Campylobacter Jejuni superinfection causing toxic megacolon in asymptomatic ulcerative colitis: Case Report

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Key points

1. *C. jejuni* is the most common cause of foodborne illness in resource-rich settings and is associated with an increased short and long term risk of inflammatory bowel disease.
2. Severe colitis or toxic megacolon not associated with C difficile, should prompt a wider search for etiology, including other pathogens and unrecognized inflammatory bowel disease.
3. The use of stool cultures when indicated can guide directed antimicrobial therapy. Recent guidelines state that stool cultures should be considered in any moderate to severe diarrheal illness (Box 1).
4. Empiric antimicrobial therapy should be administered when indicated in acute diarrheal illness (Box 1). More research is needed to determine the role of antibiotics in preventing significant life-altering sequelae such as IBD, Guillain-Barre syndrome and reactive arthritis.

BOX 1: Stool Testing and Empiric Antibiotic Therapy in Acute Diarrhea (Riddle, DuPont, and Connor 2016)

Indications for stool testing in diarrheal illness

- Dysentery (diarrhea with blood or mucus)
- Moderate to severe disease (defined as causing changes in daily activities)
- Symptoms lasting >7 days

Indications for empiric antimicrobial therapy (Azithromycin 1g in a single dose)

- > 72h in duration with fever > 38˚C
- Severe dysentery
- Moderate to severe traveller's diarrhea

Case Presentation

A previously healthy, 70 year old caucasian woman presented to the Emergency Department for evaluation of a nine day history of progressive abdominal pain and distention, watery diarrhea, anorexia and fever. Past medical history was significant for occult gastrointestinal bleeding four years prior. At that time, she underwent two colonoscopies with biopsies which detected hemorrhoids and benign polyps but no evidence of malignancy or inflammatory bowel disease (IBD). She had no family history of IBD. She denied bloody diarrhea, infectious contacts, recent travel and exposure to contaminated food. She had previously been seen at a walk-in clinic where she was started on oral rehydration therapy.

On physical exam, her vitals were normal. Her abdomen was distended but not peritonitic. A digital rectal exam was negative for frank blood. Initial laboratory investigations revealed severe hyponatremia at 123 mmol/L and leukocytosis at 14.6×10^9/L with left shift and toxic granulation.

Her CBC, VBG and lactate were normal. A stool sample was sent for culture. Rapid testing for norovirus and *c. difficile* were negative. An abdominal CT (Figure 1A) was performed which revealed pancolonic thickening and dilatation to 8.1 cm. The provisional diagnosis was viral gastroenteritis. She was admitted to the hospital to correct her hypovolemic hyponatremia with intravenous normal saline.

