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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Severe Ileocolonic Crohn's Disease Flare Associated with Fecal Microbiota Transplantation Requiring Diverting Ileostomy

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ABSTRACT

Patients with inflammatory bowel disease (IBD) are at increased risk of developing *Clostridium difficile* infection (CDI). Fecal microbiota transplantation (FMT) is an effective therapy with a high success rate in preventing recurrent CDI. However, patients with IBD have decreased response to FMT for recurrent CDI, with several reports also suggesting potential IBD flare post-FMT. We present a case of mild ileocolonic Crohn's disease in a patient treated with FMT for recurrent CDI who subsequently developed severe steroid-refractory flare requiring surgical intervention 1 week post-FMT. Greater understanding of risk factors associated with post-FMT IBD flare is indicated.

INTRODUCTION

Fecal microbiota transplantation (FMT) involves transplantation of feces from a healthy individual to another to introduce a complex, diverse community of intestinal microbes to the recipient. The intestinal microbiome of a patient with recurrent *Clostridium difficile* infection (CDI) shows decreased microbial diversity, with antibiotic treatment considered the most commonly known risk factor associated with CDI development. Multiple CDI recurrences are associated with increasing loss of microbial diversity.[1] Studies show that FMT has a roughly 90% success rate in preventing recurrence of CDI.[2]

Inflammatory bowel disease (IBD) and other systemic inflammatory conditions are also associated with disruption in the gut microbial ecosystem. Success of FMT in CDI has inspired studies to explore FMT in conditions such as IBD. While the pathophysiology of IBD still remains largely unknown, genetically susceptible individuals are thought to experience an altered immune response to commensal flora or other environmental factors leading to gastrointestinal inflammation, microbial dysbiosis, and a further decrease in microbial diversity.[3] Several studies have suggested that repeat administration of FMT can potentially decrease intestinal inflammation in ulcerative colitis.[4] However, FMT has not shown consistent success in preventing recurrent CDI in patients with IBD or treating the IBD itself.[5] Preliminary reports suggest that up to 25% of IBD patients can also experience IBD flare post-FMT.[6]

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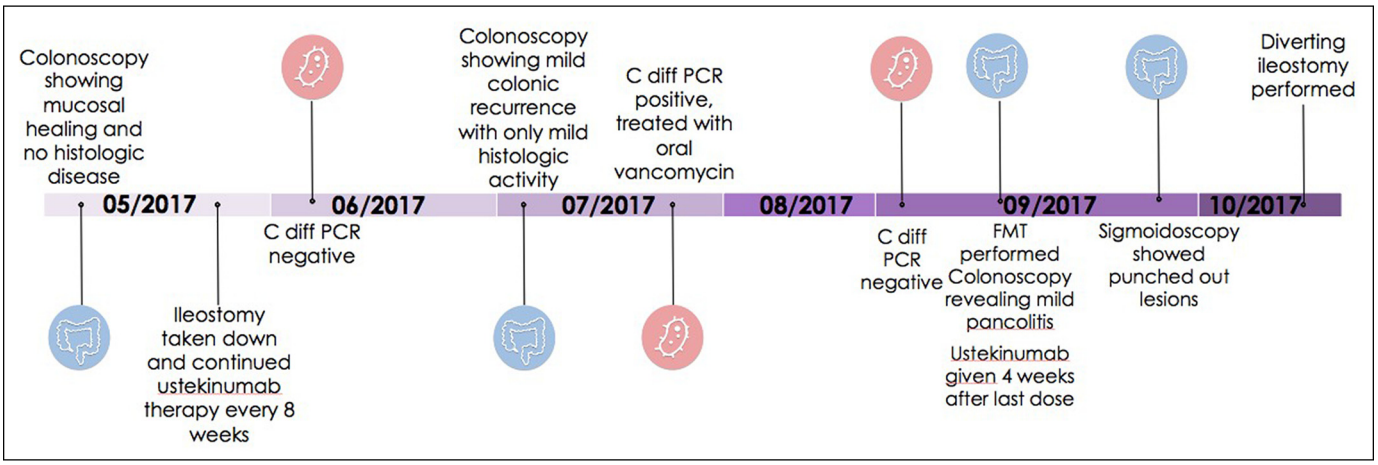

Figure 1. Timeline of events surrounding presentation.

