Elmer Press

Case Report J Hematol. 2017;6(2-3):59-61

Toxic Hemolysis in a Young Healthy Female

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Abstract

Clostridium perfringes is a gram-positive, rod-shaped, anerobic, spore-forming pathogenic bacterium. *C. perfringes* is commonly known to cause tissue necrosis and gas gangrene. However, severe life-threatening complications like hemolysis due to clostridium sepsis are rarely encountered. We present a case of a 35-year-old female presenting with endometritis complicated with severe hemolysis in the setting of sepsis secondary to *C. perfringes*. Her hospital course was complicated with multi-organ involvement, requiring broad-spectrum intravenous antibiotics. Eventually, she made an uneventful recovery by early recognition of these rare complications and prompt institution of appropriate therapy.

Keywords: *Clostridium perfringes*; Hemolysis; Toxic hemolysis

Introduction

Clostridium is a gram-positive, anerobic rod that is a normal commensal in the gastrointestinal and genitourinary tract. Of blood cultures, 0.5-2% from septic patients are due to clostridium and amongst that 20-50% are due to *Clostridium perfringes* [1]. Clostridial sepsis can rarely produce life-threatening hemolysis. This can be reversed by rapid diagnosis and treatment. Unfortunately, this is often missed as it is not commonly seen. We present one such case from *C. perfringes* endometritis with severe hemolysis to increase awareness regarding the same and improve outcomes.

Case Report

A 35-year-old Caucasian female with past medical history of fibromyalgia presented to an outside hospital with abdominal pain, nausea and vomiting. She had a tubal ligation and intrauterine device removal done the previous day. Her labs were significant for ALT 375 U/L, AST 360 U/L and hyperbilirubinemia (total bilirubin of 16 mg/dL). She subsequently was transferred to our facility for further care. On presentation, her temperature was 38 °C, blood pressure was 121/80 mm Hg, heart rate was 86/min and SpO_2 was 96%. Physical exam was significant for scleral icterus and epigastric tenderness. There was no rigidity, guarding or organomegaly. Labs showed blood urea nitrogen of 48 mg/dL, creatinine of 4.0 mg/dL, total bilirubin of 14.5 mg/dL, direct bilirubin of 4.6 mg/dL, AST of 335 U/L, ALT of 313 U/L, Hb of 10.1 g/dL, platelet count of 117,000/µL, lactate dehydrogenase of 1,910 U/L, haptoglobin of 14.7 mg/dL, and an absolute reticulocyte count of 162,000/µL. Uric acid showed frank blood and was positive for many white blood cells, bacteria, large leukocyte esterase and granular casts. Blood and urine cultures were sent. After initial supportive care with intravenous fluids and broad-spectrum antibiotics (vancomycin/piperacillin-tazobactam) and blood transfusion, a abdomen/pelvis CT was performed. It revealed extensive gas within the endometrium raising suspicion for endometritis. There was no evidence of hydronephrosis ruling out any obstruction. Transvaginal ultrasound showed increased echogenicity in the endometrium, raising concern for endometritis. Blood cultures returned positive for *C. perfringes*. Disseminated intravascular coagulation panel was negative and there was no evidence of schistocytes in the peripheral smear, ruling out thrombotic microangiopathy. The direct Coombs test was also negative excluding autoimmune hemolytic anemia. Ultrasound of the liver was normal. An extensive liver disease panel including hepatitis panel, tests for autoimmune hepatitis, was negative. Toxicology tests including levels for acetaminophen, cadmium, and mercury were all negative. Urine electrolytes showed FeNa to be less than 1.5%, thus pointing toward a pre-renal acute kidney injury (AKI). Thus, after an extensive workup, she was diagnosed with sepsis due to *C. perfringes* endometritis with massive hemolysis, AKI due to sepsis-induced acute tubular necrosis and liver dysfunction. She was aggressively hydrated and treated with ampicillin-sulbactum 3 g every 6 h for 7 days. Patient began to improve clinically. Patient was discharged to finish a 3-week course of amoxicillin-clavulanate. On discharge, all her lab parameters were improved: creatinine decreased to 1.4 mg/dL, total bilirubin 1.2 mg/dL, AST 42 U/L, ALT 154 U/L, LDH 620 U/L and haptoglobin 120.9 mg/dL.