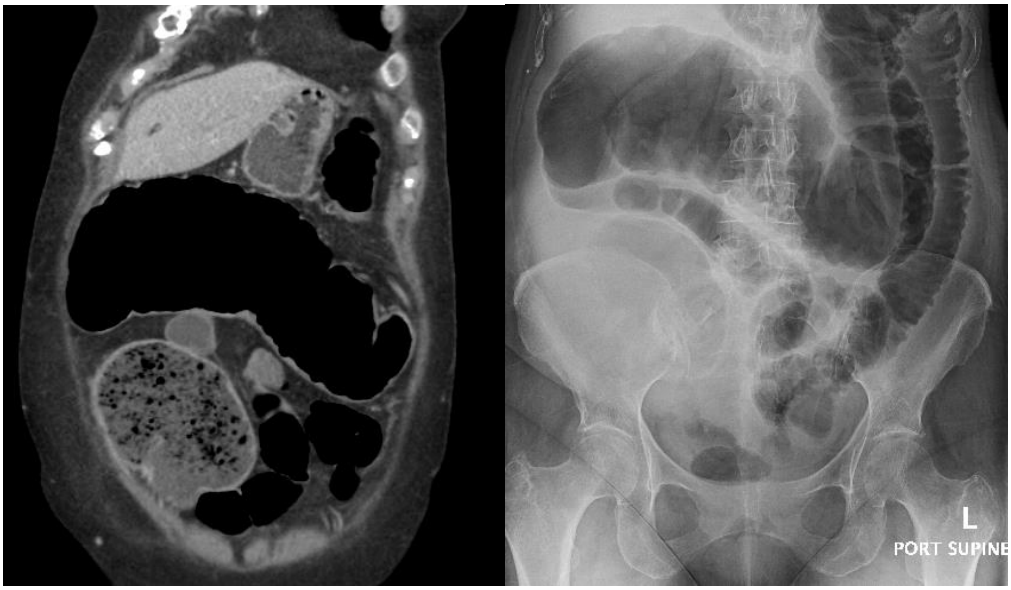

Figure 1: Coronal contrast enhanced CT showed pancolonic thickening, dilatation to 8.1cm and abnormal enhancement most in keeping with an inflammatory or infectious pancolitis (A). Two days later, an abdominal radiograph showed pancolonic dilation up to 10.5cm with possible pneumatosis (B).

36 hours after admission, she had an acute worsening of her abdominal pain and distention. When reassessed, her abdomen was rigid and peritonitic. An urgent abdominal radiograph revealed pancolonic dilatation to 10.5 cm with possible pneumatosis (Figure 1B). She was started empirically on piperacillin-tazobactam intravenously and referred for urgent surgical consultation for assessment of toxic megacolon. The patient underwent an urgent subtotal colectomy. Postoperatively, her stool culture from admission was reported as positive for *c. jejuni*. Histologic examination of the large bowel showed marked ulceration of the surface mucosa with a pseudopolyp appearance. Higher magnification of the non-ulcerated mucosa showed chronic active colitis, cryptitis and crypt abscesses consistent with a diagnosis of ulcerative colitis (Figure 2).

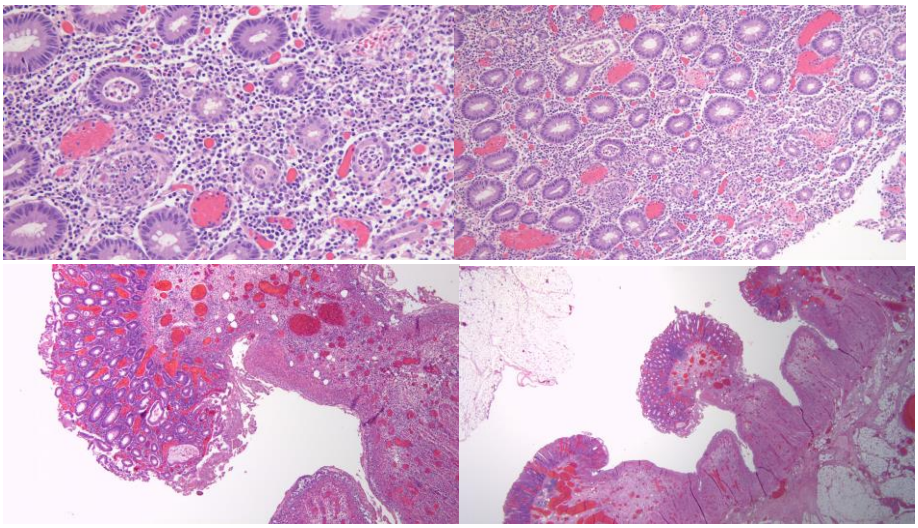

FIGURE 2: Histologic examination of the large bowel showing marked ulceration of the surface mucosa with a pseudopolyp appearance (A and B). Higher magnification of the non-ulcerated mucosa showed chronic active colitis, cryptitis and crypt abscesses (C and D).

Discussion

Campylobacter jejuni is a common cause of foodborne illness and causes acute gastroenteritis in humans. In contrast, it exists as a commensal organism in the digestive tract of other animals. As a result, there are few relevant animal models and therefore an incomplete understanding of its mechanism of colonization and virulence. Poultry are the most common source of *c. jejuni* infection (CJI) in humans. Symptoms are usually indistinguishable from other causes of bacterial gastroenteritis. However, CJI may mimic appendicitis or an acute flare of IBD. It is associated with a number of serious acute and late onset complications including cholecystitis, septic pseudoaneurysm, reactive arthritis, Guillain-Barre Syndrome. Recently, a strong association has been developed between CJI and ulcerative colitis.

