Fatal spontaneous *Clostridium bifermentans* necrotizing endometritis: a case report and literature review of the pathogen

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Abstract

*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 compared to all 13 previously described cases of *C. bifermentans* infection.

Case Report:

In October 2014, a 33-year-old woman with history of abnormal uterine bleeding status-post uncomplicated endometrial ablation 5 months prior developed new onset dysuria and greyish, malodorous vaginal discharge. Her white blood cell count was \(16 \times 10^3\) cells/mm\(^3\) and 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 b-HCG was negative. White blood cell count was \(60 \times 10^3\) cells/mm\(^3\); hematocrit 42%; platelets \(38 \times 10^3\) cells/mm\(^3\); and lactate 6.5 mmol/L.

Computed tomography (CT) scan of the abdomen/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 \(113 \times 10^3\) cells/mm\(^3\), and hematocrit was 58%, despite having received 12L of intravenous 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 26L during the first
24 hours and 51L by 72 hours. Additionally, she showed signs of disseminated intravascular coagulation (DIC) and received 46 units of blood product (fresh frozen plasma, platelets, and cryoprecipitate) over 72 hours. Trans-thoracic echocardiogram showed a large pericardial effusion with cardiac tamponade, which required pericardial drain placement with removal of 1,500mL transudative fluid. She also developed large bilateral pleural effusions and required bilateral chest tube placement with 4L per day transudative fluid output. Given the profound intra-abdominal fluid, there was concern for potential abdominal catastrophe; she thus had an exploratory laparotomy, which was negative for any signs of intra-abdominal infection or viscous perforation, though 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. HIV-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 veno-venous 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 showed diffuse cerebral edema and tonsillar herniation. A family meeting was convened, life support was withdrawn, and she expired 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 confirmed the presence of Clostridial species by immunohistochemical staining within the areas of endometrial necrosis (Image 1). Although polymerase chain reaction (PCR) assay specific for Clostridium sordellii was negative, wide-range 16S polymerase chain reaction assay of endometrial tissue was positive for Clostridium bifermentans. Post-mortem 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 one infection, presenting with necrotizing pneumonia and empyema, was fatal\(^5\) (7.7% case fatality rate). Interestingly, 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. Additionally, 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 Clostridium
*sordellii* infection, which is well known to cause a fulminant endometritis, typically in young women after medical abortion\(^\text{15}\), though can occur spontaneously\(^\text{16}\). Our patient had an endometrial ablation 5 months prior to her presentation, which was felt to be too distant in time to be a definitive risk factor. *C. 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\(^\text{17}\). *C. sordelli* also elaborates lethal toxin, which undermines the actin cytoskeleton at a cellular level, and is believed through this activity to compromise endothelial barrier integrity\(^\text{18}\). 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\(^\text{19}\). 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. *C. sordellii* and *C. 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, though this conjecture remains unproven. Of note, however, genetic exchange between large toxin protein producing strains of *Clostridium* has been previously suggested\(^\text{20}\). Moreover, within the *Clostridium* phylogeny, *C. bifermentans* and *C. sordellii* are closely related, and were not identified as separate species until 1962\(^\text{21}\). It is also remarkable that in the one prior fatal case of *C. bifermentans*, the white blood cell count was \(52 \times 10^3\) 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, though that is also
unproven. Because no cultures were positive in our case, assays to study toxin elaboration were not possible.

*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.

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References


