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CLINICAL VIGNETTE

Protein-losing Enteropathy and Ascites Associated with Clostridium difficile Infection in a Peripartum Woman

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Clostridium difficile causes antibiotic-associated colitis and is one of the most common healthcare-associated infections. The cardinal symptom of C. difficile infection is watery diarrhea but abdominal pain, fever, and leukocytosis are also common in severe cases. C. difficile infection typically follows recent antibiotic exposure and virtually all antibiotics can predispose to C. difficile. Protein-losing enteropathy (PLE) with hypoalbuminemia and ascites is an unusual manifestation of C. difficile due to inflammation of the bowel wall and leakage of albumin into the colonic lumen. Treatment involves antibiotics directed against C. difficile and supportive care. Physicians should maintain a high suspicion for C. difficile in any patient presenting with a diarrheal illness who has been exposed to antibiotics as prompt clinical recognition and timely treatment are key. We present a case of severe C. difficile colitis that occurred in a peripartum woman and was complicated by protein-losing enteropathy, ascites and pleural effusions.

Case Report

A 36-year-old female was admitted to the hospital with profuse watery diarrhea, abdominal pain, fever, and nausea and vomiting. Past medical history was significant for an emergent cesarean section for arrested dilation complicated by hemorrhage and uterine inversion 2.5 weeks prior to admission. She received IV cefazolin preoperatively. She recovered without complication and was discharged home. However, she developed abdominal pain a week after discharge. Pelvic ultrasound done by her Obstetrician was benign and she was referred to Gastroenterology for possible gastritis. She presented to the emergency department (ED) the following day with worsening pain and diarrhea thought to be acute gastroenteritis and sent home. Three days later, she returned to the ED with severe abdominal pain, profuse watery diarrhea, fever of 101° F, nausea and vomiting and was admitted to the hospital. There were no sick contacts, no recent travel or exposures to possible contaminated food sources and no family history of inflammatory bowel disease. Home medications included routine post-partum medications as well as placenta capsules and over the counter loperamide.

Vital signs showed blood pressure 123/75 mm Hg, heart rate 119 beats/min, respiratory rate 18/min, temperature 98.6 °F (after taking acetaminophen for a home temperature of 101 F) and oxygen saturation 98% on room air. Physical exam was remarkable for diffuse abdominal tenderness. Laboratory evaluation showed white blood cell count of 16,000 cells/uL, hemoglobin 12.6 g/dL, platelets 586,000/uL, sodium 134 mEq/L, albumin 3 g/dL. Creatinine, transaminases, amylase, and lipase were within normal limits. Computed tomography (CT) scan of the abdomen and pelvis revealed severe pancolitis without evidence of perforation or obstruction and a small amount of ascites (Figures 1 and 2). Aggressive hydration along with empiric levofloxacin and metronidazole were given and stool studies were collected. Over the next 24 hours, the patient developed worsening abdominal distension and pain with tenderness consistent with peritonitis. Lab testing showed worsening leukocytosis to a peak of 55, 400 cells/uL, decreasing sodium to 125 mEq/L and albumin to 2.2 g/dL. Stool studies were positive for C. difficle. Levofloxacin was discontinued and oral vancomycin was added to metronidazole for severe C. difficile infection. Repeat CT scan of the abdomen and pelvis two days later showed diffuse, severe pancolitis from rectum to cecum with significant interval increase in ascites and small pleural effusions but no evidence of toxic megacolon or perforation (Figures 3 and 4). Gastroenterology and General Surgery were consulted and recommended continued antibiotic treatment of C. difficile and supportive care. Echocardiogram revealed a normal ejection fraction and systolic function.

There was no evidence of liver, renal or heart failure to explain the patient's ascites and pleural effusions, so the diagnosis of protein-losing enteropathy (PLE) was considered and confirmed by the finding of fecal α_1-antitrypsin. Of note, the patient's placenta pills

were tested and were negative for contamination with C. difficile. The patient underwent both paracentesis and thoracentesis for symptomatic ascites and pleural effusions. There was no evidence of infection in the ascitic or pleural fluid. Over the next several days, the patient's diarrhea and abdominal pain resolved, her oral intake improved, and she was subsequently discharged home on a long taper of oral metronidazole and oral vancomyocin and made a full recovery. The final diagnosis was severe antibiotic-associated C. difficile colitis associated with PLE and ascites.

Discussion

C. difficile colitis is a common healthcare-associated infection related to recent antibiotic exposure. It is increasing in incidence and possible severity due to more virulent strains of C. difficile[1]. Risk factors, presenting symptoms and treatment are well established. Peripartum women are a specific population that are frequently exposed to antibiotics in the hospital around the time of delivery and are at risk for C. difficile infections. It is also important to highlight that PLE associated with ascites can also be a rare manifestation of severe C. difficile infections.

