Elmer Press

Case Report

J Med Cases. 2016;7(10):451-454

A Case Report of Pseudomembranous Colitis Resulting From *Clostridium difficile* Infection Successfully Treated With Fidaxomicin

Leila A. Cardoso[a, b], Joao R. Goncalves[a], Joana Costa[a], Fatima Silva[a], Ana Figueiredo[a], Adriano Rodrigues[a]

Abstract

Pseudomembranous colitis (PMC) is a serious condition caused by *Clostridium difficile*, often arising after antibiotic therapy in the healthcare setting. We describe the complex case of an elderly patient with recurrent PMC and comorbid conditions who was successfully treated with fidaxomicin after metronidazole and vancomycin failure, with no further recurrences.

Keywords: Pseudomembranous colitis; *Clostridium difficile*; Fidaxomicin

Introduction

Pseudomembranous colitis (PMC) is one of the more severe manifestations of *Clostridium difficile* infection (CDI), an infectious disease that usually comes in after broad-spectrum antibiotics treatment [1]. *C. difficile* is the main agent for PMC. *C. difficile* is a spore-forming, anaerobic, Gram-positive bacillus. Proliferating *C. difficile* produces toxins that cause several complications, including PMC, toxic megacolon, perforations of the colon, and sepsis [2]. Spores produced by *C. difficile* are highly resistant to heat, gastric acid and biocidal cleaning products and can remain viable for months on surfaces, being resistant to hospital cleaners and even solutions that are used to disinfect the hands by healthcare professionals [3, 4]. The ability to produce spores is of crucial importance in the transmission of *C. difficile*, leading to frequent recurrences after successful initial treatment. Currently, *C. difficile* is the leading cause of nosocomial diarrhea in industrialized countries [5], and the incidence of CDI is increasing in Europe [6-8]. This infection is often associated with healthcare facilities and usually appears as a nosocomial infection, and it is directly related to the length of hospital stay [9]. The main risk factor for the development of CDI is exposure to antibacterial therapy, classically broad-spectrum agents, which are able to disrupt colonic microflora [10], whereas older age (≥ 65 years old), previous hospitalization, severity of underlying disease, immunocompromised state, suppression of gastric acid secretion, tube feeding and gastrointestinal surgery, chemotherapy and obesity are also risk factors for CDI [11-14].

The clinical presentation due to colonization and infection by *C. difficile* can have a highly variable spectrum, which can range from asymptomatic carrier, mild to moderate CDI or PMC, one of the most serious manifestations of CDI with high mortality associated [15-17]. The clinical presentation of CDI is caused by toxins A and B, produced by *C. difficile*, responsible for inflammation, damage the lining of the colon and cause inflammation leading to diarrhea and colitis [18].

The clinical treatment of suspected CDI requires a rapid and accurate diagnosis, and the establishment of appropriate drug therapy. The first-line antibiotherapy in non-severe CDI/first episode is metronidazole, orally, but it appears that increasing cases of resistance to this antibiotic make a second-line treatment with vancomycin administered orally necessary. The current European guidelines recommend the use of vancomycin over metronidazole as first-line therapy in severe CDI [14, 18-20]. Although vancomycin and metronidazole are effective in a first episode of CDI, this therapy remains suboptimal essentially due to the increased number of cases of resistance to metronidazole and vancomycin [21-23].

According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, recurrence is the major challenge in the treatment of CDI, with up to 25% of patients with CDI suffering a recurrence of infection within 30 days after treatment with metronidazole or vancomycin and 45-65% of these patients present subsequent recurrences [4, 24, 25].

New drugs have emerged for the treatment of CDI, including fidaxomicin, a macrocyclic antibiotic, the first in its class. Fidaxomicin acts by inhibiting *C. difficile*'s RNA polymerase, causing *C. difficile* cell death and presents selective bactericidal activity against *C. difficile*, which is in contrast to vancomycin that is only bacteriostatic against this agent. Fidaxomicin has a narrow spectrum of action, with minimal impact on anaerobic natural commensal colonic microflora. Gram-negative organisms are inherently not susceptible to fidaxomicin, whereby

Manuscript accepted for publication September 18, 2016

[a]Servico de Medicina Interna B do Hospital Geral do Centro Hospitalar Universitario de Coimbra, Coimbra, Portugal
[b]Corresponding Author: Leila Amaro Cardoso, Servico de Medicina Interna B, Hospital Geral do Centro Hospitalar Universitario de Coimbra, 3046-853 Coimbra, Portugal. Email: leilaamarocardoso@gmail.com

doi: http://dx.doi.org/10.14740/jmc2632w

the fidaxomicin has a low risk of vancomycin-resistant enterococci (VRE) acquisition. This drug inhibits spore formation and toxin production by *C. difficile* [26-28]. Fidaxomicin acts locally and has no cross-resistance with currently available antibacterial agents. According to the results of phase III trials, this drug not only showed comparable efficacy with vancomycin in the treatment of CDI, but also showed superior efficacy in reducing disease recurrence, providing a sustained clinical cure [24, 29].

