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Antibiotic Associated Hemorrhagic Colitis: The Need to Distinguish from *Clostridium difficile* Colitis!

by Lekshmi Dharmarajan, R. Muthavarapu, Hilary Hertan, Marilou Corpuz

Presented is a case of bloody diarrhea developing within days of taking amoxicillin-clavulanate for sinusitis; both diarrhea and bleeding subsided completely shortly after discontinuing the antibiotic. Although *Clostridium difficile* colitis was the initial consideration, no single test confirmed the diagnosis. This report substantiates the sporadic case reports linking hemorrhagic colitis to the use of antibiotics such as amoxicillin-clavulanate and the need to differentiate the entity from *C. difficile* colitis, as treatment and prognosis differ.

INTRODUCTION

Antibiotic-associated diarrhea is common, but bloody diarrhea following antibiotic use is rare. The development of hemorrhagic colitis in any individual is frightening and demands urgent consideration of several causes in the etiology with the need to make a rapid diagnosis, as treatment differs with the etiology. The following is a description of amoxcillin-clavulanate associated bloody diarrhea, with dramatic recovery on discontinuing the antibiotic.

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THE CASE

A 55-year-old female was hospitalized with abdominal discomfort, cramps and bloody diarrhea; she used amoxicillin-clavulanate (Augmentin XR), 500 mg twice daily for five days for sinusitis. She noted diarrhea with bright blood the night before admission to the hospital. There was no fever or chills. Prior use of the standard form of amoxicillin was not associated with any side effects. Other medications included levothyroxin and atorvastatin. No other additional recent antibiotic use was evident from her history.

At admission, the patient was afebrile, blood pressure was 98/60 mmHg, pulse 74 per minute and regular. The abdomen was distended, diffusely tender, with no rebound or guarding; bowel sounds were present. Rectal examination confirmed bright red blood with stool. Remaining examination was non-contributory.

Soon after admission, the hematocrit dropped to 35.7% from a baseline value of 41; the white cell count was WBC 4.3 K/UL, Platelets 206 K/UL; electrolytes, renal and liver function tests were normal (serum creatinine 1.0). The sedimentation rate was 17 mm/hour.

Stool examination was negative for ova and parasites; three *C. difficile* assay for toxins A and B were

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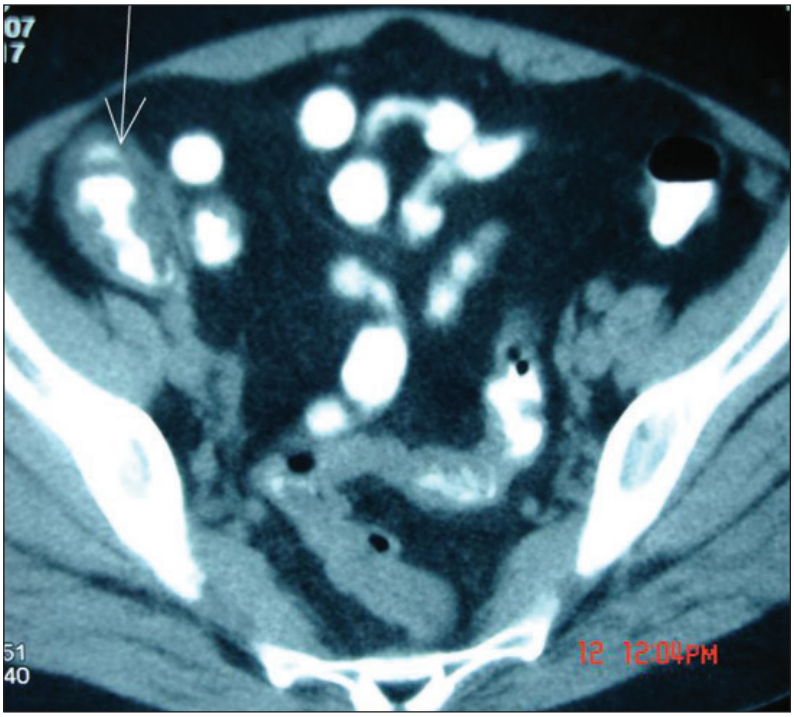

Figure 1. CT scan of the abdomen demonstrating thickening of the ascending colonic wall (arrow) with associated pericolonic stranding, suggesting a diagnosis of colitis.

