitis following a delayed hemolytic transfusion reaction (DHTR) with massive hemolysis to raise the possibility that these events are causally related.

A 77-year-old man was transfused with 5 units of red blood cells (RBCs) for a bilateral total knee replacement. He received 1 unit of autologous RBCs and 1 unit of allogeneic RBCs during surgery and three additional units of allogeneic RBCs on Postoperative Days 1 and 2. The transfused RBCs were E– because anti-E was detected in the pretransfusion blood sample. This blood sample was used also to cross-match the 4 units of allogeneic RBCs. The patient had received 2 units of blood after a prostatectomy 20 years ago, but he was not aware of other prior transfusions. There was no history of pancreatitis. His medications included atenolol (50 mg/day), nifedipine (30 mg/day), and hydrochlorothiazide (25 mg/day). On Postoperative Day 4, he was transferred to a rehabilitation hospital and started on coumadin for deep vein thrombosis prophylaxis. On Postoperative Day 5, his hematocrit (Hct) level was 30.5 percent. On Postoperative Day 7, he experienced abdominal pain and nausea and could not take his oral medications. His urine output decreased and darkened in color, and 100 RBCs per high-power field were reported in the sediment. The INR was 3.79 and coumadin was held. On Postoperative Day 9, he was weak and jaundiced, and his Hct level was 20.8 percent.

On Postoperative Day 10, he was transferred to our hospital, where his Hct level was 19.8 percent and the reticulocyte count was 9.2 percent. An antibody screen revealed anti-E, -c, -M, and -Jk^a in his plasma and circulating RBCs were negative for the corresponding antigens. The direct antiglobulin test was negative. Segments of the transfused RBC units were retrieved and revealed each of the 4 units of allogeneic units of RBCs was mismatched with at least one of the newly formed alloantibodies. We determined that the patient had experienced DHTR involving all four RBC units (estimated 800 mL of RBCs). Other pertinent laboratory tests on Postoperative Day 10 included direct and indirect bilirubin (0.7 and 1.6 mg/dL), lactate dehydrogenase (1175 U/L), haptoglobin (undetectable), and bilirubinuria. The D-dimer test was positive, but fibrin degradation products were not increased. Prothrombin time and INR were increased; antithrombin III level was 72 percent. Serum amylase and lipase levels were elevated and decreased during the subsequent 3 weeks (Table 1). A presumptive diagnosis of pancreatitis was confirmed by endosonography, which showed hyperechoic stranding of the entire pancreas, as well as parenchymal abnormalities in the uncinate process. Computerized tomography of the abdomen was technically unsatisfactory for evaluating the pancreas. No gallstones or pancreas divisum were detected. A special magnetic resonance imaging procedure to visualize pancreatic, hepatic, and biliary ducts revealed that they were of normal caliber and without stones. The test for pancreatic cancer antigen (CA 19-9) was negative. Other potential causes of pancreatitis, including alcohol abuse, hypertriglyceridemia, and hypercalcemia were excluded. The patient typically drank two beers per week, serum levels of triglycerides ranged from 41 to 63 mg/dL, and serum calcium was normal (8.1 mg/dL). Because the patient had been on long-term hydrochlorothiazide for arterial hypertension, we doubt that it was the cause of acute pancreatitis. Severe pancreatitis has been reported as a complication of mechanical hemolysis during hemodialysis.[1-3] In a retrospective study, acute pancreatitis was present in 25 percent of patients with severe hemolysis caused by microangiopathic hemolytic anemia, toxemia, glucose-6-phosphate dehydrogenase deficiency, septic abortion, malaria, Wilson disease, hypophosphatemia, or autoimmune hemolytic anemia (AIHA).[4] Acute pancreatitis was also documented in a case report of AIHA.[5] Pancreatitis and acute chest syndrome were reported in one of seven children with sickle cell disease (SCD), DHTR, and hyperhemolysis syndrome.[6] We could not find reports of acute pancreatitis in other children or adults with SCD and a DHTR. Animal models have also demonstrated hemolysis as a cause of pancreatitis.[7] Proinflammatory and immunoregulatory cytokines during hemolysis were suggested as causative factors[7] as well as heme-induced neutrophil activation, chemoattraction, and disturbance in microcirculation.[8] Cytokines and chemokines are increased during hemolytic transfusion reactions.[9]

