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ID CASE

Bacteremia and Septic Arthritis due to a Nontoxigenic Strain of *Clostridium difficile* in a Patient With Sickle Cell Disease

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A 22-year-old female with sickle cell disease presented with fevers, bilateral knee pain, and lethargy. Laboratory data revealed a leukocytosis and lactic acidosis. Blood and synovial fluid cultures grew a non-toxin-producing strain of *Clostridium difficile*. This case highlights the fact that nontoxigenic *Clostridium difficile* can cause significant disease.

Keywords. bacteremia; *Clostridium difficile*; hemoglobin SS disease; septic arthritis; sickle cell disease.

CASE

A 22-year-old African American female with sickle cell (Hemoglobin SS) disease and biopsy-proven autoimmune hepatitis on prednisone and azathioprine presented to the emergency department (ED) twice in early March with fevers and intermittent bilateral knee pain and swelling. Both times she was treated for a sickle cell pain crisis and discharged home. Blood cultures from her first presentation and second presentation grew *Clostridium* species in 1 out of 2 sets of aerobic and anaerobic bottles and 3 out of 3 sets of aerobic and anaerobic bottles, respectively. The positive cultures were obtained prior to the initiation of matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry, and thus they were not identified to species. The patient continued to have bilateral knee pain and subjective fevers for months, prompting her to present again to the ED in July. Despite not having received any antibiotics or further work-up of her prior bacteremia, as her physicians at the time believed the positive cultures in March reflected contamination, 2 sets of blood cultures drawn at the time of her ED visit in July were sterile, and she was discharged home again with pain medications. However, ultimately, she was admitted in September with persistent symptoms as well as new-onset diarrhea.

On examination at the time of admission to the hospital, she was moaning in pain, lethargic, and unable to follow commands. Significant musculoskeletal findings included bilateral lower extremity edema and tender bilateral knee effusions without warmth nor erythema. Computed tomography scan of her abdomen with oral and intravenous contrast revealed nodularity of the liver as well as mild diffuse wall thickening of the colon and mid to distal small bowel loops consistent with enterocolitis. Laboratory data upon admission were notable for a leukocytosis of 20.25 K/μL, a hemoglobin of 6.4 g/dL, and an elevated lactic acid of 5.8 mmol/L. Examination of right knee synovial fluid revealed 145 000 red blood cells and 170 500 nucleated cells/mm^3 with a neutrophilic predominance. Gram stain of the synovial fluid was negative. Blood cultures revealed Gram-variable rods after 1 day of incubation, which were identified as *C. difficile* by MALDI-TOF. The synovial fluid was cultured aerobically and anaerobically. There was no aerobic growth. However, after 72 hours of incubation, growth was present in the anaerobic culture. A Gram stain of the colonies growing on Brucella blood agar revealed Gram-variable rods, which were also identified as *C. difficile* by MALDI-TOF. Stool studies, including *C. difficile* polymerase chain reaction (PCR) testing, were ordered but never sent before the patient's diarrhea abated. While intravenous metronidazole 500 mg every 8 hours was initially prescribed, the antibiotic was changed to the oral route of administration within 72 hours, as she was less lethargic and able to reliably take medication by mouth. Although the orthopedic service initially considered performing an arthrocentesis of her left knee as well as incision and drainage of both knees, in light of her dramatic and rapid clinical improvement with metronidazole therapy, no further invasive interventions were pursued. Because of concern for possible perforation in the setting of active colitis, a colonoscopy was not performed. Ultimately, the patient completed a 4-week course of metronidazole 500 mg 3 times daily, with no adverse effects and full resolution of symptoms.

A subculture of the *C. difficile* isolate from blood was sent to the Centers for Disease Control and Prevention for ribotyping. The isolate tested negative for toxin genes tcdA, tcdB, cdtA, and cdtB by multiplex real-time PCR, and positive for the 115bp DNA sequence that replicates the pathogenicity locus in

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nontoxigenic strains. As a result, this isolate had no amplification for the tcdC-encoding gene. PCR ribotyping confirmed that the isolate was Ribotype 039. The isolate was sent to ARUP laboratories for a cytotoxin cell assay, which provided confirmation that, phenotypically, no toxin was being produced.