Case Report

An 82-year-old woman with a history of liposarcoma, type 2 diabetes mellitus, hypertension, dyslipidemia, obesity, chronic heart failure, chronic kidney disease and gallstones had previously presented with PMC. Her medications were omeprazole (20 mg/day), furosemide (40 mg/day), pravastatin (20 mg/day), insulin detemir (40 units/day), bisoprolol (5 mg/day), losartan (100 mg/day), and oxygen delivered at 1 L/min for 16 h/day.

The patient was admitted on August 2, 2013 to the Internal Medicine Department of the Hospital Geral do Centro Hospitalar Universitario in Coimbra with recurrence of PMC (first episode occurred 2 months previously), cystitis and worsened chronic heart failure. Clinical laboratory tests revealed no leukocytosis, C-reactive protein (CRP) 3 mg/dL (reference value < 0.1 mg/dL), creatinine 110.4 µmol/L (reference range 46.0 - 92.0 µmol/L), urea 9.7 mmol/L (reference range 2.5 - 6.4 mmol/L), N-terminal pro-brain-type natriuretic peptide (NT-proBNP) 118 pg/mL (reference value < 300 pg/mL) and no myocardial necrosis markers. Urinalysis revealed the presence of 100 - 200 leukocytes/field, with bacterial growth. She received empiric treatment with intravenous cotrimoxazole (480 mg every 12 h) and oral vancomycin (125 mg every 6 h).

The patient was hospitalized for cystitis and worsening chronic heart failure, after which she received supportive therapy and cefuroxime 750 mg every 8 h for 7 days. At the end of the sixth day of hospitalization, she developed PMC. She had leukocytosis (leukocytes 17.6 × 10^3/µL, reference range 4 - 10 × 10^3/µL), neutrophilia (neutrophils 14.3 × 10^3/µL, reference range 2 - 7 × 10^3/µL), CRP increased to 4.2 mg/dL and worsening renal function (urea/creatinine ratio 17.8/148.9). A stool sample tested positive for *C. difficile* toxin initially by immunochromatographic rapid test GDH and then by PCR test.

The patient was treated with oral metronidazole (500 mg every 8 h) for 6 days, which was then discontinued because of persistent diarrhea. Antibiotic therapy was switched to oral vancomycin (125 mg every 6 h) for 14 days and the diarrhea resolved after 10 days of treatment. After 1 month in hospital, the patient was discharged without diarrhea.

Two months after being discharged, the patient was readmitted as an emergency case with diarrhea (seven liquid stools per day); a *C. difficile* toxin test of the stools was positive. Physical examination found a distended abdomen, no palpable masses, and increased bowel sounds. Abdominal ultrasonography revealed no remarkable findings. Clinical laboratory results indicated leukocytosis (leukocytes 17.0 × 10^3/µL), platelets 493 × 10^3/µL (reference range 150 - 400 × 10^3/µL), blood glucose 16.5 mmol/L (reference range 4.1 - 5.9 mmol/L), urea 14.5 mmol/L (reference range 2.5 - 6.4 mmol/L), creatinine 141.1 µmol/L (reference range 46.0 - 92.0 µmol/L) and CRP 34.5 mg/dL (reference value < 0.1 mg/dL). Treatment with oral vancomycin (125 mg, every 6 h) was initiated; however, profuse diarrhea and *C. difficile* toxin positivity in the stool persisted. In addition, colonoscopy and subsequent biopsy were compatible with PMC. Specifically, colonoscopy investigating the area from the anal margin to the descending colon revealed erythematous mucosa and inflamed areas, probably related to the resolution phase of colitis. Biopsies of two colonic mucosa samples showed cellular architecture changes consistent with PMC. Consequently, oral metronidazole 500 mg every 8 h was added to vancomycin therapy. After 12 days of dual therapy with vancomycin and metronidazole, there was no clinical improvement; therefore, both antibiotics were stopped and oral fidaxomicin (200 mg every 12 h) was administered for 10 days. There was successful resolution of symptoms (diarrhea and fever resolved after 5 days) and the patient was discharged from hospital on the 10th day of fidaxomicin therapy with no further symptoms. As yet, the patient has been free of PMC recurrence. Treatment with fidaxomicin was well tolerated and no adverse events were reported by the patient.

