Abdominal Pain and Massive Intravascular Hemolysis in a 47-Year-Old Man*

Kwan C. Pun, MD; John H. Wehner, MD, FCCP

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One week prior to admission to the hospital, a previously healthy 47-year-old man was seen by a personal physician for epigastric pain. He was treated with acetaminophen and an antacid, which resulted in mild improvement. Over the next few days, however, he developed chills and rigors. On the morning of admission, he was difficult to arouse and was therefore brought to the emergency department.

Physical Examination

Vital signs: axillary temperature, 38.1°C; pulse, 129 beats per minute; respiratory rate, 44 breaths per minute; BP, 80/50 mm Hg. General: acutely ill, obtunded. Skin: jaundiced. Cardiovascular: tachycardic without murmurs or gallop. Abdomen: no bowel sounds or hepatosplenomegaly; mild right upper quadrant tenderness without rebound. Extremities: cyanotic nail beds. Rectal: Almén’s test for blood (guaiac), negative. Neurologic: obtunded, withdrew to painful stimuli, otherwise nonfocal.

Laboratory Findings

Values included the following: hematocrit, 5%; WBC count, 43,600/mm³ with 31% neutrophils, 53% band cells; platelet count, 20,000/mm³; D-dimers, 2.0 (normal, <0.5 FEU); fibrin split products, 15 mg/mL (normal, <10 mg/mL); prothrombin time, INR, 2.4; partial thromboplastin time, 76 s (normal, 23 to 36 s). Room air/arterial blood gas values revealed a pH of 7.27; PaCO₂, 26 mm Hg; PaO₂, 58 mm Hg; calculated HCO₃, 12 mmol/L; Na⁺, 125 mmol/L; K⁺, 7.8 mmol/L; and Cl⁻, 90 mmol/L. All blood specimens were hemolyzed and the serum appeared exceptionally bright red, which was consistent with marked hemoglobinemia. The plasma hemoglobin level was 5.2 g/dL. Both direct and indirect Coombs’ tests were negative. Due to the massive hemolysis, valid RBC indices could not be determined. Furthermore, the hemolysis interfered with photometric assays in determining the serum BUN, creatinine, and bilirubin values as well as valid aspartate aminotransferase and lactate dehydrogenase levels. The peripheral blood smear revealed numerous spherocytes with little evidence for microangiopathy, and there were no malarial parasites seen.

A chest radiograph showed that the right side of the diaphragm was elevated. A supine abdominal x-ray film (Fig 1) revealed a mottled gas pattern (black arrows) in the right upper quadrant without free air. A right upper quadrant ultrasound study showed a normal-appearing gallbladder wall, an echogenic stone (<5.0 mm) within the gallbladder, and no dilated ducts.

Hospital Course

The patient rapidly deteriorated and required mechanical ventilation. He was transfused type O packed RBC, fresh frozen plasma, and platelets and also received 4 million units of penicillin G, intravenously, followed by ampicillin, gentamycin, and metronidazole. Despite aggressive fluid resuscitation and maximal doses of vasoactive drugs, the patient’s hypotension and metabolic acidosis continued to worsen, and anuric renal failure ensued. Emergency hemodialysis was initiated to correct progressive hyperkalemia and acidosis. The patient subsequently died 22 h after hospital admission.

What is the probable diagnosis?
Diagnosis: Clostridium perfringens septicemia with massive intravascular hemolysis.

The clinical association of *C. perfringens* bacteremia with massive intravascular hemolysis has been described since 1949. In this syndrome, the peripheral blood smear characteristically demonstrates marked spherocytosis with little evidence of microangiopathy. Alpha toxin, one of the many exotoxins produced by Clostridium, is an enzyme that splits lecithin to phosphocholine and diglyceride, causing interference with the functional integrity of RBC membranes. This mechanism is postulated to account for the development of spherocytosis and subsequent hemolysis.

Clostridia are organisms found in the soil, the gastrointestinal tract, and the vagina. Because of its ubiquity, early reports have suggested that 50% of clostridial isolates from blood cultures may be contaminants. Investigators have postulated that *C. perfringens* may cause transient bacteremia without significant exotoxin production to cause hemolysis or hemodynamic instability. Individuals especially susceptible to severe clostridial infection include the elderly, diabetic patients, men, patients with hepatobiliary disease and other bowel disease, and patients with other underlying conditions such as leukemia or colon carcinoma.

There are only a few known infectious and noninfectious diseases that can cause massive intravascular hemolysis. Rarely, infections such as malaria, bartonellosis, babesiosis, and adult hemolytic uremic syndrome (HUS) associated with bacterial infections can cause severe intravascular hemolysis. Other noninfectious causes of severe intravascular hemolysis include incompatible blood transfusions, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria (PCH), hemolysis due to lysins such as snake venoms, and extensive acute burns.

Malaria can present with hemolytic anemia during parasitic invasion of RBCs. It presents as a chronic relapsing disorder associated with mild to moderate hemolytic anemia. A severe form of intravascular hemolysis can occur as a rare complication of *Plasmodium falciparum* malaria. Diagnosis depends on demonstration of characteristic malarial forms on the peripheral blood smear.

The most prominent manifestation of bartonellosis is Oroya fever, characterized by high fever, myalgia, arthralgia, and hemolytic anemia that can progress to delirium and coma. Death can occur within days to weeks in untreated patients. During the Oroya fever, the organism can be easily seen in the peripheral blood smear. In addition, blood cultures can recover the organisms during all stages of the disease.

