CASE REPORT

Faecal microbiota transplantation for recurring *Clostridium difficile* infection in a patient with Crohn's disease and ileorectal anastomosis

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SUMMARY

Faecal microbiota transplantation (FMT) is increasingly being used to treat refractory and recurring *Clostridium difficile* infection (CDI). Although FMT appears to be safe and highly effective in patients with a preserved colon and immunocompetence, its use in patients with inflammatory bowel disease (IBD) who are on immunomodulating therapies is controversial. In particular, patients who have undergone colectomy may have different treatment responses to FMT. In this case report, we describe the successful use of FMT in a female patient aged 19 years with Crohn's disease who underwent ileorectal anastomosis following colectomy. She had recurrent CDIs that were refractory to metronidazole, pulse-tapered vancomycin and fidaxomicin treatments. She underwent 2 FMTs, which were performed via sigmoidoscopy; her mother served as a donor. Follow-up was conducted for 12 months and indicated sustained remission of CDI.

BACKGROUND

Patients with inflammatory bowel disease (IBD) are at an increased risk for recurrent and treatment-refractory *Clostridium difficile* infection (CDI), which may lead to colectomy.[1 2] Although CDI mainly affects the colon, it has been reported in patients who have previously underwent colectomy, and CDIs in the small bowel and ileo-anal reservoirs are increasingly being reported.[3 4] The standard treatment for CDI is antibiotics, which are curative in 70–80% of cases. However, recurrent CDI is a therapeutic challenge, with 20–30% of patients experiencing recurrence within 2 weeks after completion of a first course of antibiotics.[5] Approximately 20–40% of patients experience subsequent infections after the first recurrence.[6]

Faecal microbiota transplantation (FMT) is a promising therapy for CDI. In two recent randomised trials, FMT was superior to vancomycin in treating recurrent CDI.[7 8]

In the current case report, we describe the successful use of FMT to treat a patient with Crohn's disease with relapsed CDI following subtotal colectomy and ileorectal anastomosis.

CASE PRESENTATION

An otherwise healthy young female was diagnosed with colonic Crohn's disease at 11 years of age. Treatment with intravenous methylprednisolone (40 mg daily) and metronidazole followed by a 17-week-long prednisolone taper combined with 1200 mg mesalazine and 100 mg azathioprine lead to brief symptomatic remission.

One week after completing the prednisolone taper, the patient experienced the first of a series of CDIs. On initial metronidazole treatment, she improved clinically, but her CDI relapsed after treatment cessation. Over the next years, she experienced nine recurrences of CDI, which were treated with either 400 mg metronidazole three times daily for 10 days or 250 mg oral vancomycin four times daily for 3 weeks. The CDI recurred after each treatment. Sustained clinical remission was only obtained with continuous administration of 400 mg metronidazole one to three times daily in combination with 250 mg of the non-pathogenic yeast *Saccharomyces cerevisiae* three times daily. The patient was not infected with *C. difficile* BI/NAP1/027 ribotype at any time.

Five years after her Crohn's disease diagnosis, the patient experienced increasing symptoms, including lower abdominal pain, bloody stools and vomiting. Faecal cultures were negative, and colonoscopy revealed a severe stenosis in the sigmoid colon. Infliximab treatment led to short-term improvement; however, this improvement was followed by a new CDI, which was treated with 500 mg metronidazole three times daily for 10 days. Repeated stool cultures confirmed the clearance of the infection. Increasing symptoms from the sigmoid stenosis were treated with a colectomy and the formation of an ileorectal anastomosis.

Following surgery, the patient was medication-free for 1 year. However, because of increasing rectal inflammation, a combination treatment with infliximab and azathioprine was initiated. This treatment successfully induced sustained remission.

Three years after her colectomy, the patient, having reached 19 years in age at that point, experienced a recurrence of CDI. Following an unsuccessful 10-day vancomycin trial, she was treated with vancomycin combined with *Saccharomyces boulardii* capsules for 6 weeks and then with 200 mg fidaxomicin two times per day for 10 days. The effect was transient, and CDI recurred after 3 weeks. The infection was at no time treatment refractory to neither of the used antibiotics, but eventually recurred following cessation of the treatments. After the last relapse following the fidaxomicin treatment, FMT was considered.

TREATMENT

Following preparation with 125 mg vancomycin four times daily for 6 days, the patient underwent

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FMT using donor stool from her mother, who had been serologically screened to verify the absence of HIV, Epstein-Barr virus, cytomegalovirus and hepatitis B and C. The stool cultures were verified to be free of pathogenic bacteria and *C. difficile*. Following initial recovery, the patient's CDI relapsed after 2 weeks. Another FMT procedure was performed, using the same donor and method. The second procedure led to complete recovery from CDI, which was sustained at her 1-year follow-up examination.

The FMTs were administered through the working channel of a video endoscope placed 40–60 cm above the ileorectal anastomosis, as well as in the rectum. During the endoscopy, the ileum appeared normal, and there was unspecific erythema in the rectum. No immediate or delayed adverse effects of the FMTs were observed.

OUTCOME AND FOLLOW-UP

Clostridium difficile stool cultures 12 months after the last FMT were negative. Treatment with infliximab and azathioprine was continued throughout this period.