Discussion

C. perfringes can be divided into five types A, B, C, D, and

Manuscript submitted April 29, 2017, accepted May 30, 2017

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doi: https://doi.org/10.14740/jh328w

E according to the type of exotoxin they produce [1]. In one study with 40 patients, massive intravascular hemolysis was found to occur in 7-15% of *C. perfringes* septicemias [2], whereas in another case series involving 33 patients, the incidence was 3% [1]. In both the case series, the mortality rate was extremely high ranging from 70% to 80% [1, 2].

The hemolysis is said to be mediated by the alpha toxin. It is a phospholipase consisting of C-domain and N-domain [3]. C-domain of the toxin inserts into the membrane and the N-domain hydrolyses the membrane lecithin into phosphocholine and diglycerine, disrupting the structural framework of the red blood cell (RBC) membrane [4]. This makes RBCs lose their biconcave shape and they assume the morphology of spherocytes, which ultimately get hemolyzed due to shearing stress [4]. Another component that could contribute to the hemolysis is neuraminidase. Neuraminidase can expose the cryptic T antigen present on the surface of RBC, enabling the anti-T antibodies present in serum to bind with the T antigen resulting in hemolysis [5].

In a review of the cases series of clostridium-induced hemolysis, median age of diagnosis was 65, with majority being males (55%). Diabetes and malignancy were major predisposing factors [2]. Focus of infection in majority of cases was hepatobiliary (45%), followed by intestinal/stomach (17.5%) and uterine after an invasive procedure (10%) [2]. Unlike the case series, our patient was a young female with no predisposing comorbidities.

Differential diagnosis

Differential diagnosis of the intravascular hemolysis includes infectious and non-infectious causes. Infectious causes include malaria, babesiosis, brucellosis, and hemolytic uremic syndrome (HUS) [4]. This patient did not have any travel history, history of mosquito bites, or other clinical features to suggest above causes. Absence of schistocytes in the peripheral smear ruled out thrombotic microangiopathy. Other non-infectious causes can be paroxysmal nocturnal hemoglobinuria, incompatible blood transfusions, or hemolysis due to burns and snake venom [4].

Diagnosis

Prompt diagnosis and treatment can reduce the high mortality rates. Gram stain with blood cultures, peripheral smear showing spherocytes, and imaging showing gas formation in the tissues can all aid in diagnosis. PCR also aids in diagnosis by identifying genes encoding toxin [1]. This can be helpful when bacterial load is low. In one study PLC enzyme activity was used to aid in diagnosis [6].

Treatment

Prompt surgical debridement and treatment with aqueous penicillin in doses 20 - 30 million units per day is recommended. Usually a second antibiotic such as clindamycin or gentamicin is added, since these infections could be polymicrobial [7]. Other supportive measures such as blood transfusion, correction of electrolytes, hemodialysis in renal failure, and parenteral nutrition help in recovery [7]. In our patient, surgical debridement was deemed unnecessary. The need for hysterectomy in the presence of gas in the uterine cavity is controversial, some studies have recommended hysterectomy [8], whereas some studies recommend against hysterectomy in absence of hemolysis [9]. Other possible treatment options include exchange transfusion and hyperbaric oxygen therapy [9]. Plasma free hemoglobin for maintaining tissue oxygenation in the event of massive hemolysis has also been recommended [10].

Outcomes

Median time between admission and death was found to be 8 h in one study [2], emphasizing importance of prompt detection and early treatment, in the emergency room itself. Patients without evidence of hemolysis have better long-term outcomes [2, 9]. Survival is better if there is early drainage/debridement of focus of infection [2]. Our patient responded very well to treatment and had complete resolution of her infection and hemolysis due to timely diagnosis and intervention.

Conclusion

In septic patients with fever and hemolysis, *C. perfringes* infection should be on the differential since prompt diagnosis and treatment can prevent fatalities.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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