CASE REPORT

A 35-year old man with a history of refractory ileocolonic Crohn's disease with primary sclerosing cholangitis and recurrent CDI presented with watery diarrhea and abdominal pain. His medical history included refractory Crohn's disease, first diagnosed at age 28, requiring multiple diverting ileostomies complicated by disease flare upon ileostomy takedown and non-response to multiple therapies, including thiopurines, methotrexate, infliximab, adalimumab, and vedolizumab. Despite counseling, the patient was not amenable to colectomy throughout his disease course. His disease course had been complicated by at least 7 episodes of CDI with positive *C. difficile* polymerase chain reaction (PCR) tests over the past 7 years corresponding to worsening of clinical symptoms, ultimately requiring long courses of suppressive antibiotic therapy with vancomycin and consideration for FMT in the past. He had negative *C. difficile* PCR studies between episodes.

Four months prior to this presentation, the patient was on ustekinumab maintenance therapy every 8 weeks with colonoscopy demonstrating mucosal healing and no histological evidence of active disease. An ileostomy takedown was performed at this time (Figure 1). Subsequent colonoscopy 2 months after takedown revealed mild colonic recurrence with few scattered aphthous ulcers noted in the sigmoid and descending colon; biopsies showed only mild histologic activity in the rectum. During this month, he also had an episode of CDI (positive *C. difficile* PCR) that was subsequently treated with oral vancomycin.

Two months later, the patient had mild tenderness in the lower abdomen. He was afebrile with elevated inflammatory markers (C-reactive protein 2.2 mg/dL; erythrocyte sedimentation rate 35 mm/hr), and *C. difficile* PCR and stool bacterial pathogens studies were negative. With the intention to prevent future CDI recurrences after his recent episode and history of recurrent 7 prior episodes, FMT was performed via colonoscopy, which revealed mild pancolitis (Figure 2). He received ustekinumab the night following the FMT, which was four weeks after his previous dose, due to evidence of recurrent disease despite standard ustekinumab dosing.

Two days later, the patient was readmitted with fever, abdominal pain, and frequent bloody stools. C-reactive protein and erythrocyte sedimentation rate were elevated to 12.7 mg/dL and 58 mm/hr, respectively. Stool studies were negative for infection. Sigmoidoscopy 1 week after FMT demonstrated punched-out ulcerations in the sigmoid and descending colon (Figure 3). Biopsies for cytomegalovirus were negative. Albumin decreased from 4.0 g/dL on presentation to 2.1 g/dL. Intravenous solumedrol was given for 5 days with initial improvement, but due to worsening symptoms and continued C-reactive protein elevation upon transition to

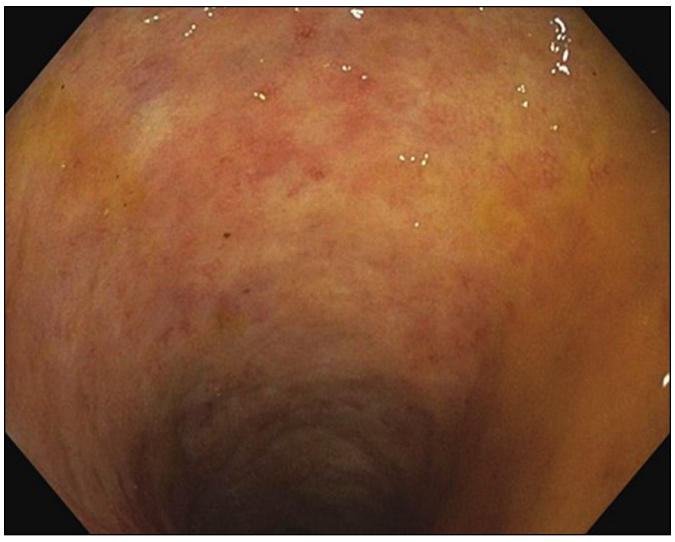

Figure 2. Colonoscopy image of colonic mucosa prior to fecal microbiota transplantation.