DISCUSSION

Increasing evidence supports the use of FMT as an efficient therapy for severe cases of recurrent CDI,[9] and it is becoming the standard of care in many centres.[10] In the present case report, we describe the use of FMT for recurring CDI in a patient with an ileorectal anastomosis following subtotal colectomy for Crohn's disease.

IBD is associated with a threefold increased risk of community-acquired CDI,[11] and a 30% risk of CDI recurrence after the first episode.[1] Furthermore, in IBD patients, CDIs are less responsive to metronidazole than in the general population,[2] and cause increased morbidity and mortality.[12]

The faecal microbiota of IBD patients is characterised by decreased biodiversity. This reduced biodiversity may increase susceptibility to CDI. Whether these changes are a cause or a consequence of IBD is unknown.[13] The faecal microbiota composition was not investigated in this patient. Many IBD patients are treated with immunomodulators and glucocorticoids, which are independent risk factors for severe infection and mortality in patients with CDI.[14 15]

In IBD patients, CDI is less frequently caused by the use of antibiotics than in the general population, as only 43% of CDI cases in active IBD patients are associated with exposure to antibiotics.[16] CDI in IBD patients represents a unique clinical challenge, and CDI can mimic and precipitate an IBD flare. Therefore, all IBD patients should be tested for CDI prior to undergoing treatment for acute flares. A positive *C. difficile* stool test does not necessarily indicate clinically significant infection, because *C. difficile* can be present as asymptomatic colonisation. In our patient, too, symptoms of CDI and active Crohn's disease were similar. The distinction between the two was mainly based on the time pattern of sudden onset of watery stools and malaise following cessation of antibiotic treatment in combination with a positive CD stool test, and documentation of CD clearance and clinical improvement during antibiotic treatment. During the last four CDIs, stable doses of immunosuppressive and biological therapy were provided, and the patient was in clinical remission during vancomycin or fidaxomicin treatment.

Colectomy does not protect against CDI; rather, it may increase the risk of CDI in patients with ileostomies and ileo-anal reservoirs (J-pouch).[17 18] As the current case report indicates, patients with an ileorectal anastomosis following colectomy may acquire CDI.

The standard treatment for CDI is antibiotic therapy with either metronidazole or oral vancomycin in the case of severe disease. In relapsing infection, prolonged treatment with tapered doses of vancomycin for 6 weeks combined with 4 weeks of *S. boulardii* has been recommended.[19] Although fidaxomicin did not improve the clinical course in our patient, the administration of 200 mg fidaxomicin two times per day for 10 days may reduce the risk of recurrence compared with vancomycin treatment.[20]

Recently, FMT was found to be superior to vancomycin for treating recurrent CDI in two randomised trials.[7 8] The cure rates were 90–94% in the FMT groups compared with 26–27% in the groups of patients treated with vancomycin. In previous case reports and case series of IBD patients treated with FMT for CDI, remission rates of up to 70% have been reported.[21] However, no report on the use of FMT for refractory or recurring CDI after subtotal colectomy has been published, although there are reports of patients with refractory and recurrent CDIs of the ileo-anal pouch undergoing successful treatment with FMT.[3] Seril and Shen[3] proposed oral vancomycin for the index CDI and early use of FMT as an algorithm for the management of CDI after colectomy.

Our patient became immunocompromised in response to combined treatment with a biological and an immunomodulator. This gave rise to concerns regarding the risks of bacterial translocation and overgrowth following FMT. A compromised immune system per se does not appear to be a problem, as FMT has been reported to be safe for patients receiving immunosuppressive treatment,[22] In IBD patients, the overall safety of FMT may not be as high as in patients with CDI without concomitant IBD.[21] The adverse events that have been reported after FMT in patients with IBD include fever, increased C reactive protein, diarrhoea, vomiting, bacteraemia and flare-ups of ulcerative colitis.[21] The risk of these adverse events may be related to the compromised gut barriers observed in these patients.[21]

The current case report suggests that FMT is an efficient and safe treatment for CDI in immunocompromised and postcolectomy patients with Crohn's disease. The current state of knowledge regarding the use of FMT in patients with IBD and CDI after colectomy is mainly based on case reports. Comparative studies examining the management of CDI after colectomy in patients with IBD are warranted to establish treatment algorithms that rank antibiotic regimens and FMT.

Patient's perspective

My experience

- After many attempts to keep the clostridia away, I was introduced to the idea of faecal transplantation. When I first heard it mentioned, I thought, 'This is simply too disgusting —I will never have that treatment! Receiving faeces from another human being is simply too odd. However, I became much more calm and positive about the treatment when I was told that the donor could be a person I knew, and after thorough discussions with the physician, I decided to try it out'.
- It did not take long after the first transplantation before I had clostridia again, and I was disappointed with yet another defeat. But, after the second treatment, I continuously improved, and I have been now been cured from clostridia for a year! This is the best decision that I have ever made.

Learning points

- Patients with inflammatory bowel disease are at an increased risk for recurrent and treatment-refractory *Clostridium difficile* infection (CDI).
- Colectomy does not protect against CDI; rather, it may increase the risk of CDI in patients with ileostomies and ileo-anal reservoirs (J-pouch).
- The current case report suggests that FMT is an efficient and safe treatment for CDI in immunocompromised and postcolectomy patients with Crohn's disease.

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