Fulminant Clostridium difficile Enteritis: A Fatal and Rare Cause of Severe Terminal Ileitis with Impending Small Bowel Perforation

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Received date: March 16, 2017; Accepted date: May 22, 2017; Published date: May 26, 2017

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Abstract

Clostridium difficile infection in small bowel is a rare clinical condition which is more common in pre-existing gastrointestinal pathologies such as inflammatory bowel disease, prior colectomy or ileostomy and systemic illnesses causing immuno-compromised status. We present a fulminant case of Clostridium difficile enteritis which was preceded by an episode of Salmonella gastroenteritis in an otherwise healthy individual. It is complicated by severe terminal ileitis and multi-organ failure with subsequent laparotomy and small bowel resection finding a near perforation over the diseased segment of the ileum. The clinical characteristics and the importance of this unusual but potentially fatal infection would be discussed.

Keywords: Clostridium difficile; Enteritis; Pseudomembranous colitis; Salmonella; Bowel perforation; Antibiotic

Introduction

Clostridium difficile enteritis (CDE) is a rare clinical condition, with only 83 cases reported in the literature over the last decades till 2013 [1]. Pre-existing inflammatory bowel disease, prior colectomy or ileostomy and immuno-compromised states are the common predisposing factors for this situation. Despite its rarity, it remains an important condition that clinician should be aware of, as the overall mortality can be up to one third [1,2] with highly variable clinical presentation, in which the classical symptom of diarrhea can be absent [3] and how it interacts with other bacterial gastroenteritis is still unclear.

Here, we would like to present a case of fulminant CDE following an episode of Salmonella gastroenteritis, resulting in near perforation of the ileum in a lady who does not have any surgically-altered gastrointestinal (GI) anatomy, whereas prompt surgery has salvaged the patient from fatal peritonitis.

Case Report

A 68 years-old Chinese lady presented to the hospital for acute onset of epigastric pain, abdominal distension and diarrheal symptoms with loose watery stool up to 6 times a day. She enjoyed good past health except that she had well controlled diabetes mellitus for 10 years. Upon admission, she was febrile and dehydrated, and blood tests revealed a creatinine level of 331 µmol/L and a WBC level of 19.7 × 10^9/L. The serum albumin level was low at 30 g/L. She received intravenous fluid (IVF) replacement and upper GI endoscopy was performed with mild gastritis identified. After a week of IVF supplement, her fever and diarrhea subsided, which was accompanied by normalization of creatinine and WBC levels. Subsequently, gastric biopsy result found H. pylori associated gastritis and she was then discharged home with one week of triple eradication therapy including amoxillin, clarithromycin and twice daily dose of proton pump inhibitor.

She was re-admitted one week later for worsening abdominal pain, vomiting and recurrence of profuse watery diarrhea. Stool tests from the last index admission grew group B Salmonella species and were negative for ova and cyst, viral study, and Clostridium difficile (C. difficile) PCR. First computer tomography (CT) of the abdomen showed non-specific colitis and terminal ileitis as suggested by mild bowel wall thickening of the terminal ileum, and the colon. She was managed as Salmonella gastroenteritis with intravenous ceftriaxone aggressive and IVF challenge. Despite the medical treatment, her clinical condition deteriorated and she suffered from acute kidney injury with creatinine rise to 362 µmol/L, severe metabolic acidosis and respiratory failure, which required intensive care unit (ICU) care for mechanical ventilation and continuous veno-venous hemofiltration support.

Her symptoms persisted with severe diarrhea up to 8 times a day with per-rectal bleeding. The serum albumin level further dropped to 19 g/L and the patient ran into disseminated intravascular coagulopathy with pan-cytopenia and prolonged prothrombin time. Repeated stool microbiological assays on day 10 were positive for C. difficile PCR and negative for bacterial culture. A sigmoidoscopy was therefore performed and it found extensive pseudo-membranous appearance which extended from rectum to sigmoid.

Treatment for pseudomembranous colitis was commenced with intravenous metronidazole (500 mg every 8 h) and oral vancomycin (500 mg every 6 h). Vancomycin (500 mg in 100 ml normal saline every 6 h) enema was added 1 week later due to poor clinical response to the initial medical regime. The clinical condition further deteriorated along with the above management and the patient developed shock and oliguria after total 20 days of medical treatment. Repeated computer tomography scan of the abdomen revealed mesenteric stranding with submucosal edema of the small bowel and whole colon from caecum to rectum (Figure 1). Laparotomy was...
decided in view of severe colitis refractory to medical treatment. Intra-operatively, two focal area of paper-thin terminal ileum with surrounding dusky changes was found at 8 cm and 12 cm proximal to the ileocaecal valve. Total 15 cm unhealthy segment of ileum was resected and macroscopic ulcers were noted over the resected ileum. Double-barrel ileostomy was created. Microscopic examination revealed inflammatory exudate, fibrin and neutrophils with focal deep fissuring ulcers. There were focal area of transmural infarction and impending perforation. The overall picture was compatible with C. difficile enteritis with impending perforation (Figures 2a and 2b).