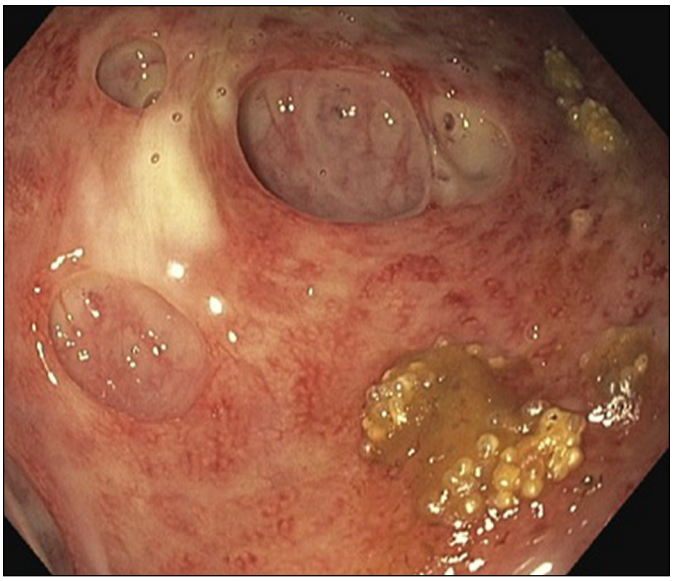

Figure 3. Colonoscopy image of colonic mucosa a week after fecal microbiota transplantation.

oral steroids, the patient requested diverting ileostomy for colonic healing while continuing on ustekinumab therapy. At follow-up 2 weeks later, he reported feeling well with no abdominal pain or fevers with healthy weight gain, and he was weaned off steroids. He has not experienced further CDI relapse and is currently continuing ustekinumab maintenance therapy every 4 weeks to maintain remission after ileostomy takedown.

DISCUSSION

While FMT has demonstrated efficacy in preventing recurrence of CDI, studies are ongoing to evaluate the success of FMT for underlying IBD. Several reports also suggest potential worsening of disease activity after FMT.[11] It is postulated that exposure to microbiota in these IBD patients with altered mucosal integrity promotes a disproportionate host immune response to the transplanted microbiota, resulting in worsening of IBD activity and disease progression.[5,7,8] Case reports suggest that greater underlying disease severity may predispose to disease flare post-FMT.[9-11] Our patient notably had only mild mucosal disease prior to FMT. A similar case described a patient with quiescent ulcerative colitis for more than 20 years who developed a flare of ulcerative colitis after FMT, which was successfully treated with oral steroids.[12]

Potential etiologies of our patient's rapid flare after FMT were explored. While the passage of unrecognized pathogens in the donor stool may have precipitated his flare, stool studies and biopsies performed were negative for infectious etiologies or cytomegalovirus. While our patient was on immunosuppressive therapy with maintenance ustekinumab escalated to every 4 weeks, multiple studies have demonstrated safe and effective FMT for CDI in immunocompromised patients.[6,9,13] It is possible that the flare was impending and occurred coincidentally after the FMT. However, the timing of his acute flare 2 days after FMT, with colonoscopy performed at the time of FMT only showing mild mucosal disease, suggests that the FMT intensified this flare.

Because of the increasing use of FMT for recurrent CDI in patients with IBD, it is important to further understand the effect of this therapy on patients with active and inactive IBD.[6] Prospective studies will help elucidate optimal patient selection and timing of IBD treatment optimization and FMT in patients with IBD.[14] Greater understanding of the risk factors associated with post-FMT IBD flare is also warranted.

DISCLOSURES

Author contributions: V. Tran, J. Phan, B. Nulsen, L. Huang, M. Kaneshiro, G. Weiss, W. Ho, J. Sack, C. Ha, and D. Uslan wrote, edited, and approved the final version. JS Sauk wrote, edited, revised, and approved the final version of the manuscript, and she is the article guarantor.

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