Necrotizing *Clostridium difficile* Enteritis Complicating Fulminant Colitis

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Abstract

Background: *Clostridium difficile* infections result from an imbalance in normal bacterial flora, allowing *C. difficile* bacteria overgrowth. Whereas such bacterial overgrowth is typically confined to the colon, there have been reports of an increasing prevalence of *C. difficile* infections involving the small bowel, with the majority of patients presenting with a history of partial or total colectomy. We present two rare cases of necrotizing *C. difficile* enteritis complicating fulminant *C. difficile* colitis.

Case Presentations: A 74-year-old male presented with a two-week history of watery diarrhea and escalating abdominal pain without recent antibiotic use. Work-up was significant for leukocytosis, bandemia, lactic acidosis, and elevated creatinine. Initial diagnosis of *C. difficile* was treated with intravenous fluoroquinolone and metronidazole. He deteriorated and a total colectomy with small bowel resection was performed. Final pathology revealed pseudomembranous colitis with focal mucosal ischemia and pseudomembranous necrotizing enteritis. Post-operatively the patient's condition fluctuated, requiring re-initiation of antibiotics and vasopressor therapy; he ultimately recovered. A 72-year-old female presented with severe abdominal pain and septic shock two weeks after total abdominal colectomy with end ileostomy for severe *C. difficile* colitis. An exploratory laparotomy appeared normal, without an identifiable pathology source. Post-operatively she required vasopressor support and mechanical ventilation. She received intravenous metronidazole and vancomycin enemas. *Clostridium difficile* assays confirmed the diagnosis of relapsed pseudomembranous enteritis. Antibiotic therapy continued without further incident.

Conclusion: *Clostridium difficile* enteritis presents a unique challenge because of its difficulty in diagnosis, a fact underscored by the high morbidity and mortality of small bowel of *C. difficile* infections. *Clostridium difficile* enteritis should be suspected in patients not improving after recent colectomy for *C. difficile* colitis. Continuation of antibiotics and total colectomy should be considered in patients with un-explained acute intra-abdominal pathology or persistent sepsis after colectomy for fulminant *C. difficile* colitis.

Keywords: *Clostridium difficile*; fulminant colitis; necrotizing pseudomembranous enteritis; pseudomembranous colitis

PSEUDOMEMBRANOUS COLITIS often occurs secondary to an imbalance in the distribution of the normal bacterial flora within the colonic cavity that allows the overgrowth of *Clostridium difficile* bacteria. This outgrowth of bacteria often manifests after a course of antibiotics resulting from the destruction of normally present colonic bacterial flora [1]. Common treatment for *C. difficile* include vancomycin or, in-

creasingly, fecal microbiota transplantation [2,3]. Although such bacterial overgrowth is usually restricted to the colon, a number of cases of *Clostridium difficile* infections (CDI) involving the small bowel have been reported recently [4–12]. Whereas typically these patients have had a history of total or segmental colectomy, we present here two cases of necrotizing *C. difficile* enteritis colitis complicating fulminant *C. difficile* colitis.

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Case 1

A 74-year-old previously healthy male presented to the emergency department with a two-week history of watery diarrhea and escalating diffuse abdominal pain. He had no recent antibiotic use with the last use for peri-operative prophylaxis for spinal surgery five months prior to this presentation. On examination, he had abdominal distention with diffuse tenderness but soft without rebound or rigidity. Laboratory studies were significant for leukocytosis (50,000 per microliter), bandemia (17%), lactic acidosis (3.1 mmol/L), elevated creatinine (5.0 mg/dL), and an abdominal/pelvic computed tomography (CT) scan significant for pancolitis (Fig. 1). Infectious work-up, including *C. difficile* analysis, was sent.

On the basis of the patient's presentation and initial work-up, a presumed diagnosis of *C. difficile* colitis was made and was treated with aggressive fluid resuscitation with intravenous fluoroquinolone and metronidazole therapy. Despite aggressive non-operative treatment he continued to deteriorate over the next several hours and was subsequently taken to the operating room. At laparotomy, a 14-cm long segment of a proximal ileum was found to be necrotic and the large bowel was markedly edematous. Although the results of the *C. difficile* toxin essays were still unknown at time of surgery, Wright stain revealed numerous fecal leukocytes. The diagnosis of fulminant *C. difficile* colitis and mesenteric infarction secondary to global hypoperfusion was presumed, and total abdominal colectomy with small bowel resection was performed. Given persistent hemodynamic instability, the patient's abdomen was left open with a planned second-look laparotomy. On re-operation in 48 h, no further intestinal

pathology was noted. A side-to-side enteroenterotomy with end ileostomy and tube gastrostomy was made.