C. difficile is the leading cause of nosocomial diarrhea in industrialized countries [5], and the incidence of CDI is on the rise in Europe [6-8, 30]. The clinical presentation of *C. difficile* colonization and infection can vary greatly, ranging from asymptomatic carriage, to mild to moderate CDI or PMC; the latter is one of the most serious manifestations of CDI and associated with a high mortality rate [15-17].

Our patient had a number of factors that contributed to her worsening condition and were predictive of PMC recurrence. These were treatment with a broad-spectrum antibiotic, cefuroxime; concomitant treatment with a proton pump inhibitor; age over 75 years; comorbidities (liposarcoma, type 2 diabetes mellitus, hypertension, hyperuricemia, dyslipidemia, chronic heart failure, and obesity) and multiple hospital admissions. Our patient was considered to be at high risk of PMC recurrence and indeed suffered a recurrence soon after completing first-line treatment with vancomycin.

Clinical management of suspected CDI relies on rapid and accurate diagnosis, and the initiation of appropriate drug therapy. Oral metronidazole is the first-line antibiotic therapy for non-severe/first episode CDI; however, response to metronidazole is often poor, possibly because of the attainment of poor concentrations in the gut [18], necessitating the need for second-line treatment with oral vancomycin. Current European guidelines recommend the use of vancomycin over metronidazole as first-line therapy in severe CDI [14, 18-20]. Although vancomycin and metronidazole are effective in a first episode of CDI, therapy remains suboptimal essentially due to the high rate of recurrence with metronidazole and vancomycin treatment [21-23]. According to the ESCMID guidelines, recurrence is the major challenge in the treatment of CDI, with up to 25% of patients experiencing recurrence of infection within 30 days of metronidazole or vancomycin treatment, and of these, 45-65% of patients present with subsequent recurrences [4, 24, 25].

Recently approved therapies for the treatment of CDI include fidaxomicin - the first-in-class macrocyclic antibiotic. It acts by inhibiting the RNA polymerase of *C. difficile*, causing cell death [26]. Fidaxomicin has selective bactericidal activity against *C. difficile*, which is in contrast to vancomycin's bacteriostatic activity against this organism. Fidaxomicin has a narrow spectrum of action, with minimal impact on naturally occurring commensal anaerobic microflora in the colon. Gram-negative organisms are inherently non-susceptible to fidaxomicin, with a low risk of vancomycin-resistant enterococci arising from its use [26-28]. Fidaxomicin inhibits spore formation and toxin production by *C. difficile* [26-28]. It acts locally and is not associated with cross-resistance with currently available antibacterial agents. According to the results of phase III trials, fidaxomicin was non-inferior to vancomycin for initial cure of CDI, but significantly reduced the rate of disease recurrence, contributing to an increase in sustained clinical cure [24, 31]. Considering these findings and the presence of risk factors predictive of recurrence, it may have been prudent to administer fidaxomicin for the treatment of the first recurrence of PMC in our patient. However, our case occurred in 2013, when access to fidaxomicin and clinical experience of its use were limited. Today, fidaxomicin has demonstrated efficacy and safety in the treatment of CDI, including a previously published case study describing the successful treatment of severe CDI following prior failure of metronidazole and vancomycin in a 49-year-old patient undergoing peritoneal dialysis [32]. However, there are currently limited clinical data for fidaxomicin treatment of the more serious PMC. Our report of a complex case of PMC successfully treated with fidaxomicin following prior antibiotic treatment failure adds to the information available for this antibiotic in this setting. Of note in our case, there was successful resolution of PMC despite its late administration. Moreover, after clinical resolution of PMC at the end of treatment, there has been no recurrence of PMC in our patient since 2013. Therefore, fidaxomicin may be an appropriate alternative therapy in cases of recurrence, and may be appropriate even during the first episode of CDI in patient at high risk of recurrence.

Acknowledgments

Medical writing services were provided by Rhian Harper Owen on behalf of Astellas Pharma EMEA to assist with grammar and English translations. Astellas Pharma EMEA had no role in study design, data collection or the decision to publish the manuscript.