Babesiosis manifests as an acute febrile illness with hemolytic anemia. Patients present with high fever, hemoglobinuria, jaundice, and renal failure. The disease usually is self-limited except in asplenic individuals for whom it may be fatal. Differentiation from *C. perfringens* sepsis can be made by demonstration of the intraerythrocytic parasite in a peripheral blood smear. Alternatively, a diagnosis of babesiosis can be made via an indirect fluorescent antibody test or enzyme-linked immunosorbent assay.

HUS is another disorder that can be associated with acute renal failure, thrombocytopenia, and hemolysis. Patients often complain of acute headache with a sudden onset of thrombocytopenia. It is occasionally associated with infections such as *Escherichia coli* 0157:H7, Streptococcus, and Shigella. Patients with HUS will have typical histologic findings in the kidney with fibrin deposits and intimal hyperplasia in the affected arterioles and glomerular capillaries. Additionally, the blood smear will almost always demonstrate microangiopathy. Unlike *C. perfringens* toxemia, HUS is potentially treatable with dialysis and blood transfusions.

Patients with paroxysmal nocturnal hemoglobinuria usually present with venous thrombosis with variable degrees of anemia. Episodes of hemolysis tend to be recurrent and chronic with manifestation of hemoglobinuria. The diagnosis of paroxysmal nocturnal hemoglobinuria is made by a positive acid hemolysis (Ham's) test in which RBCs demonstrate increased sensitivity to complement lysis as a consequence of the deficient expression of surface proteins (CD55) normally attached to RBC membranes.

PCH can also cause intravascular hemolysis due to an autoimmune mechanism initiated by viral infections and precipitated by low temperatures. Attacks are characterized by intravascular hemolysis; fever and chills; back, leg, and abdominal pain; headache; and malaise. Patients may be asymptomatic between attacks. PCH can be differentiated from *C. perfringens* sepsis by the detection of anti-RBC antibodies in the biphasic Donath-Landsteiner test. Autoantibodies, IgG, are detected at low temperatures when they attach to the RBC P-antigen and cause complement fixation. When the RBCs are warmed, they are intravascularly lysed by complement.

The treatment of choice for *C. perfringens* bacteremia is intravenously administered penicillin G in doses of 10 to 24 million units daily. Most of the treatment recommendations are based on animal models and retrospective studies of patients with gas gangrene caused by *C. perfringens*. In animal and *in vivo* studies, the combination of penicillin and clindamycin has better efficacy than penicillin alone in the suppression of toxin synthesis. Alternatively, *in vitro* studies have also shown chloramphenicol to be effective against all species of Clostridia. Clostridial infection is often associated with other bacterial infections. Thus, broad-
Spectrum antibiotic coverage should be added empirically based on the clinical setting. Surgical debridement of all involved gangrenous tissue is crucial in preventing propagation of the organism and its subsequent exotoxin production. The mortality rate of *C. perfringens* sepsis ranges from 70 to 100%. As stated by Dr. Sherwood Gorbach regarding clostridial myonecrosis, “This is a disease that begins where other diseases end, with death,” (see *N Engl J Med* 1979; 301[23]:1276-81)

In our patient, *E. coli* and *C. perfringens* grew from all of the four blood cultures over the period of the subsequent 24 and 48 h, respectively. The *E. coli* bacteremia could have potentially contributed to the overall hemolysis. However, the degree of hemoglobinemia and anemia seen with this patient is rarely seen in *E. coli* sepsis. An autopsy revealed acute gangrenous cholecystitis and calculi within the common bile duct. The presence of gas-forming organisms in this setting is diagnostic of emphysematous cholecystitis. The right upper quadrant mottled gas pattern may represent gas within the gallbladder lumen, colon, or duodenal bulb. In approximately 58% of patients with gangrenous cholecystitis, sonography may demonstrate asymmetric wall thickening, intraluminal membranes, and striated wall edema. Acoustical shadows conforming to the shape of the gallbladder (gas produced within the gallbladder) may suggest acute emphysematous cholecystitis. In patients with nondiagnostic plain radiographs or sonography, CT may establish the diagnosis. Emergency cholecystectomy is the treatment of choice. Unfortunately, our patient presented late with irreversible septic shock, refractory massive intravascular hemolysis, and anuric renal failure complicated by progressive hyperkalemia. Although surgical intervention was considered, the patient’s condition never stabilized to the point that he could tolerate general anesthesia.

**Clinical Pearls**

1. *C. perfringens* sepsis is associated with massive intravascular hemolysis characterized by significant spherocytosis with little evidence of microangiopathy.
2. In the setting of biliary tract disease or presentation of acute abdominal pain with hemolysis, a high index of suspicion for *C. perfringens* sepsis is necessary.
3. In the appropriate clinical setting, rapid empiric therapy with high-dose penicillin G or clindamycin or both should be started.

4. Sonographic features suggesting gangrenous cholecystitis include asymmetric wall thickening, intraluminal membranes, and striated wall edema, while acoustical shadows conforming to the shape of the gallbladder may suggest emphysematous cholecystitis.

5. CT may establish a diagnosis of emphysematous cholecystitis when plain radiographs and sonography are nondiagnostic.

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**Suggested Readings**


