FECAL MICROBIOTA TRANSPLANTATION IN RECURRENT NAP1/B1/027 CLOSTRIDIUM DIFFICILE INFECTION (CDI) RESISTANT TO VANCYMYCN AND METRONIDAZOLE IN A PATIENT WITH ULCERATIVE COLITIS (UC): A CASE REPORT

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FECAL MICROBIOTA TRANSPLANTATION IN RECURRENT NAP1/B1/027 CLOSTRIDIUM DIFFICILE INFECTION (CDI) RESISTANT TO VANCYMYCN AND METRONIDAZOLE IN A PATIENT WITH ULCERATIVE COLITIS (UC): A CASE REPORT

Abstract: Most of the studies showed that IBD patients with inflammatory bowel diseases (IBD) with CDI have more of the whole range of short- and long-term worst outcomes than those without CDI. Initial infection with the BI/NAP1/027 epidemic clone was found to be a significant risk factor for relapse. However, current literature is suggesting increasingly that for patients with infections that fail to resolve with traditional antibiotic regimens, FMT’s average cure rate of >90%. We report a case of a 40-year-old man, diagnosed with ulcerative colitis (UC) in 2012 who presented in our clinic for 20 watery stools per day with mucus and blood, hypogastric pain, pyrexia and chills. Rectosigmoidoscopy and histopathological examination diagnosed active lesions of ulcerative colitis with Clostridium difficile toxins A/B enzyme immunoassays (EIA) testing initially negative. The patient was non-responder at day 10 of intravenous (iv) corticotherapy and received induction therapy with Infliximab 5 mg/kg. EIA testing for Clostridium difficile was repeated at day 12 of hospitalization with positive results for toxins A/B, and associated oral therapy with Vancomycin and Metronidazole was initiated without clinical response in day 7, reasons for what intravenously therapy with Tigecycline was started with good response. Patient was discharged after 10 days of Tigecycline, but came back twice for two relapses of Clostridium difficile colitis treated successfully with Tigecycline, reasons for what fecal transplantation was performed in Matei Bals Institute, which induced remission of both CDI and UC. Keywords: FECAL MICROBIOTA, TRANSPLANTATION, CLOSTRIDIUM DIFFICILE, INFECTION, ULCERATIVE COLITIS.

Most of the studies showed that IBD patients with CDI have more of the whole range of short- and long-term worst outcomes than those without CDI. Patients with ulcerative colitis have more severe outcomes than those with Crohn’s disease (1). Rates and severity of Clostridium difficile infection (CDI) in hospitals in North America and Europe have increased since 2000 and correlate with dissemination of an epidemic strain characterized by higher than usual toxin A and B production, the presence of a third toxin, binary toxin, and
high-level resistance to antibiotics. The strain, which is restriction endonuclease analysis group BI, pulse-field gel electrophoresis type NAP1, and polymerase chain reaction ribotype 027, is designated BI/NAP1/027 (2, 3, 4).

**CASE PRESENTATION**

A 40-year-old man, was admitted in our department in May 2014, for 20 watery stools per day with mucus and blood, hypogastric pain, pyrexia and chills.

His medical history includes chronic hepatitis B infection in treatment with entecavir 0.5 mg per day and UC diagnosed in 2012, in treatment with azathioprine at a dose of 150 mg per day (2.5 mg/kg). He confessed cessation of smoking for one year, previously being a chronic smoker of 20 cigarettes per day.

Should be mentioned in his medical history multiple flares of UC since diagnosis due to low-compliance to medication, also self-discontinuation of azathioprine 2 weeks before hospital admission because of lack of money.

At clinical examination the patient was apyretic, underweight with a BMI of 17.5 kg/m² with skin and mucosal pallor, tachycardia and with tenderness in lower abdomen with palpation.

Laboratory tests showed moderate leukocytosis, important increase in C-reactive protein levels and hypochromic microcytic anemia.

Stool test were negative for infections. *Clostridium difficile* toxins A/B enzyme immunoassays (EIA) tested negative.

Rectosigmoidoscopy revealed: absent vascular pattern, edema, erythema, friability of the mucosa and erosions. Continuous lesions on 60 cm explored (fig.1).

Histopathological examination showed: Diffuse chronic mucosal inflammation, cryptitis, regenerating epithelium with erosion and superficial fibrino-leukocytic exudate, HE, 200 x (fig. 2)

Fig. 1. Rectosigmoidoscopy absent vascular pattern, edema, erythema, friability of the mucosa and erosions.

Fig. 2. Histopathological examination diffuse chronic mucosal inflammation, cryptitis, regenerating epithelium with erosion and superficial fibrino-leukocytic exudate, HE, 200x

The severity of UC flare was framed in a Mayo score of 12 points.

The patient received intravenous (iv) corticotherapy with lack of response at day 10.

First induction dose of infliximab 5
Fecal microbiota transplantation in recurrent NAP1/B1/027 *Clostridium difficile* infection (CDI) resistant to vancomycin and metronidazole in a patient with ulcerative colitis (UC).  

Case report

mg/kg was administered with the maintenance of oral corticotherapy. EIA testing for *Clostridium difficile* was repeated at day 12 of hospitalization with positive results for toxins A/B.

We decided to stop further administration of infliximab and start tapering corticotherapy until *Clostridium difficile* eradication. We initiated oral Vancomycin 1000 mg per day in association with oral Metronidazole 1500 mg per day and *Saccharomyces boulardii* capsules 500 mg per day. After three days the patient developed digestive intolerance with vomiting and the regimen was changed to i.v. Metronidazole 1,500 mg/day.

