Antibiotic-Associated Pseudomembranous Enteritis Due to *Clostridium difficile*

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Although pseudomembranous colitis is relatively common following antibiotic exposure, there have been few reported cases of pseudomembrane formation involving the small intestine. Herein we report a case of pseudomembranous enteritis of the small and large intestine that occurred after antibiotic exposure. The etiologic organism appears to be *Clostridium difficile*, as evidenced by the characteristic pseudomembranous lesions and a positive ELISA for toxin A in an ileal tissue specimen.

In the preantibiotic era, pseudomembranous enteritis was relatively rare. It was not until the early 1950s that it became a common complication secondary to antibiotic use [1]. Although there were early suggestions that pseudomembranous enteritis was associated with *Staphylococcus aureus* [2, 3], it is now well recognized that the etiologic agent of antibiotic-associated pseudomembrane formation is *Clostridium difficile* and its subsequent toxin production. Early reports of enteritis revealed the presence of lesions predominantly in the small bowel [1, 4]. The distribution of antibiotic-associated pseudomembrane formation caused by *C. difficile* is generally restricted to the colon [1], with abrupt termination at the ileocecal valve [5]. There are only a few recent reports of *C. difficile*-associated pseudomembrane formation involving sites other than the colon [6–9]. We report a case in which antibiotic-associated pseudomembranous enteritis was seen throughout the small intestine and colon and *C. difficile* toxin A was recovered from an ileal specimen. We also review the relevant literature.

A 66-year-old man was admitted to the Veterans Affairs Medical Center in Palo Alto, California, for foul-smelling emesis; the initial diagnosis was small-bowel obstruction. His medical history was significant for colon carcinoma and subsequent right hemicolectomy; Duke's stage A rectal carcinoma, which necessitated abdominal perineal resection and colostomy; small bowel obstructions secondary to adhesions; type II diabetes mellitus; and peptic ulcer disease. Therapy with intravenous cefotetan (1 g every 12 hours for 23 days) was initiated. A radiological examination revealed no specific obstruction, but multiple dilated small-bowel loops and fecal impaction of the remaining colon were noted. The patient remained hospitalized for 47 days, and his course was complicated by a urinary tract infection with *Pseudomonas aeruginosa*. The latter was treated with intravenous ciprofloxacin (400 mg every 12 hours for 7 days) and then with oral ciprofloxacin (500 mg twice daily for 7 days).

Five days after discharge he returned to the medical center with a distended abdomen. An examination revealed that the abdomen was soft and nontender, and semisolid output from his colostomy was noted. His temperature was 38.2°C, and his leukocyte count was 19,800/mm³, with 54% segmented neutrophils, 30% band forms, 9% lymphocytes, and 4% monocytes. The following morning the patient was lethargic and hypotensive. His abdomen became markedly distended, and there was no output from his colostomy. He underwent exploratory laparotomy, which revealed an extremely distended, ischemic-looking small bowel with dense adhesions. Approximately 132 cm of the small bowel was resected, leaving 15 cm of ileum and 122 cm of duodenum and jejunum. Inspection of the resected ileal lumen during the operation revealed a pseudomembrane. Since *C. difficile* pseudomembranous enteritis was suspected, a portion of ileal tissue was sent to the laboratory for possible isolation of *C. difficile* toxin. The specimen was found to be positive for *C. difficile* toxin A by means of a monoclonal ELISA for detection of the toxin (BioWhittaker, Walkersville, MD).

Gross pathological examination of the resected ileum revealed that it was edematous and thickened; however, there was no evidence of ischemia or abscess formation.

The patient was returned to the intensive care unit and, because of ileus, began receiving intravenous vancomycin and metronidazole (1.5 g every 24 hours and 500 mg every 6 hours, respectively). He developed multisystem organ failure and died 3 days later. Postmortem examination revealed that the small bowel was edematous, with areas of diffuse focal hemorrhage. The ileal mucosa was eroded and covered with necrotic debris suggestive of a pseudomembrane. Areas of the remaining large bowel also were suggestive of pseudomembrane formation and were surrounded by ulceration. Microscopic examination of sections of the small bowel revealed transmural inflammation with a necrotic mucosa that was covered by a membrane composed of debris, neutrophils, and fibrin (figure 1).

This patient presented with abdominal symptoms 29 days...
after receiving an extended course of therapy with intrave­
nous cefotetan and 5 days after completing a course of ther­
apy with intravenous and oral ciprofloxacin. It is likely that 
this patient’s enteritis was at least in part due to his antibiotic 
exposure. Although he did not present with the profuse or 
watery diarrhea typically seen in pseudomembranous enteri­
tis, Medich et al. [10] and Triadafilopoulos et al. [11] have 
described several patients who presented with an acute abdo­
men but did not have diarrhea.

There are only a few recent reports of C. difficile 
involve­
ment of the small bowel, and even fewer reports of cases in 
which pseudomembrane formation was noted. Testore et al. 
[6] reported a case of pseudomembranous enteritis that did 
not involve the colon and in which C. difficile was isolated at 
autopsy. This strain produced toxins in vitro. Pseudomem­
brane formation in the small bowel and isolation of toxin in 
stool have been reported by Hyams et al. [7] (whose case 
involved an infant and was not associated with antibiotic 
exposure) and by LaMont et al. [8] (whose case involved one 
of six patients with chronic inflammatory bowel disease). 
Shortland et al. [9] isolated C. difficile and its toxin from a 
patient with pseudomembranous colitis and involvement of 
the ileal conduit but of no other portions of the small intesti­
ne. C. difficile toxin A was isolated from an ileal specimen 
from our patient, and pseudomembrane formation was 
noted. Taylor et al. [12] isolated C. difficile from a jejunal 
aspirate, and Testore et al. [13] were able to isolate C. difficile 
from three of 100 jejunal segments obtained at autopsy, 
thereby demonstrating the presence of the organism in the 
small bowel.

It is possible that because of our patient’s prior hemicolec­
tomy and rectal resection, the mucosa of the small intestine 
had become colonized with organisms more characteristic of 
the colon, and subsequent antibiotic exposure may have led 
to a breakdown of their protective effects against C. difficile. 
Development of flora in the small intestine similar to that of 
the colon in patients with an ileostomy has been docu­
mented. Vince et al. [14] evaluated the effluent from the ileal 
stoma of three patients. One to 3 weeks after the ileostomy, 
the flora resembled fecal flora.

In the hamster model of pseudomembranous enterocolitis, 
lesions typically involve the cecum and terminal ileum [15]. 
Several investigators have also studied the effects of C. diffi­
cile toxins in rabbits, mice, and rats. Lyerly et al. [16] admin-
istered toxin A (enterotoxin) and toxin B (cytotoxin) to hamsters, mice, and rats. In all three models, fluid accumulation and hemorrhage in the small intestine were noted. It is unclear why animal models develop ileocolitis whereas humans seem to develop colitis only. It is possible that since there is now effective treatment for pseudomembranous colitis and the diagnosis is usually based on identification of toxin by assay, fewer intestinal specimens are examined; instead, the small intestine is examined only at surgery or necropsy. Although some investigators may question the practicality and safety of examining the small bowel by endoscopy, biopsy, or aspiration, small-bowel involvement may be more common than currently believed.

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References