

Infliximab use in ulcerative colitis flare with *Clostridium difficile* infection: A report of two cases and literature review

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ABSTRACT

Clostridium difficile infection (CDI) is a major cause of morbidity and mortality in patients with inflammatory bowel disease (IBD), especially in ulcerative colitis (UC). The incidence and severity of CDI in IBD has shown an increasing trend in the last two decades. Patients with IBD are predisposed to CDI secondary to the recurrent use of antibiotics, corticosteroids, and immunosuppressants and secondary to dysbiosis. It is clinically challenging to distinguish the symptoms of CDI from an IBD flare. The worsening of IBD symptoms demands escalation of steroids or initiation of biologics. However, the management of CDI in IBD, not responding to antibiotics, is not well described beyond a few case reports. We report two cases of CDI with active UC flare. The patients did not respond to antibiotics or intravenous corticosteroids but had rapid resolution of CDI symptoms after receiving infliximab infusion. The optimal dosing and infusion frequency of infliximab in management of CDI in UC/IBD remains to be established.

Keywords: *Clostridium difficile*; comorbidity; dual; infliximab; tumor necrosis; treatment; ulcerative colitis.

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Inflammatory bowel disease (IBD) patients, especially those with ulcerative colitis (UC), are at a high risk of developing *Clostridium difficile* infection (CDI) and related complications. CDI has been reported in 1.8%–5.7% of the patients hospitalized for UC [1]. IBD patients with CDI have poor outcomes with increased severity of relapse, longer hospital stay, and high rates of colectomy and mortality [2]. Approximately 10% of IBD patients develop CDI at the time of diagnosis or during the course of their disease [3, 4]. Colon involvement increases the risk of CDI by several fold compared with small bowel disease. Probably due to this reason, UC patients have a higher risk of developing CDI compared to Crohn's disease (CD) patients [1]. IBD patients also have a higher rate (8% vs 1%) of asymptomatic carriage of *C. difficile* than the general healthy population

[5]. The management of CDI in IBD, not responding to antibiotics, is a challenge.

Here we report two cases of UC flare secondary to CDI.

CASE REPORTS

Case 1 – A 21-year-old female with the history of pan-UC presented with bloody diarrhea. She was having approximately 20 bowel movements a day along with lower abdominal pain, fever, tenesmus, and urgency.

The patient was diagnosed with pan-UC 3 years ago using colonoscopy and mucosal biopsies. She achieved clinical remission with high prednisone dose for 3 weeks with a gradual tapering off and was on maintenance therapy with azathioprine and mesalamine. Due to financial

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reasons, she discontinued all her medications after a few months of remission. She stayed in remission until 3 months ago when she was admitted to an outside hospital with fever, abdominal pain, and bloody stools. Stool studies were negative for infection including that with *C. difficile*. Colonoscopy showed mucosal inflammation in the rectum and sigmoid and descending colon. Mucosal biopsies indicated acute or chronic colitis without dysplasia. Intravenous steroids were initiated, and the patient was discharged on oral prednisone with a gradual tapering off. Prior to the current admission, she received two doses of infliximab.

Patient appeared sick on initial presentation. She was afebrile and tachycardic with a heart rate of 112/min and had soft blood pressure of 98/49 mmHg without orthostatic hypotension and 95% oxygen saturation. Her bowel sounds were hypoactive, and the abdomen was diffusely tender to palpation.

Laboratory workup was significant for an elevated white blood cell (WBC) count of 21,000/ μ L with left shift, microcytic anemia with hemoglobin of 11 g/dL, erythrocyte sedimentation rate (ESR) 29 mm/h, and C-reactive protein (CRP) 18 mg/dL. Other renal and liver chemistries were normal. Stool polymerase chain reaction (PCR) was positive for toxin-producing *C. difficile* with a negative hyper-virulent 027-NAP1-B1 strain. Computed tomography of the abdomen with intravenous contrast (Fig. 1A, B) showed multifocal, moderate mural thickening throughout the colon, most pronounced in the ascending colon. The appendix was dilated with mild periappendiceal fat stranding along with enlarged right lower quadrant mesenteric lymph nodes. Flexible sigmoidoscopy (Fig. 2) showed friable, granular mucosa with pseudo membrane formation, which was consistent with Mayo Class 2 endoscopic disease activity. Mucosal biopsies showed chronic active colitis with moderate ac-

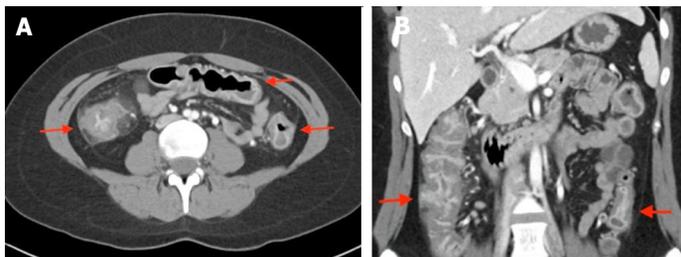


FIGURE 1. CT scan of abdomen and pelvis with intravenous contrast shows moderate wall thickening throughout the colon, most pronounced in the ascending colon.

tivity and granulation tissue. The test for cytomegalovirus stain showed negative results.