In summary, the patient described in this report experienced massive hemolysis (4 units of RBCs) during a DHTR. Although we cannot determine the precise time of onset of hemolysis, no allogeneic RBCs were detectable 7 to 9 days after transfusions. Symptoms of pancreatitis started between 6 and 8 days after transfusions. The patient recovered slowly, but completely. This experience, together with other published case reports of pancreatitis associated with hemolysis, causes us to suggest that acute pancreatitis may be an unrecognized, but important, complication of hemolytic transfusion reactions.

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TABLE 1. Serum amylase and lipase concentrations in a patient with a DHTR

Days after transfusions	Amylase (U/L)*	Lipase (U/L)†
11	468	604
14	285	352
19	160	145
21	128	ND‡
92	92	43

* Normal values, 25 to 125 U/L.
† Normal values, 0 to 50 U/L.
‡ ND = not done.

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Dry-heat sensitivity of human B19 and porcine parvoviruses

Guidelines to support marketing[1] and clinical studies[2] of fibrin sealant products require manufacturers to demonstrate effective steps for inactivation and/or removal of clinically significant nonenveloped viruses in the manufacturing process, such as hepatitis A and parvovirus B19 (B19). Until recently, a lack of suitable cultured cells for titration of B19 infectivity precluded investigation of B19 in clearance studies. For this reason, porcine parvovirus (PPV) and minute virus of mice (MVM) were often used as models for B19. When B19-permissive cultured cells became available, the susceptibilities of B19 and model viruses were compared in wet-heat and low-pH studies. Blümel[3] and Boschetti[4] with colleagues found that B19 is less resistant than PPV and MVM because of considerable differences between viral capsids.

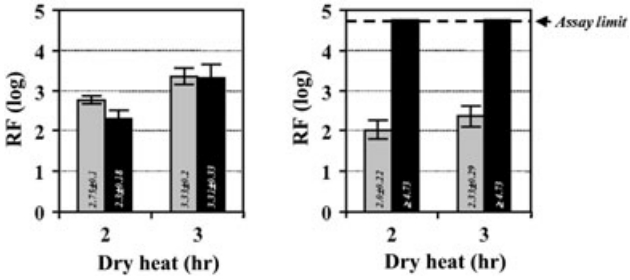

Fig. 1. Effect of 100°C dry-heat process on infectivity of fibrinogen spiked with PPV (▨) and B19 (■) and lyophilized. (Left) 0.5 to 0.7 percent moisture; (right) 1.3 to 1.7 percent moisture. B19 inactivation data are from Prikhod'ko and coworkers.[5] Each data point represents the results of at least two independent experiments, and error bars indicate the standard deviations. RF = reduction factor.

To investigate whether PPV and B19 respond differently to dry-heat treatment, fibrinogen was spiked with PPV, lyophilized under controlled moisture conditions, and then heated at 100°C in a side-by-side experiment with B19 as described earlier in dry-heat inactivation studies of B19.[5] The residual moisture of lyophilized samples was 0.5 or 1.3 percent increasing up to 0.7 and 1.7 percent, respectively, after dry heating for 3 hours. PPV samples were analyzed with endpoint titrations on PK13 cells.

In line with reports about B19 inactivation by pasteurization, the resistance of B19 to dry heat was significantly less than PPV at 1.3 to 1.7 percent residual moisture (Fig. 1). Dry heat inactivated at least 4.73 log of B19 and 2.0 ± 0.22 and 2.33 ± 0.29 log of PPV after 2 and 3 hours, respectively. At 0.5 to 0.7 percent residual moisture of fibrinogen, however, both viruses exhibited similar resistance. The virus reduction factors were 2.75 ± 0.1 and 3.33 ± 0.2 log for PPV and 2.3 ± 0.18 and 3.31 ± 0.33 log for B19 after 2 and 3 hours of dry-heat treatment, respectively.

Our findings suggest that PPV is more resistant to dry heat than B19 and that low moisture may stabilize B19 but not PPV against heat. Also, these findings underline the fact that PPV is a useful model for B19.

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