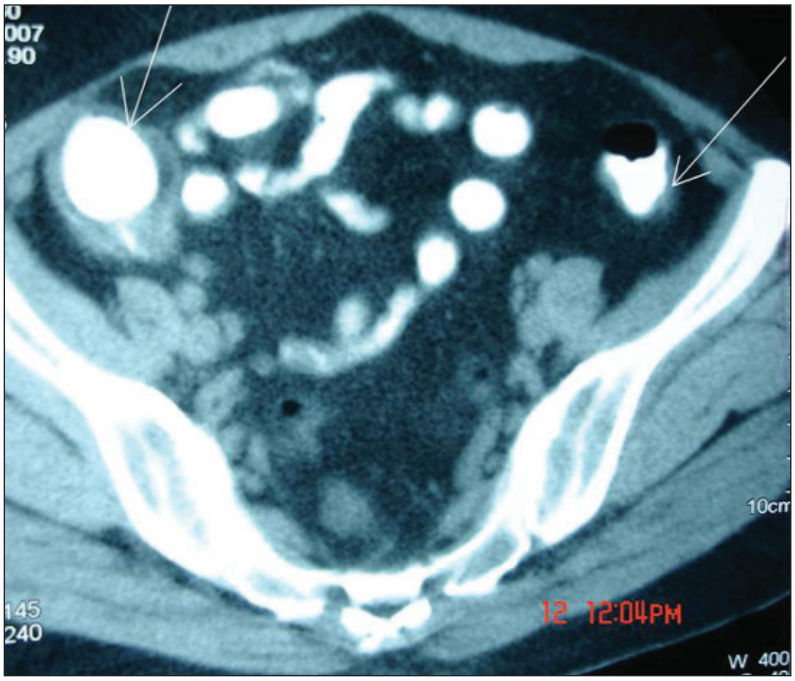

Figure 2. CT scan, in addition demonstrates thickening of the transverse colonic wall (arrow). There is no evidence of bowel obstruction.

negative. Stool cultures yielded normal flora and were negative for enterohemorrhagic *E. coli*, *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia*. Computerized tomography scan of the abdomen demonstrated ascending and transverse colon wall thickening (Figures 1, 2).

The patient was placed on intravenous fluids; amoxicillin-clavulanate was discontinued and empirical oral vancomycin and metronidazole therapy were initiated for presumed *C. difficile*-associated disease (CDAD). The bloody diarrhea and abdominal cramps resolved by the next day. The patient made a dramatic recovery and was discharged three days after admission. Colonoscopy was not performed during hospitalization to minimize risk of complications from instrumentation of inflammed bowel. Elective colonoscopy was performed weeks later. Barring a hyperplastic polyp at 60 cms, there were no other notable findings; diverticuli were absent. Colonoscopic biopsies performed at random from the cecum, ascending and sigmoid colon demonstrated mild chronic inflammation with lymphoid aggregates and focal eosinophilic cryptitis (Fgures 3, 4).

DISCUSSION

Considerations at admission in a patient with diarrhea and bright red bleeding included: bacterial or parasitic colitis, *C. difficile* colitis, inflammatory bowel disease, diverticular disease with bleeding, and less likely hemorrhoidal bleeding or neoplasm (1–7) (Table 1). Many bacteria cause hemorrhagic colitis. As antibiotics are used to treat bacterial infections, it is often difficult to decipher whether colitis resulted from the bacterial infection or the treatment (antibiotic) used for infection (4). Although initial differential diagnosis considered *C.difficile* colitis as likely, the temporal relationship of abdominal discomfort on initiating Augmentin XR,

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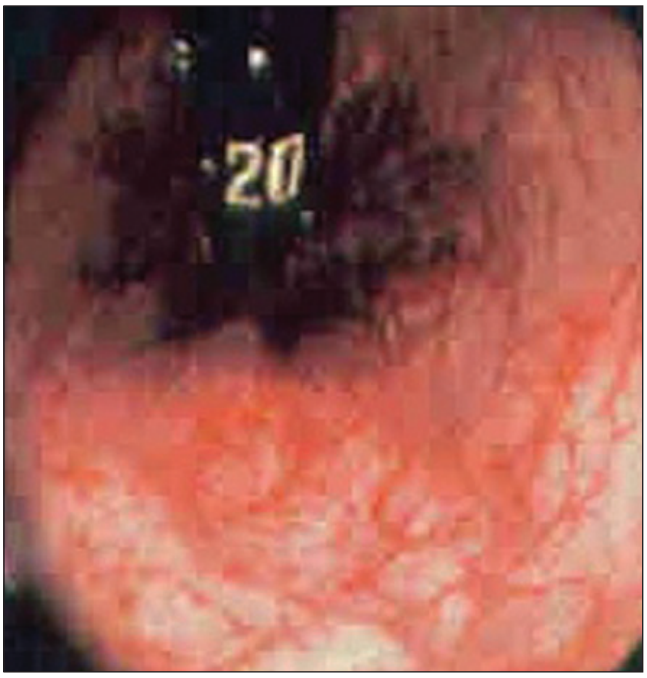