Treatment was initiated with oral vancomycin and intravenous metronidazole along with aggressive intravenous hydration. General surgery department was consulted, and it recommended against acute surgical intervention. Patient failed to improve over the next 72 h; thus, a decision was made to start intravenous methyl prednisone 40 mg daily with a gradual tapering off. WBC count, ESR, and CRP levels started improving, but diarrhea persisted. Infliximab levels were less than 1 mcg/mL. The patient received a dose of 10 mg/kg infliximab, resulting in the resolution of diarrhea over the next 24 h. She successfully completed a 2-week course of vancomycin and metronidazole and had completely recovered from the flare at a follow-up visits after 2 and 6 weeks.

Case 2 – A 19-year-old male with a history of pan-UC presented with diarrhea and abdominal pain. He complained of watery diarrhea, on and off mixed with blood, associated with urgency and lower abdominal pain.

The patient was diagnosed with pan-UC 4 months ago using colonoscopy and mucosal biopsies. Oral mesalamine was initiated, and he achieved a clinical remission within few weeks. He had experienced two episodes of CDI since the onset of UC. The first episode was treated with oral metronidazole and the second with a 4-week taper

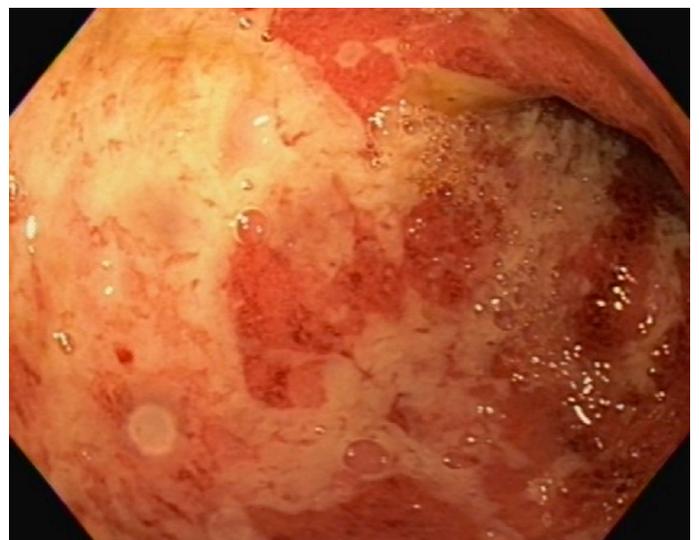


FIGURE 2. Endoscopic view of sigmoid colon showing friable, granular mucosa with pseudo membrane formation consistent with severe *Clostridium difficile* infection.

of oral vancomycin. He remained asymptomatic for more than a month.

Patient's vital signs were stable on presentation. There was no fever, tachycardia, or hypotension. Abdomen was tender to palpation with normal bowel sounds. Laboratory workup showed hemoglobin levels of 10 g/dL and ESR 25 mm/h. Other hematology and biochemistries were within the normal range. Stool PCR was positive for toxin-producing *C. difficile* with a negative hyper-virulent strain.

Treatment was initiated with oral vancomycin and intravenous steroids. Patient had resolution of hema-tochezia, but severe diarrhea persisted. He received 5 mg/kg infliximab infusion after 5 days, resulting in complete resolution of diarrhea within 24 h. He was re-evaluated in the clinic after 3 months and continues to do well on infliximab infusion every 8 weeks.

DISCUSSION

C. difficile is a gram-positive, anaerobic, spore-forming, toxin-producing bacillus transmitted through the fecal-oral route. In the late 1970s, it was first recognized as a causative agent of antibiotic-related pseudomembranous colitis [6]. It slowly emerged as the leading cause of gastroenteritis-related mortality, and the incidence of CDI has been steadily rising over the decades. In 2011, *C. difficile* was responsible for approximately half a million cases of infection and 29,000 deaths in the US [7]. Since 2005, the hyper-virulent strain of *C. difficile*, commonly referred as NAP1/B1/027, has been responsible for frequent outbreaks in North America, England, Europe, and parts of Asia [8]. Community-acquired CDI is seen in the absence of antibiotic use. It is also emerging in increasing proportions; a 2011 US study reported an adjusted national rate of 51.9 per 100,000 population [7].

