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Case Report

Community-acquired diarrhea associated with *Clostridium difficile* in an HIV-positive cancer patient: first case report in Latin America

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SUMMARY

Clostridium difficile is the most important cause of nosocomial diarrhea, mainly associated with antibiotic use and immunodeficiency. Although, an increased incidence of community-acquired *C. difficile* infection (CA-CDI) has been reported worldwide, this infection has been under-diagnosed in Latin America. This is the first report of a CA-CDI case in Latin America, in an HIV-positive patient with cancer.

1. Introduction

Clostridium difficile is recognized as the main cause of diarrhea and pseudomembranous colitis in hospitalized patients. Risk factors for the development of *C. difficile* infection (CDI) include advanced age, hospitalization, and severe illness. Cancer patients and HIV-infected patients have immunological failures that predispose them to CDI. These patients are at risk of CDI, independent of antibiotic or healthcare facility exposure, because of their clinical condition and the use of chemotherapeutic agents, which usually affect the immune system.[1]

In Brazil, research into the incidence of *C. difficile* is still scarce, although studies carried out in hospitals in Rio de Janeiro, São Paulo, and Porto Alegre (southern and southeastern regions) have reported high and increasing incidences compared to European and Costa Rican hospitals, with the occurrence of complicated cases of CDI and deaths resulting from severe infection.[2] However, community-acquired CDI (CA-CDI) infection has been under-diagnosed. This is the first report of a CA-CDI case in an HIV-positive patient with cancer in Latin America, pointing to the importance of investigating this pathogen in community-acquired diarrhea in developing countries, especially among patients with an immunodeficiency.

2. Case report

A 68-year-old woman who was HIV-positive was admitted to a cancer reference hospital in northeastern Brazil in May 2013. She presented with clinical symptoms of diarrhea, which had lasted for 6 days. She had been diagnosed with rectal cancer in early 2012. In December 2012, she underwent rectosigmoidectomy and abdominal lymphadenectomy. She was on adjuvant chemotherapy (regimen of folinic acid, 5-fluorouracil, and oxaliplatin), having received the first cycle in March 2013. She had not used antibiotics

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since January 2013. An initial screen for *C. difficile* toxins was carried out, as per the protocol for all patients who hold risk factors and suffer from diarrhea.

Analysis of a diarrhea stool sample collected on the third day of hospitalization revealed the presence of *C. difficile* toxin A/B (ProSpecT *Clostridium difficile* Toxin A/B Microplate, Remel). Alcohol shock was performed on the stool sample, followed by culture on cefoxitin–cycloserine–fructose agar (CCFA, Oxoid) and fastidious anaerobe broth (FAB) for 5 and 15 days, respectively, incubated under anaerobic conditions (anaerobic jar 90% N_2, 10% CO_2). Then the FAB was inoculated onto another CCFA. Characteristic *C. difficile* colonies on CCFA appeared yellowish, with a ground-glass appearance; they were circular with slightly filamentous edges and flat to low with a rounded elevation. The colonies were lipase- and lecithinase-negative. These colonies were inoculated onto Brucella agar with 5% lysed sheep blood and vitamin K (5 mg/ml) for identification and molecular tests.

The identification was confirmed by testing with a RapID ANA II system (Remel) and by *tpi* gene PCR amplification.[3]

The amplification results for *tcd*A and *tcd*B gene fragments of PaLoc (Pathogenicity locus) were positive, while the results for the binary toxin gene *cdt*B and evidence of deletion of the putative regulatory gene *tcd*C were negative, using a previously reported method.[3] Molecular strain typing was conducted using pulsed-field gel electrophoresis (PFGE), as described previously, using *Sma*I genomic DNA digestion.[3] DNA fragment patterns were compared to the database of the National Microbiology Laboratory, Canada, using BioNumerics v. 4.6 software (Applied Maths); the isolate was typed as NAP4.

Antibiotic susceptibility was determined by Etest on Brucella agar with 5% sheep blood and vitamin K (5 mg/ml). The isolate was resistant to azithromycin (>256 μg/ml), ciprofloxacin (25 μg/ml), tetracycline (128 μg/ml), and cefotaxime (>32 μg/ml), but susceptible to clindamycin (0.125 μg/ml), ceftriaxone (1.5 μg/ml), metronidazole (0.025 μg/ml), chloramphenicol (3 μg/ml), rifampin (<0.002 μg/ml), levofloxacin (4 μg/ml), moxifloxacin (1.5 μg/ml), and vancomycin (0.5 μg/ml).

Laboratory studies showed a low leukocyte count (1.462×10^9/l; neutrophils 0.520×10^9/l and lymphocytes 0.340×10^9/l), hemoglobin (7.5 g/dl), and platelets (108×10^9/l). Intestinal parasites (protozoa and helminths) and the main gastrointestinal viruses and bacterial enteric pathogens were not detected in the stool sample. In accordance with the clinical and laboratory findings, the woman was diagnosed with CA-CDI.

The diarrhea ceased approximately a week after the beginning of metronidazole treatment (40 mg/kg/day for 14 days) and commercial probiotic therapy.

3. Discussion

Little information is available on the risk factors for CA-CDI. Some cases have been associated with antibiotic treatment, while others lack this risk factor. In the case reported here, despite the absence of hospitalization and use of antibiotics in the last 4 months, the woman presented several risk factors that led her to develop *C. difficile*-associated disease, such as age, immunosuppression, and co-morbidities (cancer and HIV positivity), in addition to the use of antineoplastic drugs. Chemotherapeutic agents such as 5-fluorouracil may induce intestinal mucositis associated with severe inflammatory changes in the colonic mucosa. Colonic inflammation can cause intestinal necrosis, which promotes an anaerobic environment for *C. difficile* organisms.[1]

CDI may account for 10% to 50% of diarrhea among hospitalized HIV-seropositive patients, and recent evidence suggests that *C. difficile* has become the most important pathogen causing bacterial diarrhea in HIV-seropositive patients in the USA, suggesting that these patients are at increased risk because of their underlying immunosuppression, exposure to antimicrobials, exposure to healthcare settings, or a combination of these factors.[2,4]

HIV-seropositive individuals, particularly those with lower CD4 counts, are at increased risk of bacterial enteric infection, including by *Escherichia coli*, *Salmonella spp*, and *Campylobacter spp*.[4] However, in this case there was no infection by other pathogens.

The isolated strain did not show high resistance to antibiotics, a finding in accordance with community-acquired cases, which often occur without exposure to antibiotics and comprise about 20% to 22% of CDI cases.[5]

The isolated NAP4 strain was toxigenic (*tcd*A and *tcd*B gene fragments of the PaLoc were positive), which explains the symptoms of diarrhea. NAP4 has been a common cause of healthcare-associated CDI, although it has become less common in recent years. NAP4 strains have been isolated from cattle and dogs. These could be considered possible sources for the woman's infection. Although food contamination by *C. difficile* has not been investigated in Brazil, increasing rates of CDI have raised questions about the origins of new human strains, sources of human *C. difficile* acquisition, and risk factors for the development of infection.[5]

Additional studies in the field of molecular epidemiology and the sources of strains causing CA-CDI will advance understanding of the evolving epidemiology of human CDI and could help in the development of new strategies to prevent it.

To our knowledge, this is the first report of a documented case of community-acquired *C. difficile*-induced disease associated with HIV and cancer in Latin America. The existence of a reservoir of *C. difficile* outside the hospital environment is a situation that should be of concern for individuals who are HIV-positive and/or suffer from cancer. Public health authorities and scientists should consider CDI as an emerging infection in the community in these patients.

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Conflict of interest: No conflict of interest to declare.

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