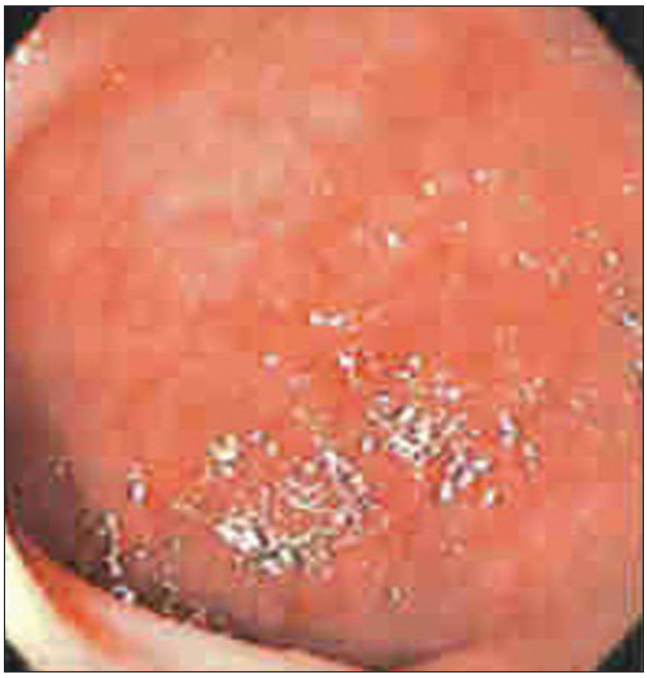

Figures 3 and 4. Colonoscopy performed weeks later demonstrates mild chronic inflammation; histopathology confirmed lymphoid aggregates with mild eospinophilic cryptitis in the ascending, transverse and sigmoid colon.

followed by development of bloody diarrhea and total resolution of manifestations on stopping the drug rendered amoxicillin-clavulanate associated colitis as a possibility. Further, notably absent were fever, leukocytosis, elevation in serum creatinine and any stool tests confirmatory for *C. difficile* infection. Tests for other etiology e.g. *E. coli* O157:H7, parasites, and colonoscopy were non-yielding.

The link between antibiotics and diarrhea with or without bleeding are varied. *C. difficile* colitis with diarrhea has received considerable attention in the past few years, and is common. Diarrhea occurring from antibiotic use commonly results from alteration of the normal flora, increased gut motility, impaired fermentation of carbohydrates, reduced digestion of bile, and resultant osmotic or secretary diarrhea, and are well described in several reviews (1–2). *C. difficile* is responsible for many cases of antibiotic-associated colitis and diarrhea. Bleeding is uncommon in such situations and diarrhea resolves within days of discontinuing the antibiotic. *C. difficile* colitis has developed following use of several antibiotics, including those used to treat *C. difficile* infection. Histologically, in *C. difficile* colitis, there is patchy necrosis, ulceration and pseudomembrane formation (consisting of debris, fibrin and white cells) (3,7).

Recently, amoxicillin-clavulanate induced hemorrhagic colitis has received emphasis in the literature. The first described case of acute hemorrhagic colitis following use of oral penicillin derivatives was in 1978, where abdominal cramps and bloody diarrhea developed four days after oral penicillin therapy; in this case pseudomembranes were not present (8). While diarrhea with abdominal cramps is a frequent association with amoxicillin, Miller, et al reported amoxicillin induced hemorrhagic colitis in two patients who required hospitalization (9); the patients had an onset within two days of using amoxicillin and were discharged from hospital by day six, with no endoscopic findings in colonoscopy performed four months later. A study of 22 cases of antibiotic associated colitis (from Europe) were all negative for *C. difficile*; five of the six patients who underwent colonoscopy had stool cultures positive for cytotoxin-

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Table 1
Diarrhea with bleeding: some causes (1–9)

- Bacterial: *Staphylococcus aureus, Shigella spp., Salmonella spp.,* enteroinvasive and enterohemorrhagic *Escherichia coli, Campylobacter Chlamydia, Mycobacterium avium* complex and *Clostridium difficile*
- Parasitic: *Entamoeba histolytica, Pneumocystis jirovecci, Toxoplasma gondii, Strongyloides stercoralis*
- Viral: Cytomegalovirus, Herpes simplex virus, Norovirus (rarely)
- Fungal: Histoplasmosa capsulatum
- Inflammatory
  - Ulcerative colitis
  - Crohn's colitis
- Medications
  - Antibiotics: erythromycin, penicillin derivatives including ampicillin, amoxicillin-clavulanate
  - Others: Nonsteroidal anti-inflammatory agents, anticoagulants, oseltamivir
- Ischemia of the bowel
- Miscellaneous: Lymphomas

Table 2
***C. difficile* versus antibiotic-associated hemorrhagic colitis: considerations in differentiation (1–3,7,10)**