Ulcerative colitis (UC) is a common subtype of IBD characterized by episodic T-cell mediated inflammation of the colonic mucosa. In most cases, the rectum is involved and the disease extends proximally and continuously along the colon. Common features include frequent bouts of bloody diarrhea, colicky abdominal pain, urgency, tenesmus, and incontinence. Rarely, patients are asymptomatic at the time of diagnosis. These patients represent about 1% of the total affected population and have a better prognosis with a lower complication rate (Park et al. 2014). It has been proposed that common enteric pathogens, especially *c. jejuni* and *salmonella*, play a role in the pathogenesis and progression of this chronic disease (Arora et al. 2016) and lead to exacerbations (Antonelli et al. 2012). Toxic megacolon and perforated viscus are rare complications of severe disease.

Toxic megacolon often arises as a complication of IBD or pseudomembranous colitis (Autenrieth and Baumgart 2012)**.** It is defined by acute nonobstructive dilatation of the colon with signs of

systemic toxicity. It is considered to be a surgical emergency as the risk of perforation is high. In this case, toxic megacolon was not anticipated due to our initial diagnosis of infectious colitis, which was made based on the absence of bloody diarrhea and our patient's elevated white count. While her culture was positive for CJI, we did not consider the possibility that this had provoked a flare of underlying, asymptomatic ulcerative colitis. Furthermore, our patient had no history of bloody stools and had recent colonoscopies with biopsies which found no evidence of IBD.

A literature search of MedLINE, EMBASE and Google revealed four large scale epidemiological studies associating acute CJI with increased short and long term risk of UC (García Rodríguez, Ruigómez, and Panés 2006; Gradel et al. 2009; Helms, Simonsen, and Mølbak 2006; Ternhag et al. 2008). It is believed that c. jejuni causes dysfunction of the epithelial barrier which causes increased translocation of intestinal microflora resulting in a dysregulated immune response in a susceptible host. (García Rodríguez, Ruigómez, and Panés 2006; Gradel et al. 2009; Kalischuk and Buret 2010)**.** A small retrospective chart review reported that 2.3% of UC flares were complicated by CJI. These patients had a higher rate of hospitalization, UC-related colectomy and all-cause mortality at 1-year follow-up (Arora et al. 2016).

We conclude that our patient had early, asymptomatic UC with its first acute flare instigated and complicated by severe CJI. To our knowledge, this is the first reported case in which CJI caused an acute and severe flare of previously asymptomatic UC resulting in toxic megacolon and requiring urgent colectomy. This highlights the recently described trend towards increased rates of colectomy and all cause mortality in co-presentations of UC and CJI. This case is significant as it demonstrates a severe complication of acute CJI with the pathogen having been identified only after colectomy. In most cases, acute gastroenteritis is self limited. However, guidelines have evolved to favour a lower threshold for stool testing (Riddle, DuPont, and Connor 2016). This trend will continue with the introduction of rapid assays to direct early antimicrobial treatment. This offers the potential of reducing the risk of life altering complications including toxic megacolon.

More research is underway to develop a better understanding of the effect of CJI on UC flares and to describe the optimal management of such co-presentations. Even in patients with known IBD, the presence of bloody diarrhea should prompt investigations for common enteric pathogens including *Salmonella, Shigella, Campylobacter, Yersinia, c. difficile, and STEC (Shane et al. 2017)*. In co-presentations with CJI, it has been reported that targeted antimicrobial therapy alone improved symptoms in 61 percent of patients (Park et al. 2014). Future research will describe the effect of such therapy on long-term outcomes. Early targeted therapy for superinfections may reduce morbidity, mortality and cost by decreasing the number of patients developing toxic megacolon and requiring operative management.

Severe colitis requiring hospitalization resulting from intestinal superinfection in IBD may be avoided with early, judicious use of antimicrobials. In this case our patient presented after nine days of severe diarrheal illness but had not undergone microbial assessment. Classically, stool testing was reserved for very select cases. However, according to the most recent guidelines, any moderate-to-severe diarrheal illness should undergo stool testing for common pathogens to allow

for targeted antimicrobial therapy (Riddle, DuPont, and Connor 2016). Rapid, non culture-based enteric assays will come to the forefront in the near future. If these were available in our case, targeted antimicrobial therapy could have been initiated sooner which may have attenuated our patient's disease course.

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