Dysbiosis appears to play a vital role in the pathogenesis of both IBD and CDI [9]. Dysregulation of immune tolerance to the commensal gut microbiota possibly leads to mucosal inflammation in IBD. Reduced microbiota diversity also promotes *C. difficile* transmission and germination. The cytotoxic effects of *C. difficile* toxin damage the epithelial barrier, promote bacterial adhesion, and increase mucosal permeability, thus, contributing to the pathogenesis of IBD [10]. The fundamental question of whether CDI is a cause or outcome of IBD still remains unanswered. CDI may cause superimposed colitis in IBD or might precipitate an IBD flare with two sepa-

rate, but simultaneous, ongoing inflammatory processes [10]. Probably this is the reason that UC flare patients co-infected with *C. difficile* have poorer long-term outcomes than those not infected with this bacterium [11]. Another hypothesis is that *C. difficile* might be just a colonizer in IBD patients, and disease flares are completely independent of its presence [10].

It is a diagnostic dilemma to differentiate whether the symptoms are due to a flare of chronic IBD or new CDI. American College of Gastroenterology (ACG) 2013 guidelines recommend that all IBD patients with a disease flare or new-onset diarrhea must be tested for CDI (12). PCR detects toxin-producing genes and is currently the preferred test for CDI. It is a rapid test with high sensitivity (>90%) and high specificity (>95%) [13]. Enzyme immunoassay detects toxins A and B in stools. It is rapid, cost effective, and has variable sensitivity (63%–94%) and specificity (75%–100%) [14]. It is important to emphasize that PCR can detect *C. difficile* isolates that contain inactive toxin genes, which are not actively transcribing toxins, leading to false-positive tests. A positive PCR also cannot differentiate between an asymptomatic carrier and an active infection. Testing should be performed only on unformed stool to reduce the false-positive rates.

An American Gastroenterology Association expert review recommends that IBD should be considered as a severity marker of CDI and vancomycin or fidaxomicin should be considered as first-line antibiotics. Patients with mild to moderate disease are treated with 125 mg oral vancomycin four times a day. Those with severe or complicated disease should be given a higher oral dose of 500 mg vancomycin four times a day combined with 500 mg intravenous metronidazole 8 hourly and vancomycin enemas along with early surgery consultation [12].

The second important decision is regarding the management of immune suppression with ongoing infection. ACG 2013 guidelines recommend simultaneously starting empirical therapy for CDI and IBD flare in cases of severe colitis while awaiting *C. difficile* test results. The ongoing immunosuppressive medications should be continued while treating CDI. The initiation of corticosteroids or anti-tumor necrosis factor (TNF) therapy is discouraged in the first 72 h [12]. Using a combination of immunomodulators and antibiotics in CDI tends to have worse outcomes than using antibiotics alone [15]. Intravenous corticosteroids are commonly the first choice in escalation of immunosuppression when CDI

symptoms do not improve with antibiotics alone. The patient should be monitored closely for worsening of CDI symptoms or impending complications like toxic megacolon or perforation.

Infliximab is a chimeric Ig G4 monoclonal antibody targeting TNF- α (TNF- α). It is frequently used for induction of rapid remission in patients with fulminant UC. However, it has not been very well studied for use in UC flare secondary to CDI [16]. Induction of TNF- α by *C. difficile* toxins A and B in addition to other cytokines in causing inflammation suggests the potential role of anti-TNF therapy in CDI [17]. Anti-TNF therapy was found to be protective against CDI in a study [18]. In another population-based study, infliximab was not found to be associated with an increased risk of developing CDI [19]. Infliximab infusion resulting in therapeutic trough levels resulted in resolution of recurrent CDI symptoms in a single reported case of UC [20]. Infliximab drug level of less than 0.5 $\mu\text{g/mL}$ requires dose escalation or shortening of interval between the infusions [21]. Contrary to the above evidence, Razik et al. reported more episodes of recurrent CDI in IBD patients on infliximab, whereas those on adalimumab did not show an increased risk. Azathioprine, methotrexate, and cyclosporine did not increase the risk of recurrent CDI [22]. Similarly, Zhang et al. [23] showed an increased risk of CDI in IBD patients on infliximab and antibiotics. A recent population-based study in Canada showed increased risk of CDI among IBD patients who were on corticosteroids or anti-TNF agents [24].

Immunotherapy, with intravenous immunoglobulin (IVIG), has been attempted in recurrent CDI with limited success in small studies [25, 26]. The rationale is that patients with severe or recurrent CDI have lower serum antitoxin antibody levels [27]. Fecal microbiota transplantation is less effective in clearing recurrent CDI in IBD patients than in patients without IBD (74.4% vs 92.1%) [28]. It was also associated with IBD flare in one-fourth of the patients in the same study.

There is a paucity of literature on the use of corticosteroids, infliximab, or IVIG in CDI associated with IBD. Furthermore, there is contradicting data on the beneficial effect of infliximab in CDI. Both of our patients did not respond to antibiotics and corticosteroids for 72 h but showed rapid improvement with infliximab infusion. Checking serum infliximab levels during a flare might be useful in guiding further therapy for CDI. Prospective studies in the future will likely provide more insight on the use of biologics in IBD flare associated with CDI.

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