Well-described risk factors for developing C. difficile colitis included antibiotic exposure, prolonged hospitalization, presence of comorbidities, use of proton pump inhibitors, gastrointestinal surgery, and advanced age[2]. Peripartum women, who are defined as women four weeks before and after delivery, are another group of patients at risk for C. difficile infection[2,3]. Risk factors for peripartum women are similar to general population. Also decreased immunity associated with pregnancy increases risk of infection. However, the major risk factor for peripartum women to develop C. difficle colitis appears to be exposure to prophylactic and therapeutic antibiotics[3].

Prophylactic antibiotics are given to peripartum women to decrease the risk of maternal and neonatal infections. Antibiotics are administered at the time of delivery to women who test positive for Group B Streptococcus during the 35-37th weeks of pregnancy in order to reduce the risk of transmission and possible infection in the infant. Prophylactic antibiotics are also routinely given to decrease risk of perioperative infection associated with cesarean sections, as well as for preterm premature rupture of membranes. Therapeutic antibiotics are given for peripartum infections, including chorioamnionitis, endomyometritis, and mastitis. Regardless of the indication, the use of any antibiotic disrupts the normal bacterial flora of the gut and increases the risk of C. difficile infection. While all antibiotics can cause increased risk of C. difficile, more offensive antibiotics include clindamycin, ampicillin, and gentamicin[2,3]. These antibiotics are frequently used in obstetric medicine given their broad antimicrobial coverage.

Clinical manifestations of C. difficile infection include watery diarrhea and other associated symptoms depending on severity. In a report of an outbreak of C. difficile in peripartum women in one hospital, diarrhea was present in all peripartum women with C. difficile infection. Additional signs and symptoms on presentation can vary and include fever, leukocytosis and acute renal failure[3]. Severe C. difficile infection is considered to be present if a patient has a severity score of 2 points or greater. One point each is given for an age older than 60, temperature of > 38.3°C, albumin level of <2.5 mg/dL, and a WBC count of >15,000 cells/mm^3; two points are given for hospitalization in the intensive care unit.[1] Others factors suggesting severe disease include the presence of comorbidities or immunodeficiency, systemic inflammatory response syndrome (SIRS), organ failure, hypoalbuminemia, pancolitis, ileus, toxic megacolon, or intestinal perforation.[2] Treatment recommendations often differ when severe disease is present[1].

Uncommon associated manifestations of C. difficile infection can include peritonitis and protein losing enteropathy leading to ascites. Peritonitis is a known, albeit rare, complication of C. difficile infection. The presence of peritonitis necessitates evaluation for worsening of disease to colonic perforation or toxic megacolon[2]. PLE is also a rare complication of C. difficile infection[4-7]. PLE is a syndrome of gastrointestinal (GI) protein loss resulting from inflammation of the bowel wall that results in hypoalbuminemia and edema and can present in the form of ascites and pleural and pericardial effusions. As protein is lost in the GI tract, the liver is unable to synthesize proteins at the rate of GI loss leading to decreased intravascular oncotic pressure and third spacing of fluid[7]. Laboratory tests reveal decreased in total protein, albumin, immunoglobulins, and ceruloplasmin[4]. Diagnostic paracentesis reveals a low serum-ascites albumin gradient[4,5]. Elevated fecal α_1-antrypsin confirms the diagnosis, as α_1-antitrypsin is a protein that is not actively absorbed or secreted[4]. Management of PLE is aimed at treating the underlying disease and supporting nutritional status.

The first step in treating a patient with a suspected or confirmed C. difficile infection is to discontinue

treatment with the offending antibiotic when possible. Antiperistaltic and opiate agents should be avoided. The choice of initial antibiotic therapy depends on the severity of disease. Oral metronidazole is typically used as first-line therapy for most cases of C. difficile colitis. Oral vancomycin may be preferred if markers of severe C. difficile infection are present. The first recurrence is often treated with metronidazole but if a patient has 3 or more recurrences, they may need prolonged regimens and tapering doses of oral vancomycin[1].