Initially, the patient improved clinically and metronidazole was discontinued 72 h post-operatively. However, the following day he deteriorated significantly and vasopressor therapy was re-initiated. Furthermore, he re-developed significant leukocytosis and became acidotic (pH 7.09–7.21). Simultaneously, the final pathology report revealed pseudomembranous colitis with focal mucosal ischemia, pseudomembranous necrotizing appendicitis as well as pseudomembranous necrotizing enteritis that was extending to resection margins (Fig. 2). Intravenous metronidazole and enteral vancomycin therapies were then re-initiated with resultant rapid clinical improvement. After discontinuing antibiotics 10 d later, he re-developed abdominal pain, diarrhea, and leukocytosis. Once again, metronidazole-vancomycin therapy was restarted and continued for four weeks. He then went on to have an un-eventful recovery without any further setback.

Case 2

A 72-year-old female presented with severe abdominal pain and septic shock two weeks after total abdominal colectomy with end ileostomy for severe *C. difficile* colitis. After her initial colectomy, the patient had an un-eventful recovery and was discharged home seven days after surgery. Metronidazole was discontinued upon discharge. On re-admission, her abdomino-pelvic CT scan revealed dilated loops of small bowel with moderate amount of intra-peritoneal fluid. She underwent an exploratory laparotomy, which appeared normal and no identifiable source of

FIG. 1. Computed tomography (CT) scan demonstrating bowel wall thickening in the setting of colitis.

FIG. 2. (a) Pseudomembranous colitis. (b) Pseudomembranous appendicitis. (c) Ischemic-necrotizing enteritis (d) Necrotizing enteritis.

pathology was noted. Post-operatively, she remained hemodynamically unstable, requiring vasopressor support and mechanical ventilation. She was re-started empirically on intravenous metronidazole and vancomycin enemas. Subsequent *C. difficile* assays returned positive and the diagnosis of relapsed pseudomembranous enteritis was confirmed. Antibiotic therapy was continued for 21 d without any subsequent complications.

Discussion

Clostridium difficile infection is typically believed to be a disease of the colon without extra-colonic involvement. To our knowledge, only three cases of necrotizing CDI of the small bowel occurring in the setting of fulminant *C. difficile* colitis have been published [1,5]. Herein we presented a series of patients with relapsed CDI after appropriate treatment of CDI colitis. Proper diagnosis and aggressive surgical management followed by continuous antibiotic therapy allowed for successful outcome in our patients. These cases not only highlight a rarely seen clinical entity of necrotizing *C. difficile* enteritis, but also underscore the importance of consideration of CDI enteritis in patients with intra-abdominal catastrophe after recent colectomy for fulminant CDI colitis.

Clostridium difficile enteritis and colitis may present similarly. Patients typically present with diarrhea, abdominal pain, elevated temperatures, and leukocytosis. A delay in diagnosis often leads to worsened bowel edema, perforation, peritonitis, sepsis, and death. In fact, *C. difficile* enteritis carries significant morbidity with reported mortality rates are

as high as 60%–83% [8]. Whereas the incidence of CDI of the colon has been increasing, small bowel CDIs remains rare [4,7]. Interestingly, of 35 cases of *C. difficile* enteritis reported in the literature (including our case), more than half have occurred in the last few years [9]. This alarming trend underscores the importance of high index of suspicion of *C. difficile* enteritis. It also suggests the increasing awareness of CDI in patients who have recently undergone total or partial colectomy [13].

