Fatal Spontaneous Clostridium bifermentans Necrotizing Endometritis: A Case Report and Literature Review of the Pathogen

Open Forum Infectious Diseases

BRIEF REPORT

Fatal Spontaneous *Clostridium bifermentans* Necrotizing Endometritis: A Case Report and Literature Review of the Pathogen

Andrew Hale,[1] James E. Kirby,[2,3] and Mary Albrecht[1,4]

[1]Division of Infection Diseases, [2]Department of Clinical Microbiology, Beth Israel Deaconess Medical Center, Departments of [3]Pathology, and [4]Medicine, Harvard Medical School, Boston, Massachusetts

Clostridium bifermentans is a rare pathogen in humans. A fatal case of fulminant endometritis with toxic shock and capillary leak secondary to *C bifermentans* infection in a young woman is described, and this is compared to all 13 previously described cases of *C bifermentans* infection.

Keywords. capillary leak; *Clostridium bifermentans*; *Clostridium sordellii*; hyperleukocytosis; toxic shock syndrome.

In October 2014, a 33-year-old woman with history of abnormal uterine bleeding status post an uncomplicated endometrial ablation 5 months prior developed new onset dysuria and grayish, malodorous vaginal discharge. Her white blood cell count was 16×10^3 cells/mm^3 and her hematocrit was 39%. She was prescribed levofloxacin but never filled it. Three days later, she was hospitalized after multiple syncopal events at home. On admission, blood pressure was 74/24 mmHg. She was afebrile, without rash, and extremities were cool. Abdominal exam was notable for obesity but was otherwise benign. Pelvic examination showed no cervical motion tenderness, cervical discharge, or other abnormality. Urine β-human chorionic gonadotropin was negative. White blood cell count was 60×10^3 cells/mm^3; hematocrit 42%; platelets 38×10^3 cells/mm^3; and lactate 6.5 mmol/L. Computed tomography (CT) scan of the abdomen and pelvis showed ascites, and a pelvic ultrasound was unremarkable. Empiric antibiotic therapy with vancomycin, cefepime, and metronidazole was initiated, and she was transferred to the intensive care unit. Twelve hours after admission, her white blood cell count rose to 113×10^3 cells/mm^3, and hematocrit was 58%, despite having received 12 liters of intravenous (IV) normal saline. Lactate increased to 13.5 mmol/L. Tobramycin, clindamycin, and doxycycline were added for sepsis. Despite vasopressor support, she required massive IV fluid resuscitation to maintain pressures and perfusion, receiving 26 liters during the first 24 hours and 51 liters by 72 hours. In addition, she showed signs of disseminated intravascular coagulation (DIC) and received 46 units of blood product (fresh frozen plasma, platelets, and cryoprecipitate) over 72 hours. Transthoracic echocardiogram showed a large pericardial effusion with cardiac tamponade, which required pericardial drain placement with removal of 1500 mL transudative fluid. She also developed large bilateral pleural effusions and required bilateral chest tube placement with 4 liters per day transudative fluid output. Given the profound intra-abdominal fluid, there was concern for potential abdominal catastrophe; thus, she had an exploratory laparotomy, which was negative for any signs of intra-abdominal infection or viscous perforation, although there was massive ascites. The uterus was hyperemic but not grossly infected or boggy. Vaginal swabs did not isolate *Staphylococcus aureus* or yeast; cervical swabs were negative for gonorrhea and chlamydia by nucleic acid amplification testing. Blood smear showed marked neutrophilia and no evidence of hematologic malignancy. Bone marrow biopsy was negative for malignancy. Human immunodeficiency virus-1 antibody was negative. Blood, urine, pleural fluid, pericardial fluid, peritoneal fluid, and sputum cultures were negative for microorganisms. She developed profound anasarca, and a repeat pelvic or ophthalmologic exam was unable to be performed because of massive edema. Her clinical picture was felt to be consistent with a toxin-mediated process, potentially related to *Clostridium sordellii* given how this pathogen typically presents. Thus, to remove potential toxin, empiric plasmapheresis was started on hospital day 3, which showed immediate improvement in hemodynamics, and fluid was able to be removed with continuous venovenous hemofiltration. On hospital day 4, her edema had improved and the team was able to examine her pupils, which were found to be fixed and dilated. A CT head scan showed diffuse cerebral edema and tonsillar herniation. A family meeting was convened, life support was withdrawn, and she died shortly thereafter. An autopsy demonstrated diffuse edema and evidence of DIC in all organs. Diffuse endometrial necrosis was noted on histopathological examination of the uterus. Special stains demonstrated large, boxcar-shaped, Gram-positive rods within endometrial tissue. Uterine tissue submitted to the Centers for Disease Control and Prevention confirmed the presence of clostridial species by immunohistochemical

Received 16 December 2015; accepted 9 May 2016.