In conclusion, C. difficile colitis is a common hospital-associated infection and it is important to recognize the increased risk of this infection in peripartum women. The patient we presented was exposed to cefazolin at the time of her cesarean section and subsequently developed severe C. difficile colitis as defined by the presence of SIRS, leukocytosis, hypoalbuminemia and pancolitis. C. difficile testing can take a day or two for results and empiric treatment with oral metronidazole or oral vancomycin depends on the clinical scenario and physician's judgment. PLE is a rare manifestation of C. difficile colitis and can result in ascites, hyponatremia, and pleural effusions. Antibiotic treatment of C. diffiile, nutritional support and supportive care are recommended. Our patient developed significant PLE leading to ascites and pleural effusions that required paracentesis and thoracentesis for symptom management but improved after several days of antibiotic treatment with oral vancomyocin and metronidazole. We believe that all patients presenting with acute diarrheal illnesses that have had a recent hospitalization or exposure to even one dose of antibiotics should be tested for C. difficile infection. The use of antimotility agents is controversial and should be avoided as they may be harmful and associated with worse outcomes in patients[8]. Judicious use of antibiotics by healthcare providers is key to decreasing the likelihood of this infection.

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Figures 1 and 2.
CT scan abdomen/pelvis shows marked wall thickening of the entire length of the colon with significant surrounding inflammatory change consistent with a severe pancolitis. There is a small amount of ascites within the bilateral lower quadrants and pelvis.

Figure 1

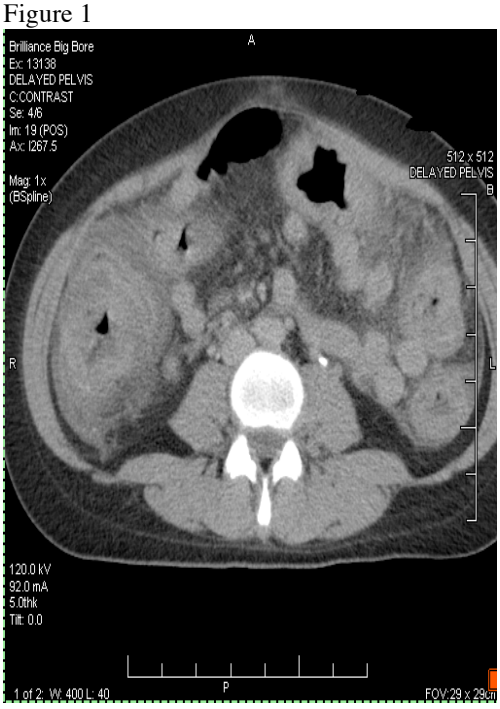


Figure 2

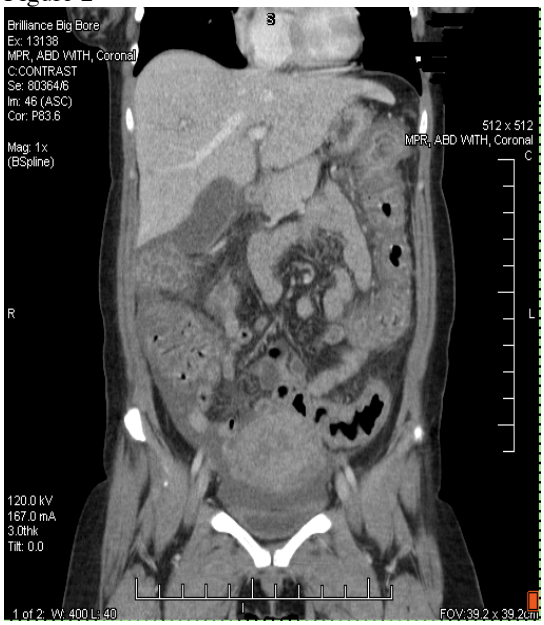
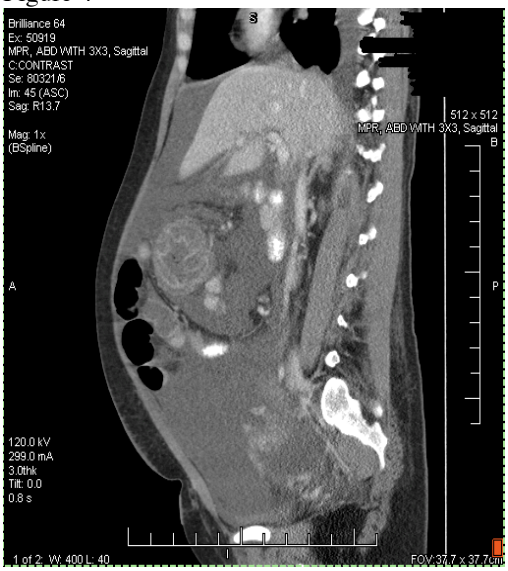


Figure 4



Figures 3 and 4.

CT scan abdomen and pelvis two days later shows diffuse, severe pancolitis from rectum to cecum with significant interval increase in the abdominal pelvic ascites and small pleural effusions.

Figure 3