Prompt diagnosis and management of *C. difficile* enteritis appears to be paramount to patient survival. The optimal treatment of small bowel CDI remains unclear, and stratification of the disease severity as in CDI of the colon could be used to initiate an appropriate management plan [9]. Current guidelines provide an outline for diagnosis and management of CDI but still do not have clear strategies on how to manage fulminant CDI extending beyond the colon to the small intestine [14]. In a series of 11 patients, more than 50% responded to metronidazole alone [9]. In another series, all patients were treated with a combination of metronidazole and vancomycin [8]. Thus, similarly to colonic CDI, patients with mild to moderate *C. difficile* enteritis should be treated with metronidazole. However, oral vancomycin may be appropriate as the first line treatment for severe CDI as well as in those patients who do not improve within 72 h of initiation of treatment with metronidazole [9]. In mice, vancomycin alone was shown to be as effective in treatment of CDI as vancomycin and metronidazole in combination [2]. However, it is worth noting that both groups of mice treated succumbed to CDI relapse shortly after discontinuation of treatment. In our first patient, the diagnosis and treatment of

C. difficile colitis was timely and effective. However, despite resection of the necrotic segment of small bowel and total colectomy, his post-operative clinical condition continued to deteriorate until the diagnosis of *C. difficile* enteritis was established. Prompt initiation of the appropriate antibiotic therapy had a dramatic effect on his illness and subsequent complete recovery. Similarly, the second patient had dramatic improvement after relapsed CDI was suspected and treated. Therefore, continuation of antibiotic therapy with metronidazole or vancomycin for patients with CDI not improving or with relapsing intra-abdominal sepsis in the post-operative period should be considered.

Antibiotic use and inflammatory bowel disease (IBD) predispose patients to small bowel CDI similar to that seen in CDI of the colon. Prior surgeries of the colon as well as host factors including advanced age or immunocompromised status are additional risk factors for small bowel CDI [8,9,15]. In fact, more than 90% of reported patients with *C. difficile* enteritis had a history of total colectomy or recent gastrointestinal surgery [9]. In two of the few previously reported case of necrotizing *C. difficile* enteritis, one patient succumbed to CDI after elective rectosigmoid resection for rectal cancer, whereas another patient had a relapse of previously treated *C. difficile* colitis after undergoing aortic valve replacement [5]. In one of our cases, CDI of the small bowel was concomitant to the colonic CDI without recent surgery. Unfortunately, this extremely rare clinical phenomenon may be the beginning of the alarming trend of severe colonic CDI extending toward the small intestine.

Several theories have been proposed to explain the pathogenesis and development of *C. difficile*-associated pseudomembranous enteritis. Given that most patients with *C. difficile* enteritis had had a colectomy, diversion, ileocolonic anastomosis, or an ileoanal pouch anastomosis, it has been hypothesized that the altered bowel anatomy may lead to a redistribution of the bacterial flora within the small intestine. It was noticed that in these patients, ileal microflora was similar to the colonic environment, thus predisposing them to CDI [9,10,16]. Another theory is that changes in the small bowel epithelium occur secondary to the modification of flow of bowel contents. This is usually associated with partial loss of the intestinal villi. These changes were demonstrated in patients who had undergone an ileal pouch procedure [17,18]. Stasis in the affected limb has also been thought to contribute to the development of *C. difficile*-associated enteritis. Kralovich et al. [6] presented a case of CDI that developed after antibiotic treatment in a de-functionalized ileal branch of a patient who had undergone a jejuno-ileal bypass procedure 31 y prior. They hypothesized that peristalsis and the presence of a patent ileocecal valve protect the small intestine from colonization in patients with normal anatomy. In addition to delays in diagnosis, the severity of *C. difficile* enteritis compared with colitis can be explained by the increased permeability of the enterocytes [11]. The exact etiology of *C. difficile* enteritis in our patients remains unknown, however, prompt initiation of the appropriate empiric therapy was paramount to successful clinical outcome.

Conclusion

Clostridium difficile infection of the small bowel is a rare but serious abdominal emergency. It carries a high rate of

mortality and morbidity if the diagnosis is delayed. It should be suspected in all patients with diarrhea, abdominal pain, elevated temperatures, and leukocytosis in the setting of previous abdominal colectomy. Moreover, it may occur concomitantly or as a complication of *C. difficile* colitis. Surgical management should include total abdominal colectomy and resection of any compromised small bowel segment. Importantly, antibiotic therapy targeting *C. difficile* may need to be re-initiated in patients who fail to demonstrate clinical improvement after a total colectomy for fulminant *C. difficile* colitis. Overall, our cases underscore the importance to consider *C. difficile* enteritis in patients with un-explained acute intra-abdominal pathology or persistent sepsis after colectomy for fulminant *C. difficile* colitis.