Correspondence: A. Hale, Lowry Medical Office Building, 110 Francis Street, Suite GB, Boston, MA 02215 (ahale@bidmc.harvard.edu).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofw095

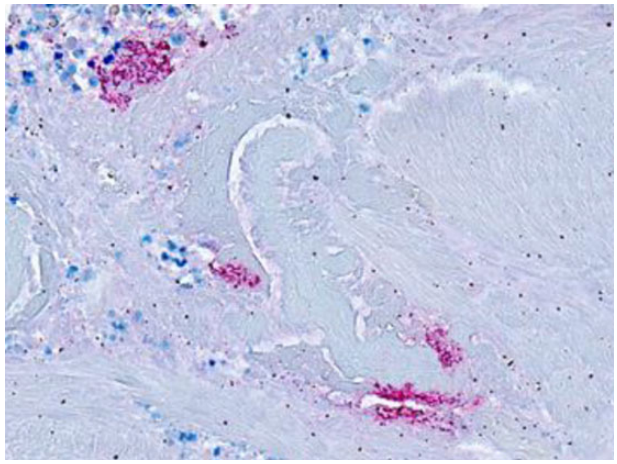

Figure 1. Positive immunohistochemical staining (dark pink) for *Clostridium* species within areas of endometrial necrosis.

staining within the areas of endometrial necrosis (Figure 1). Although polymerase chain reaction (PCR) assay specific for *C sordellii* was negative, wide-range 16 S PCR assay of endometrial tissue was positive for *Clostridium bifermentans*. Postmortem endometrial cultures were negative.

DISCUSSION

The *Clostridium* family represents a diverse group of Gram-positive, spore-forming, obligate anaerobic bacteria that are found widely throughout the environment and are known to secrete a wide array of toxins [1]. *Clostridium bifermentans* was first isolated in 1902 in putrefied butcher's meat [2]. It is found in sewage, soil, and occasionally the intestinal flora of humans. The frequency of *C bifermentans* causing human infection is quite rare; our search of PubMed revealed only 13 prior case reports. Sites of infection are diverse (Table 1) [2–14]. Of these prior reported cases, only 1 infection, presenting with necrotizing pneumonia and empyema, was fatal [5] (7.7% case fatality rate). A disproportionate number of infections were in men (85%; see Table 1). The case we now report is quite unique. Histopathology showed infection of the uterus, a site of infection not previously described. In addition, our patient's course was fulminant and rapidly fatal, which is not a characteristic feature in prior cases of *C bifermentans* infection. Our patient's course was much more in line with what has previously been described in *C sordellii* infection, which is well known to cause a fulminant endometritis, typically in young women after medical abortion [15], although it can occur spontaneously [16]. Our patient had an endometrial ablation 5 months before her presentation, which was felt to be too distant in time to be a definitive risk factor. *Clostridium sordellii* is known to cause a severe leukocytosis in part related to production of the neuraminidase NanS, which stimulates promyelocytic proliferation and prevents margination and movement of leukocytes out of the intravascular space [17]. *Clostridium sordellii* also elaborates lethal toxin, which undermines the actin cytoskeleton at the cellular level, and is believed through this activity to compromise endothelial barrier integrity [18]. Lethal toxin exhibits a marked propensity for inducing rapid morbidity and contributes to the profound capillary leak, hemoconcentration, and toxic shock syndrome often seen in *C sordellii* infections [19]. The constellation of findings in our patient (severe capillary leak, profound leukocytosis and hemoconcentration, and improvement with plasmapheresis) was very suspicious for *C sordellii*. However, unexpectedly, PCR testing revealed evidence of *C bifermentans* in endometrial tissue. *Clostridium sordellii* and *Clostridium septicum*-specific PCR assays were negative. We thus surmise that this particular strain of *C bifermentans* may have elaborated toxins similar to the *C sordellii* lethal toxin and NanS, although this conjecture remains unproven. Of note, however, genetic exchange between large toxin protein producing strains of *Clostridium* has been previously suggested [20]. Moreover, within

Table 1. Review of 13 Prior Cases of *Clostridium bifermentans* Infection

Author Name	Publication Year	Site of Infection	Patient Age in Years	Patient Sex	Maximum WBC in 10^3 Cells/mm^3	Outcome
Bitner	1971	Abdominal wall	45	Female	19	Survived
Nolan	1972	Septic arthritis of knee	18	Male	10	Survived
Misra	1980	Necrotizing pneumonia and empyema	41	Female	52	Death
Panwalker	1983	Necrotizing pneumonia and empyema	60	Male	24	Survived
Pencek	1986	Brain abscess	36	Male	9	Survived
Kolander	1989	Endocarditis	28	Male	7	Survived
Nachman	1989	Liver abscess	6	Male	25	Survived
Rechtman	1991	Abdominal abscess	65	Male	9	Survived
Moyano	1994	Endocarditis	26	Male	16	Survived
Rehany	1994	Panophthalmitis	13	Male	9	Survived
Scanlan	1994	Osteomyelitis and bacteremia	81	Male	3	Survived
Chaudry	2014	Endocarditis	22	Male	7	Survived
Edagiz	2015	Empyema	60	Male	18	Survived

Abbreviation: WBC, white blood cells.

the *Clostridium* phylogeny, *C bifermentans* and *C sordellii* are closely related and were not identified as separate species until 1962 [21]. It is also remarkable that in the one prior fatal case of *C bifermentans*, the white blood cell count was 52×10^3 cells/mm^3; no other reported cases until ours showed an extreme leukocytosis. This may suggest that the toxins alluded to above may be present in only a small, lethal subset of strains, although that is also unproven. Because no cultures were positive in our case, assays to study toxin elaboration were not possible.