- *Clostridium difficile* colitis
  - Risk factors: prior antibiotic use, older adults, residence in healthcare institutions, immunosuppressed states
  - Etiology: *C. difficile*, including epidemic strains
  - Clinical features: onset days or weeks after antibiotic use, fever is common, bloody diarrhea not prominent
  - Lab: Marked leukocytosis, elevated creatinine level (perhaps secondary to volume depletion) to >50% of prior value. Diagnosis through stool *C. difficile* toxin enzyme immunoassay for toxins A and B, tissue culture cytotoxicity assay for toxin B, culture for *C. difficile*
  - Location: Colon involvement is a pancolitis, tendency to involve distal colon and rectum; pseudomembranes suggestive finding
  - Complications: toxic megacolon, ileus, colonic perforation, septic shock
  - Therapy involves use of metronidazole or vancomycin
  - Resolution after treatment with antibiotics usually not dramatic.
- Antibiotic associated hemorrhagic colitis
  - Risk factors: Recent antibiotic use; linked to non-steroidal anti-inflammatory drug use; any age, especially relatively younger and healthy adults
  - Implicated organism: *Klebsiella oxytoca*
  - Clinical features: Systemic symptoms (fever, leukocytosis) not prominent unless part of the process which demanded antibiotic use to start with. Bloody diarrhea may be a feature
  - Lab: tests are negative for *C. difficile* or other etiology
  - Location: Ascending (and likely transverse) colon predominantly involved, rectal sparing; pseudomembranes not a feature
  - Discontinuing antibiotic therapy is critical and dramatically effective

producing *Klebsiella oxytoca* (this organism was not isolated in our case); these five cases were on amoxicillin-clavulanate or amoxicillin and a couple were also on non-steroidal anti-inflammatory agents; colonoscopy demonstrated right sided hemorrhagic colitis with rectal sparing in the described cases and pseudomembranes were absent (10). The first reported case of colitis linked to *K. oxytoca* from North America involved a 79-year-old diabetic who was hospitalized to the intensive care unit with hemorrhagic colitis, where the stool cultures grew *K. oxytoca* (11). Most recently, a report described a male who developed hemorrhagic colitis shortly following the use of amoxicillin for sinusitis; stool samples were negative for *C. difficile* antigens but grew *K. oxytoca* (12). Thus infection with *K. oxytoca* is a consideration in cases where antibiotic associated colitis is negative for *C. difficile.*

The mechanisms for *K. oxytoca* causing hemorrhagic colitis are not clear; implicated are allergic vas-

culitis, hypersensitivity, toxic response to antibiotic and associated bacterial overgrowth (9,13,14). In Japanese experiments, *K. oxytoca* strains in antibiotic associated colitis could produce cytotoxin that were toxigenic in cultures of HEp-2, Vero, Chinese hamster ovary and HeLa cells (15,16). This effect was observed in antibiotic associated hemorrhagic colitis in humans (17). *K. oxytoca* is a gram negative organism that is also seen in healthy individuals. It is resistant to ampicillin, suggesting overgrowth of the organism during penicillin therapy (8).

Amoxicillin-clavulanate increases nocturnal motility of the small bowel, as measured by transit studies. Oro-cecal transit time showed only minimal alterations with ampicillin, making it more likely that clavulanate is the basis, but this needs further validation (18,19). It is noteworthy, that amoxicillin-clavunate also causes colitis in rat experiments.

The diagnosis is clinical and critical; absent fever and leucocytosis, with bloody colitis immediately following use of certain antibiotics favors antibiotic associated hemorrhagic colitis rather than *C. difficile* colitis. Table 2 provides some features that may help differentiate the two entities (1–3,7,10). In contrast, with antibiotic-associated hemorrhagic colitis, the dilemma is in predicting whether there would be recurrence with reuse of the same antibiotic in the affected individual.

While speculative, we suggest that in the case described, the problem was possibly related to gut kinetics of the long-acting preparation of amoxicillin-clavulanate (Augmentin XR). It is conceivable that large amounts of drug were released in a localized area of the bowel, leading to injury; the individual had taken the standard form of amoxicillin-clavulanate (Augmentin) in the past without adverse effects. Re-challenge would have been interesting, but was not attempted. ■

Key Points

- Dramatic bloody diarrhea shortly after antibiotic use is unlikely to be *C. difficile* related.
- Amoxicillin-clavulanate is a rare cause of antibiotic associated hemorrhagic colitis, perhaps induced through cytotoxin-producing *Klebsiella oxytoca*.
- Differentiating the two entities is critical as prognosis and treatment differ; in *C. difficile* colitis use of specific antibiotics may be required, while in antibiotic-associated colitis drug withdrawal is paramount.

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