Author Disclosure Statement

The authors have no relevant conflicts of interest or financial disclosures for this study.

References

1. Tjandra JJ, Street A, Thomas RJ, et al. Fatal *Clostridium difficile* infection of the small bowel after complex colorectal surgery. ANZ J Surg 2001;71:500–503.
2. Erikstrup L, Aarup M, Hagemann-Madsen R, et al. Treatment of *Clostridium difficile* infection in mice with vancomycin alone is as effective as treatment with vancomycin and metronidazole in combination. BMJ Open Gastroenterology 2015;2:4–8.
3. Wang J, Xiao Y, Lin K, et al. Pediatric severe pseudomembranous enteritis treated with fecal microbiota transplantation in a 13-month-old infant. Biomed Rep 2015;3:173–175.
4. Boland E, Thompson JS. Fulminant *Clostridium difficile* enteritis after proctocolectomy and ileal pouch-anal anastomosis. Gastroenterol Res Pract 2008;2008:985658.
5. Hayetian FD, Read TE, Brozovich M, et al. Ileal perforation secondary to *Clostridium difficile* enteritis: Report of 2 cases. Arch Surg 2006;141:97–99.
6. Kralovich KA, Sacksner J, Karmy-Jones RA, Eggenberger JC. Pseudomembranous colitis with associated fulminant ileitis in the defunctionalized limb of a jejuno-ileal bypass. Report of a case. Dis Colon Rectum 1997;40:622–624.
7. Lavalley C, Laufer B, Pepin J, et al. Fatal *Clostridium difficile* enteritis caused by the BI/NAP1/027 strain: A case series of ileal *C. difficile* infections. Clin Microbiol Infect 2009;15:1093–1099.
8. Lundeen SJ, Otterson MF, Binion DG, et al. *Clostridium difficile* enteritis: An early postoperative complication in inflammatory bowel disease patients after colectomy. J Gastrointest Surg 2007;11:138–142.
9. Navaneethan U, Giannella RA. Thinking beyond the colon—Small bowel involvement in clostridium difficile infection. Gut Pathog 2009;1:7.
10. Tsutaoka B, Hansen J, Johnson D, Holodniy M. Antibiotic-associated pseudomembranous enteritis due to *Clostridium difficile*. Clin Infect Dis 1994;18:982–984.
11. Yee HF Jr, Brown RS Jr, Ostroff JW. Fatal *Clostridium difficile* enteritis after total abdominal colectomy. J Clin Gastroenterol 1996;22:45–47.
12. Jacobs A, Barnard K, Fishel R, Gradon JD. Extracolonic manifestations of *Clostridium difficile* infections. Presentation

- of 2 cases and review of the literature. *Medicine* (Baltimore) 2001;80:88–101.
13. Seril D, Shen B. *Clostridium difficile* infection in the postcolectomy patient. *Inflamm Bowel Dis* 2014;20:2450–2465.
 14. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108:478–498
 15. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008;103:1443–1450.
 16. Neut C, Bulois P, Desreumaux P, et al. Changes in the bacterial flora of the neoterminal ileum after ileocolonic resection for Crohn's disease. *Am J Gastroenterol* 2002;97: 939–946.
 17. Apel R, Cohen Z, Andrews CW Jr, et al. Prospective evaluation of early morphological changes in pelvic ileal pouches. *Gastroenterology* 1994;107:435–443.
 18. Shen B, Goldblum JR, Hull TL, et al. *Clostridium difficile*-associated pouchitis. *Dig Dis Sci* 2006;51:2361–2364.

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Abbreviations Used

CDI = *Clostridium difficile* infection
CT = computed tomography

Cite this article as: Tung VS, Lopez A, Orenstein SB, Novitsky YW (2017) Necrotizing *Clostridium difficile* enteritis complicating fulminant colitis. *Surgical Infections Case Reports* 2:1, 9–13, DOI: 10.1089/crsi.2016.0054