Post-operatively, medical treatment with intravenous metronidazole was continued for 3 days more with total 4-week duration of treatment given. The diarrhea resolved and the hemodynamics of the patient was stabilized. The surgical wound healed satisfactorily and the patient tolerated resumption of oral diet well. Later stool specimen from the ileostomy was negative for both bacterial culture and C. difficile PCR. She underwent rehabilitation and remains free from GI symptoms after 6 months of follow-up. Surgical closure for the double-barrel ileostomy was arranged.

Discussion

CDE was previously considered to be exceedingly rare and only scanty reports were published until the recent ten years when the number of cases has increased considerably. It carries an extremely high mortality ranging from 23% to 32% in the two largest literature reviews [1,2]. The usual clinical presentations include fever, septic shock, diffuse abdominal pain or distension, ileus, diarrhea or high output from the ileostomy in stoma patients and infrequently, small bowel obstruction or small bowel perforation [1,2,4-8]. The virulent BI/NAP1/027 strain was suggested to be a possible culprit for the increasing severity and prevalence of the disease [2,9].

It had been postulated that colonization of small bowel with C. difficile is guarded against by the rapid peristalsis of the small bowel as well as the mechanical action of the intact ileocaecal valve [10]. Also, the small bowel mucosa seems to require higher concentrations of C. difficile toxins for infection to occur [11]. However, these potential defense mechanisms are easily jeopardized by lower GI surgery such as ileostomy creation with mucosal metaplasia of the small bowel and changes in the intestinal flora, simulating the colonic environment [12,13]. Thus, previous reports on severe CDE are mostly associated with inflammatory bowel diseases or prior surgery to the bowel which
disabled the natural protection of the small bowel against *C. difficile* [1,2,10,14-17]. Our case is exceptional in that she had no pre-existing gastrointestinal condition and the CDE was only potentially facilitated by a preceding episode of Salmonella gastroenteritis and a short course of antibiotic usage.

Symptoms of non-typhoidal Salmonellosis are usually relatively mild and most patients would make a recovery without specific treatment. Nevertheless, Salmonella co-infection with *C. difficile* colitis were described in a few case reports whereas it may result in severe diseases with fatal pseudomembranous colitis, especially in those patients with immunocompromised conditions such as advanced age or HIV infection [18-21]. To our knowledge, our patient is the first reported case of life-threatening *C. difficile* and Salmonella co-infection in which the terminal ileum being the most affected site instead of the colon as evidenced by the surgical specimen. Pathophysiologically, it is poor understood that how the Salmonella interacts with *C. difficile* infection or if it necessitates a more severe clinical illness. However, acute intestinal inflammation by Salmonella species was observed to cause dramatic alterations in the luminal environment triggering changes in the composition of the intestinal microbiota. The numbers of normal intestinal commensal microbes, mostly belonging to the Firmicutes and Bacteroides phyla, are significantly reduced [22]. These disruptions in intestinal microbiota could actually facilitate the opportunistic infection of *C. difficile* in the ileum in our patient and the pre-existing mucosal damage by the Salmonella bacteria may increase the risk of developing a more rapid and fulminant course of the infection.

Due to the depth of the involved segment, standard colonoscopy usually fails to reach the diseased mucosa for endoscopic examination. The diagnosis still highly relies on the stool assays and radiological imaging. A review on CT scan findings in four patients with CDE by Wee et al. suggest mesenteric or retroperitoneal fatty stranding is an universal feature. Other common radiological features include varying degrees of ascites, distension by gas or fluid and mural thickening of the small bowel [23]. In our patient, there were mesenteric stranding and mild bowel wall thickening of the terminal ileum in the CT scan compatible with the previous radiological review. However, these signs are vastly non-specific and overlap with other causes of terminal ileitis such as Crohn's disease and ischaemic colitis. Therefore, a high clinical index of suspicion is required and the possibility of CDE should be considered in any cases of small bowel enteritis. The safety and efficacy of deep enteroscopy in the use of diagnosis of CDE has not been studied.

In conclusion, we report a severe case of CDE with impending small bowel perforation which possibly triggered by a preceding episode of Salmonella gastroenteritis. The patient was refractory to standard medical treatment and timely surgery had prevented the expectable sequela of life-threatening peritonitis in this patient. This case illustrates the characteristics and clinical course of CDE, and alerts the clinicians to maintain a high level of suspicion in diagnosis and to manage the condition early in a proper manner. Further studies focusing on the risk factors, diagnosis modalities and optimal treatment are encouraged to enhance the understandings of this specific illness.

**Disclosure**

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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**References**