DISCUSSION

The genus *Clostridium* comprises obligately anaerobic (or occasionally aerotolerant), Gram-positive rods. *C. difficile* causes symptoms ranging from mild self-limiting diarrhea to the development of full-scale pseudomembranous colitis [1]. Extra-intestinal *C. difficile* infections account for less than 0.2% of all *C. difficile* infections [2]. *C. difficile* bacteremia is even more uncommon and is generally part of a polymicrobial bacteremia involving other intestinal flora [2]. A recent literature review identified only 44 cases of *C. difficile* bacteremia between 1962 and 2015 [2]. Moreover, while review of the literature describes postinfectious sterile inflammatory arthritis as a complication of gastrointestinal *C. difficile* infection [3–5], cases of septic arthritis due to the organism itself are rare (Table 1). When it does occur, the majority of published septic arthritis cases [3, 6] involve prosthetic joints [7–12]. Review of the literature yielded only 1 case report of native large joint septic arthritis in an 11-year-old boy, also with Hemoglobin SS disease, who experienced right-sided shoulder discomfort and was found to be bacteremic with *C. difficile* despite having no gastrointestinal symptoms [13]. This publication did not describe ribotyping on the bacterial isolate in that case to assess for toxin production.

C. difficile diagnostic assays are designed to detect the absence or presence of organisms or toxins in patient fecal samples. However, these tests are unable to differentiate asymptomatic carriers from those patients with veritable disease. The majority of clinical laboratories utilize Food and Drug Administration–approved molecular tests that detect genes encoding *C. difficile* toxins. These nucleic acid amplification tests are rapid and highly sensitive, yet the positive predictive value can be low if the test is not ordered in the appropriate clinical context. The ProGastro Cd test (Prodesse, Waukesha, WI) and the GeneOhm Cdiff assay (BD Diagnostics, San Diego, CA) target toxin B (tcdB), while the Xpert *C. difficile* test (Cepheid) is a multiplex assay that amplifies 2 genes, tcdB and a gene that regulates toxin production (tcdC). In addition, multiplex gastrointestinal panels such as BioFire FilmArray (Biomerieux, Inc., Durham, NC) include a *C. difficile* toxin gene as one of its targets. Less expensive, less sensitive membrane enzyme immunoassays like the C. DIFF QUIK CHEK COMPLETE (Alere North America, LLC, Orlando, FL) have been used in some laboratories as screening tests before performing the molecular tests. In addition to assaying for toxins A and B in fecal samples, the test detects *C. difficile* antigen, glutamate dehydrogenase, as a screen for the presence of *C. difficile* in the stool. Clinicians may attempt to recover *C. difficile* from clinical samples, also called toxigenic culture, but the process is laborious and time consuming, requiring multiple days for isolation and identification. If isolates are recovered, whole-genome sequencing and ribotyping may be performed using research-only assays.

Only strains that carry the pathogenicity locus (PaLoc) possess the genetic information for the *C. difficile* enterotoxin, TcdA, and the cytotoxin, TcdB. Historically, only strains producing TcdA and/or TcdB were thought to cause *C. difficile* infection [1]. Outbreaks with more virulent strains such as B1/NAP1/027 and ribotype78 are associated with significant mortality [14, 15]. This case highlights that a non-toxin-producing isolate can be responsible for severe extra-intestinal disease due to *C. difficile*.

Table 1. Review of Cases of Septic Arthritis due to *C. difficile*

Case No.	Ref	Year	Sex	Age	Joint	Prosthetic Joint	Comorbid Conditions	Diarrhea	*C. difficile* Bacteremia	*C. difficile* Therapy	Surgical Intervention	Outcome
1	13	1994	F	31	Hip	Yes	Sickle cell disease	No	No	Metronidazole	Incision and drainage	Died
2	8	1995	M	16	Knee	Yes	Osteosarcoma of femur on chemotherapy	No	No	Ornidazole	Above knee amputation	Survived
3	12	1999	F	83	Hip	Yes	Unknown	Yes (toxin negative)	No	Metronidazole	Prosthesis removal	Survived
4	15	2009	M	11	Shoulder	No	Sickle cell disease	No	No	Metronidazole	Incision and drainage	Survived
5	14	2010	F	66	Hip	Yes	Chronic kidney disease	Unknown	Yes	Metronidazole	Incision and drainage	Survived
6	11	2013	F	61	Knee	Yes	Hypothyroidism	No	No	Metronidazole	Above knee amputation	Survived
7	10	2013	F	47	Shoulder	Yes	Alcoholic hepatitis	No	No	Metronidazole	Prosthesis removal	Unknown
8	9	2013	M	61	Hip	Yes	AIDS, type 2 diabetes	No	Yes	Metronidazole	Incision and drainage	Survived

CONCLUSION

To our knowledge, this is the first reported case indicating that non-toxin-producing strains of *C. difficile* can cause severe extraintestinal disease, including septic arthritis of a native large joint. In order to provide timely and appropriate therapy, it is important for clinicians and microbiologists to be aware of the various potential manifestations of infection with *C. difficile*.

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