At day ten of treatment the patient had a decrease in the number of stools (9 per day, with no blood but with the presence of pus), still with persistent abdominal pain. Blood tests showed no modification regarding inflammatory panel with increased values in serological inflammatory markers, severe hypochromic microcytic anemia that required blood transfusions and severe hypoalbuminemia.

Fecal cytology showed the presence of leukocytes.

Nucleic acid amplification test (NAAT) for *Clostridium difficile* toxin genes was positive for hipervirulent NAP1/B1/027 strain.

Oral vancomycin was continued with increased dosage 2,000 mg per day (500 mg every 6 hours) in association with vancomycin enemas 500 mg four times per day.

After ten days of previous regimen due to lack of response we added tigecycline 50 mg every 12 hours intra-venously for 16 days with clinical response consisted in normalization in the frequency and consistency of stools.

The patient was discharged from hospital with the recommendation to continue vancomycin in a tapering regimen 250 mg four times daily with halving doses weekly until 125 mg every other day for 7 days in association with *Saccharomyces boulardii* capsules 500 mg per day. Oral corticotherapy tapering was continued.

After one month the patient was readmitted to the hospital for the recurrence of watery bloody stools and severe abdominal pain.

We performed EIA retesting for *Clostridium difficile* which was positive for both toxins A and B and fecal cytology which showed the presence of leukocytes.

Patient received a second course of intravenous tigecycline 50 mg every 12 hours with favorable evolution and the normalization of stools at day 7.

At two weeks follow up the patient presented with the second relapse of *Clostridium difficile* colitis and again was treated with tigecycline in association with oral metronidazole, oral vancomycin and *Saccharomyces boulardii* capsules with favorable evolution.

After this third recurrence of Clostridium difficile infection patient received fecal microbiota transplantation (FMT) in Matei Bals Institute with a donor from the personal of the Hospital, through a nasogastric tube.

One month after, the patient had a fourth recurrence of *Clostridium difficile* colitis meeting the same pattern as the previous and we performed a second procedure of FMT (changing the donor with one person from the patient’s village).

At further follow-ups for a period a 2 years the patient was in clinical remission of inflammatory bowel disease with the normalization of clinical examination, weight
gain and with normal range for serological inflammatory markers, on maintenance therapy with oral 5-ASA 3 g/day.

**DISCUSSION**

The endoscopic finding of pseudo membranes found in 50% of *Clostridium difficile* infected patients (according to data from last decade) is less common (13%) in IBD patients with CDI (7) and our case had also an endoscopic aspect of ulcerative colitis flare.

A strong pre-test suspicion for CDI (as in our case watery diarrhea, severe hypoalbuminemia, severe anemia, severe acute inflammatory syndrome), empiric therapy for CDI should be considered regardless of the laboratory testing result, as the negative predictive values for CDI are insufficiently high to exclude disease in these patients (8). In our patient the clinical presentation of Clostridium difficile colitis mimics an underlying IBD flare and the first test for toxins in the stool was negative, and that made us to escalate the immunosuppressive therapy that lead to a very severe evolution of this patient.

Toxins A+B EIA testing commonly used as first diagnosis test for *Clostridium difficile* infection has a sensitivity of single sample testing low (72%) and may increase by 10% with second stool testing (84%). Three sample testing increase sensitivity to 86%(8).

Currently, standard recommendations for treatment of mild CDI include metronidazole or vancomycin, with data suggesting that vancomycin is more efficacious than metronidazole in severe CDI (1).

This is the first Romanian report of a case of *Clostridium difficile* colitis with the BI/NAP1/027 strain in a patient with ulcerative colitis, community acquired. Rafila et al report in their study that PCR ribotype 027 was found to be the most dominant type in CDI in Bucharest, accounting for 68% of the Romanian isolates during 2011-2012, 84% healthcare associated and 16% community acquired (9). Now we report resistance of this strain to metronidazole or vancomycin and a good response to tigecycline therapy, which practically saved the life of this patient.

We think that Infliximab worsened the evolution of C difficile infection in our patient, our point of view differs from Seicean A et al (10). FMT was indicated because of repeated relapses of C difficile colitis, according to current data from the literature (5). FMT practically cured both diseases, with the condition of a good quality donor.

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**REFERENCES**

SUCCESSFUL DIETARY INTERVENTION IN PATIENTS WITH SYSTEMIC SCLEROSIS AND FRUCTOSE MALABSORPTION

Gastrointestinal involvement is frequent in systemic sclerosis (SSc) and leads to an important decrease in patients’ quality of life. A recent study aimed to evaluate the prevalence of fructose malabsorption in 80 patients with systemic sclerosis recruited between 2011 and 2014. The study group was composed of 23 patients with diffuse cutaneous SSc (dcSSc) and 57 patients with limited cutaneous SSc (lcSSc). Gastrointestinal symptom severity was quantified using the Global Symptomatic Score (GSS). A respiratory test was performed according to strict protocols to estimate fructose absorption following the ingestion of 250 ml 10% fructose solution. Fructose malabsorption was shown in 40% of SSc patients with a higher prevalence in patients with lcSSc (78.1% in lcSSc vs 21.9% dcSSc patients). Fructose malabsorption was strongly correlated with higher GSS scores (p=0.000004). However, BMI values did not differ significantly between individuals with or without fructose intolerance. Patients that exhibited fructose malabsorption were placed on a low fermentable oligosaccharides, disaccharides, monosaccharides and polyol diet (low-FODMAP) for a period of 5 weeks. Symptoms like nausea, vomiting, diarrhea, constipation and abdominal pain were reduced significantly (up to 0%) by the low-FODMAP diet. The study emphasizes the importance of personalized dietary interventions in SSc patients. (Marie I, et al. Fructose Malabsorption in Systemic Sclerosis. Medicine 09.2015, doi: 10.1097/MD.0000000000001601. 94 : 39 : e1601).