Clinical microbiological case: a heart transplant recipient with diarrhea and abdominal pain

P. Muñoz, J. Palomo, J. Yáñez and E. Bouza

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EvolvEtion

Clostridium difficile toxin B was detected in the fecal samples of both episodes and a further course of treatment with oral metronidazole was administered, with good clinical response. Colonoscopy was not performed due to megacolon-associated risk of perforation. Symptoms disappeared rapidly.

Four days after the end of therapy after the second episode, CD toxin-positive watery diarrhea returned. The patient was treated for 14 days with oral vancomycin (125 mg every 6 h) and for replenishment of the normal flora with oral administration of the yeast Saccharomyces boulardii. He responded to therapy and no more relapses were documented. The patient received a total of 50 days of antiviral therapy and was discharged.

Discussion

1. The diagnosis is recurring C. difficile infection. Toxin-producing C. difficile has been reported as the etiologic agent of pseudomembranous colitis and up to 20–25% of cases of antibiotic-associated diarrhea. Incidence seems to be significantly increasing worldwide, even taking into account improved diagnosis and increased awareness [1–6]. The most important factor in the pathogenesis of disease is exposure to antibiotics that disturb the homeostasis of the colonic flora. Nosocomial transmission has also been described [3].

Tissue culture assay is the standard method to test for C. difficile; neutralisation of toxin cytopathic effect by C. difficile antitoxin confirms the diagnosis [7].

However, C. difficile-associated diarrhea (CDAD) may pose important diagnostic problems in the heart transplant setting. Clinical presentation may be atypical and sometimes quite severe; differential diagnosis with other entities causing diarrhea in this population is required (CMV, adenovirus) and relapses may be difficult to manage. C. difficile colitis may occur, as was the case in our patient, in conjunction with CMV gastrointestinal infection, which may make diagnosis difficult [8].

2. C. difficile is reported to be the main cause of bacterial diarrhea in immunosuppressed patients although quite frequently may pass undetected [9]. The incidence of CDAD is increased in solid organ transplant recipients and clinical presentation may be unusually severe [10]. In our experience, 16.6% of HT recipients suffer C. difficile-associated diarrhea. Patients had been in the hospital a median of 64 days and the diagnosis was established 51 days after transplantation. Two patients (14%) each had three severe relapsing episodes [11].

All patients had received antimicrobials before the episode (median 2.4 per patient, including prophylactic agents). Liquid diarrhea was present in all the patients, with a median of 10 movements per day. Other manifestactions were abdominal pain (29%), fever (14%) and gastrointestinal bleeding (14%). Duration of symptoms was 15 (1–48) days [11].

Heart transplant recipients are susceptible to many risk factors for developing CDAD: surgery, frequent hospital admissions, exposure to antimicrobials and immunosuppression.

Although nearly all patients respond to oral vancomycin or metronidazole [12], 10–20% have a relapse of diarrhea following treatment [13,14], and approximately 1% have further relapses [15].

3. About 15–25% of patients will respond within a few days to discontinuation of the antibiotic therapy that originated the disease. This first step of management may be taken into consideration in patients with non-severe CDAD whenever possible.

Non-responding patients or those with severe disease should be treated with antimicrobials. Metronidazole is the drug of choice because its activity is similar to that of vancomycin in patients with moderately severe disease, its reduced risk of vancomycin resistance induction and its lower cost [3]. When oral administration is not feasible, IV metronidazole should be used, because IV vancomycin is not effective. Treatment is usually administered for 7–10 days, although nearly all patients respond in about 5 days [12].

A substantial proportion of patients (10–20%) have a relapse, usually 3–10 days after treatment has been discontinued [13,14], even with no further antibiotic therapy. Relapse usually results from either a failure to eradicate C. difficile spores from the colon or is due to reinfection from the environment [3,16].

Nearly all patients with a second relapse respond to another course of metronidazole if given early. The frequency of relapses does not seem to be affected by the antibiotic selected for treatment, the dose of these drugs, or the duration of treatment [3].

Third or multiple relapses should be treated with vancomycin and with other measures attempting to inhibit the growth and
toxin production of *C. difficile* and to allow normal microbial flora restoration. Gradual tapering of the dosage of vancomycin over 1–2 months, administration of ‘pulse-dose’ vancomycin, use of anion-exchange resins to absorb *C. difficile* toxin A and administration of vancomycin plus rifampin or immunoglobulins have all been proposed [13,14,17–19].

There have been several reports concerning the treatment of recurrent colitis by direct reconstitution of the intestinal flora. This was attempted with oral administration of lactobacilli and/or the yeast *S. boulardii* and even by means of rectal instillation of stool from a healthy donor [20,21]. Nevertheless, methods to deal effectively with relapses are not standardised.

In our patient, combined oral treatment with vancomycin and *S. boulardii* was successful and he had no further relapses during a 6-month follow-up. Doctors dealing with heart transplant recipients should be aware of the increasing incidence of *C. difficile* diarrhoea in this population.

REFERENCES