References

1. Bartlett JG, Moon N, Chang TW, Taylor N, Onderdonk AB. Role of Clostridium difficile in antibiotic-associated pseudomembranous colitis. Gastroenterology. 1978;75(5):778-782.
2. George RH, Symonds JM, Dimock F, Brown JD, Arabi Y, Shinagawa N, Keighley MR, et al. Identification of Clostridium difficile as a cause of pseudomembranous colitis. Br Med J. 1978;1(6114):695.
3. Gerding DN, Muto CA, Owens RC, Jr. Measures to control and prevent Clostridium difficile infection. Clin Infect Dis. 2008;46(Suppl 1):S43-49.
4. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol. 2002;97(7):1769-1775.
5. Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, Monnet DL, et al. Clostridium difficile infection in Europe: a hospital-based survey. Lancet. 2011;377(9759):63-73.
6. Lyytikainen O, Turunen H, Sund R, Rasinpera M, Kononen E, Ruutu P, Keskimaki I. Hospitalizations and deaths associated with Clostridium difficile infection, Finland, 1996-2004. Emerg Infect Dis. 2009;15(5):761-765.
7. Soes L, Molbak K, Strobaek S, Truberg Jensen K, Torpdahl M, Persson S, Kemp M, et al. The emergence of Clostridium difficile PCR ribotype 027 in Denmark - a possible link with the increased consumption of fluoroquinolones and cephalosporins? Euro Surveill. 2009;14(15).
8. Vonberg RP, Schwab F, Gastmeier P. Clostridium difficile in discharged inpatients, Germany. Emerg Infect Dis. 2007;13(1):179-180.
9. Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial Clostridium difficile diarrhea. Infect Control Hosp Epidemiol. 2002;23(11):653-659.
10. Wistrom J, Norrby SR, Myhre EB, Eriksson S, Granstrom G, Lagergren L, Englund G, et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. J Antimicrob Chemother. 2001;47(1):43-50.
11. Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, Toye B, et al. Host and pathogen factors for Clostridium difficile infection and colonization. N Engl J Med. 2011;365(18):1693-1703.
12. Bliss DZ, Johnson S, Savik K, Clabots CR, Willard K, Gerding DN. Acquisition of Clostridium difficile and Clostridium difficile-associated diarrhea in hospitalized patients receiving tube feeding. Ann Intern Med. 1998;129(12):1012-1019.
13. Bishara J, Farah R, Mograbi J, Khalaila W, Abu-Elheja O, Mahamid M, Nseir W. Obesity as a risk factor for Clostridium difficile infection. Clin Infect Dis. 2013;57(4):489-493.
14. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-455.
15. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. Clin Infect Dis. 2008;46(Suppl 1):S12-18.
16. Sunenshine RH, McDonald LC. Clostridium difficile-associated disease: new challenges from an established pathogen. Cleve Clin J Med. 2006;73(2):187-197.

17. Poutanen SM, Simor AE. Clostridium difficile-associated diarrhea in adults. CMAJ. 2004;171(1):51-58.
18. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014;20(Suppl 2):1-26.
19. Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. Lancet Infect Dis. 2005;5(9):549-557.
20. Leffler DA, Lamont JT. Treatment of Clostridium difficile-associated disease. Gastroenterology. 2009;136(6):1899-1912.
21. Carmeli Y, Eliopoulos GM, Samore MH. Antecedent treatment with different antibiotic agents as a risk factor for vancomycin-resistant Enterococcus. Emerg Infect Dis. 2002;8(8):802-807.
22. Al-Nassir WN, Sethi AK, Li Y, Pultz MJ, Riggs MM, Donskey CJ. Both oral metronidazole and oral vancomycin promote persistent overgrowth of vancomycin-resistant enterococci during treatment of Clostridium difficile-associated disease. Antimicrob Agents Chemother. 2008;52(7):2403-2406.
23. Huang H, Weintraub A, Fang H, Nord CE. Antimicrobial resistance in Clostridium difficile. Int J Antimicrob Agents. 2009;34(6):516-522.
24. Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. N Engl J Med. 2010;362(3):197-205.
25. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011;364(5):422-431.
26. Venugopal AA, Johnson S. Fidaxomicin: a novel macrocyclic antibiotic approved for treatment of Clostridium difficile infection. Clin Infect Dis. 2012;54(4):568-574.
27. Tannock GW, Munro K, Taylor C, Lawley B, Young W, Byrne B, Emery J, et al. A new macrocyclic antibiotic, fidaxomicin (OPT-80), causes less alteration to the bowel microbiota of Clostridium difficile-infected patients than does vancomycin. Microbiology. 2010;156(Pt 11):3354-3359.
28. Mullane KM, Gorbach S. Fidaxomicin: first-in-class macrocyclic antibiotic. Expert Rev Anti Infect Ther. 2011;9(7):767-777.
29. Crook DW, Walker AS, Kean Y, Weiss K, Cornely OA, Miller MA, Esposito R, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. Clin Infect Dis. 2012;55(Suppl 2):S93-103.
30. Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, Delmee M, et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID). Lancet Infect Dis. 2014;14(12):1208-1219.
31. Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, Sears P, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2012;12(4):281-289.
32. Windpessl M, Wallner M. Fidaxomicin for Clostridium difficile Colitis in a peritoneal dialysis patient with underlying mitochondriopathy. Perit Dial Int. 2014;34(1):137-138.