CONCLUSIONS

Clostridium bifermentans is a rare cause of infection in humans. Our case represents a novel manifestation of *C bifermentans* in regards to both site and severity. Further characterization of this rare pathogen is warranted.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Ryan K, Ray C. Sherris Medical Microbiology. 4th ed. McGraw Hill; **2004**.
2. Scanlan D, Smith M, Isenberg H, Hilton E. *Clostridium bifermentans* bacteremia with metastatic osteomyelitis. J Clin Microbiol **1994**; 32:2867–8.
3. Bittner J, Munteanu-Ivanus N, Radulesco D, et al. [Gangrene of the abdominal wall due to *Clostridium bifermentans*]. Sem Hop **1971**; 47:1900–4.
4. Nolan B, Leers WD, Schatzker J. Septic arthritis of the knee due to *Clostridium bifermentans*. Report of a case. J Bone Joint Surg Am **1972**; 54:1275–8.
5. Misra D, Hurst D. Necrotising pneumonia and empyema caused by *Clostridium bifermentans*. Thorax **1980**; 35:310–1.
6. Panwalker A, Trager G. Necrotizing pneumonia and empyema caused by *Bacillus cereus* and *Clostridium bifermentans*. Am Rev Respir Dis **1983**; 128:333–4.
7. Pencek T, Burchiel K. Delayed brain abscess related to a retained foreign body with culture of *Clostridium bifermentans*. Case report. J Neurosurg **1986**; 64:813–5.
8. Kolander S, Cosgrove E, Molavi A. Clostridial endocarditis. Report of a case caused by *Clostridium bifermentans* and review of the literature. Arch Intern Med **1989**; 149:455–6.
9. Nachman S, Kaul A, Li K, Slim M, et al. Liver abscess caused by *Clostridium bifermentans* following blunt abdominal trauma. J Clin Microbiol **1989**; 27:1137–8.
10. Rechtman D, Nadler J. Abdominal abscess due to *Cardiobacterium hominis* and *Clostridium bifermentans*. Rev Infect Dis **1991**; 13:418–9.
11. Moyano R, Gómez-Mateos J, Lozano de León F, et al. *Clostridium bifermentans*: an exceptional agent of endocarditis. Clin Infect Dis **1994**; 18:837.
12. Rehany U, Dorenboim Y, Lefler E, Schirer E. *Clostridium bifermentans* panophthalmitis after penetrating eye injury. Ophthalmology **1994**; 101:839–42.
13. Chaudhry R, Venugopal S, Bahadur T, et al. Prosthetic valve endocarditis due to *Clostridium bifermentans*: a rare entity. JMM Case Reports **2014**; 1–3. Available at: http://www.microbiologyresearch.org/docserver/fulltext/jmmcr/1/2/jmmcr001230.pdf?expires=1463922580&id=id&accname=guest&checksum=4613A47E5B99E1FA73AA210702BDC074. Accessed 5 December 2015.
14. Edagiz S, Lagace-Wiens P, Embil J, et al. Empyema caused by *Clostridium bifermentans*: a case report. Can J Dis Med Microbiol **2015**; 26:105–7.
15. Fischer M, Bhatnagar J, Guarner J, et al. Fatal toxic shock syndrome associated with *Clostridium sordellii* after medical abortion. N Engl J Med **2005**; 353:2352–60.
16. Hogan S, Ireland K. Fatal acute spontaneous endometritis resulting from *Clostridium sordellii*. Am J Clin Pathol **1989**; 91:104–6.
17. Aldape M, Bryant A, Ma Y, Stevens L. The leukemoid reaction in *Clostridium sordellii* infection: neuraminidase induction of promyelocytic cell proliferation. J Infect Dis **2007**; 195:1838–45.
18. Geny B, Khun H, Fitting C, et al. *Clostridium sordellii* lethal toxin kills mice by inducing a major increase in lungvascular permeability. Am J Pathol **2007**; 170:1003–17.
19. Popoff M. Purification and characterization of *Clostridium sordellii* lethal toxin and cross-reactivity with *Clostridium difficile* cytotoxin. Infect Immun **1987**; 55:35–43.
20. Voth D, Ballard J. *Clostridium difficile* toxins: mechanism of action and role in disease. Clin Microbiol Rev **2005**; 18:247–63.
21. Maclennan J. The histotoxic clostridial infections of man. Bacteriol Rev **1962**; 26:177–274.