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Case report

IVIG – A cure to severe refractory NAP-1 *Clostridium difficile* colitis? A case of successful treatment of severe infection, which failed standard therapy including fecal microbiota transplants and fidaxomicin☆

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ABSTRACT

The mainstay treatment of *Clostridium difficile* infections (CDI) is antimicrobials with growing support for fecal microbiota transplants. We report the first case of an elderly man with severe refractory NAP-1 pseudomembranous CDI who failed all medical therapy and two fecal transplants with response only seen after administration of intravenous immunoglobulin.

Introduction

Clostridium difficile has become an increasingly important and common cause of healthcare-associated infections, accounting for almost half a million infections in the United States in 2011 with over 29,000 deaths within 30 days of the initial diagnosis [1]. *Clostridium difficile* infections (CDI) typically manifest as antibiotic-associated diarrhea and range in severity from asymptomatic silent carriers to severe life-threatening toxic megacolon. Over the past decade, the incidence of these infections continues to increase with a trend towards more severe disease [2]. The standard of care in management is antimicrobials with increasing use of fecal microbiota transplants. This case reports presents a patient with severe refractory NAP-1 pseudomembranous CDI who failed these mainstay therapies and only had symptom alleviation following infusion of intravenous immunoglobulin (IVIG).

Case report

The patient was a 68-year-old man with a history of coronary artery disease, chronic kidney disease on hemodialysis, hypertension, and severe peripheral arterial disease who initially presented to the hospital with worsening right lower extremity ischemia. Two weeks prior to admission, he had been hospitalized at two outside hospitals with similar rest pain and was recommended to undergo a below-knee amputation (BKA). During the course of these hospitalizations, he was also diagnosed with *Clostridium difficile* infection, treated effectively with oral metronidazole with complete resolution of abdominal pain and diarrhea.

Upon presentation, he was admitted to the vascular surgical service for chronic right leg ischemia with tissue gangrene. He developed sepsis and was started on intravenous vancomycin and piperacillin-tazobactam prior to surgery, which occurred four days after admission. Antimicrobials were continued for a total of five days after surgery. He tolerated the procedure; however, approximately one week post-operatively, he developed severe frequent

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episodes of watery diarrhea, found to be infected with the NAP-1 strain of *Clostridium difficile* identified by PCR assay.

Over the course of two months, he failed multiple therapeutic modalities for *Clostridium difficile* infection including antimicrobials and two fecal microbiota transplants. Guided by the infectious disease and gastroenterology specialists, he was treated with oral vancomycin, rectal enemas of vancomycin, and both intravenous and oral metronidazole. His condition deteriorated with worsening leukocytosis, transverse colonic distension on abdominal x-ray measuring approximately 6–7 cm, and persistent severe abdominal pain with 20–25 watery bowel movements per day. He underwent a colonoscopy-guided fecal microbiota transplant (bacteriotherapy) with Open Biome 37-0020-D in the cecum, followed by a trial of cholestyramine. Approximately one week after the first fecal transplant, his symptoms worsened. At that time, imaging with CT abdomen/pelvis with contrast showed severe, diffuse pancolitis with wall thickening, pericolonic inflammatory changes, surrounding ascites fluid, and increased distension of the colon. He then underwent a second fecal transplant to no avail. Colonoscopy showed inflamed mucosa with a significant pseudomembrane burden. This significant worsening of infection burden despite fecal transplants and standard antimicrobials prompted a discussion between the specialists to opt for surgical resection versus a trial of fidaxomicin. Ultimately, he underwent a 7-day course of fidaxomicin without resolution of his symptoms. Although surgery seemed to be his best and possibly only option, his multiple co-morbidities, poor nutritional status, and deconditioning made his surgical risk prohibitively high, and colonic resection was deferred in light of relative clinical stability and no systemic signs to suggest toxicity.

Intravenous immunoglobulin (IVIG) has shown promise in cases of severe refractory *C. difficile* colitis [3,4]; thus, after failing all standard medical therapies, this patient was given IVIG over 3 days (Gamunex-C 10% 1 g/kg on the first day, followed by 0.5 g/kg on the second and third days). Three days after completing the IVIG infusions, the frequency of bowel movements decreased to 3–5 times per day, and the patient reported significant improvement in his abdominal pain. Repeat imaging with CT abdomen/pelvis on day 6 after receiving IVIG demonstrated significant improvement in his colitis but with some residual disease in his right colon. Due to concern for residual disease given these radiographic findings and persistent loose stools (albeit less frequent), a "booster" dose of Gamunex-C 10% 1 g/kg was given one week following the initial dose. No further radiographic evaluation was obtained until 3 months later when he was re-admitted for MRSA bacteremia likely secondary to an endovascular infection. At that time, he reported complete resolution of his abdominal pain and diarrhea, and his stool tested negative for *C. difficile* by PCR. Follow-up imaging with CT of abdomen/pelvis showed no evidence of colitis or inflammation.

Discussion

In this case report, we described the successful treatment of severe refractory NAP-1 pseudomembranous *C. difficile* colitis associated with megacolon using IVIG. Despite treatment with multiple medical modalities including fecal microbiota transplants and fidaxomicin, clinical and radiographic improvement was not observed until after administration of the immunoglobulin. The proposed mechanism of using IVIG in *Clostridium difficile* infections is inferred from the difference in the innate humoral immunity among asymptomatic and symptomatic colonizers. A prospective study of 271 hospitalized patients by Kyne et al. showed a 48-fold increased likelihood of developing diarrhea if serum levels of anti-toxin A IgG was 3.00 ELISA units or less [5]. For unclear reasons, the symptomatic colonizers seemed to be deficient in antibodies against Toxin A [6], and thus, it is proposed that the pooled human immune gamma globulins provide passive immunity against this toxin. It remains unclear how IVIG specifically works against the NAP-1 strain of *C. difficile*. To our knowledge, this is the first case report of using IVIG in a severe refractory *Clostridium difficile* infection after failing fecal microbiota transplants and all medical treatments including fidaxomicin, and it adds to the growing evidence that IVIG should be considered among the arsenal for fighting this debilitating and potentially life-threatening infection.

References

[1] Fernanda CL, et al. Burden of *Clostridium difficile* infection in the Unites States. N Engl J Med 2015;372:825–34.
[2] Freeman J, et al. The changing epidemiology of *Clostridium difficile* infections. Clin Microbiol Rev 2010;23:529–49.
[3] Hassoun A, Ibrahim F. Use of intravenous immunoglobulins for the treatment of severe *Clostridium difficile* colitis. Am J Geriatr Pharmacother 2007;5(1):48–51.
[4] McPherson S, Rees C, Ellis R, Soo S, Panter S. Intravenous immunoglobulin for the treatment of severe, refractory, and recurrent *Clostridium difficile* diarrhea. Dis Colon Rectum 2006;49(5):640–5.
[5] Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. N Engl J Med 2000;342:390–7.
[6] O'Horo J, Safdar N. The role of immunoglobulin for the treatment of *Clostridium difficile* infection: a systematic review. Int J Infect Dis 2009;13(6):663–7.