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

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*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 abnormally high white blood cell count was 16 × 10^3 cells/mm^3 and her hematocrit was 39%. She was prescribed levofloxacin, but the infection did not improve. 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, with vancomycin, cefepime, and metronidazole was initiated, with the patient's hemodynamics and clinical status improving. 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 A family meeting was convened, life support was withdrawn, and she died shortly thereafter.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...
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 fulminating 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**

<table>
<thead>
<tr>
<th>Author Name</th>
<th>Publication Year</th>
<th>Site of Infection</th>
<th>Patient Age in Years</th>
<th>Patient Sex</th>
<th>Maximum WBC in 10⁶ Cells/mm³</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitner</td>
<td>1971</td>
<td>Abdominal wall</td>
<td>45</td>
<td>Female</td>
<td>19</td>
<td>Survived</td>
</tr>
<tr>
<td>Nolan</td>
<td>1972</td>
<td>Septic arthritis of knee</td>
<td>18</td>
<td>Male</td>
<td>10</td>
<td>Survived</td>
</tr>
<tr>
<td>Misra</td>
<td>1980</td>
<td>Necrotizing pneumonia and empyema</td>
<td>41</td>
<td>Female</td>
<td>52</td>
<td>Death</td>
</tr>
<tr>
<td>Panwalker</td>
<td>1983</td>
<td>Necrotizing pneumonia and empyema</td>
<td>60</td>
<td>Male</td>
<td>24</td>
<td>Survived</td>
</tr>
<tr>
<td>Pencek</td>
<td>1986</td>
<td>Brain abscess</td>
<td>36</td>
<td>Male</td>
<td>9</td>
<td>Survived</td>
</tr>
<tr>
<td>Kolander</td>
<td>1989</td>
<td>Endocarditis</td>
<td>28</td>
<td>Male</td>
<td>7</td>
<td>Survived</td>
</tr>
<tr>
<td>Nachman</td>
<td>1989</td>
<td>Liver abscess</td>
<td>6</td>
<td>Male</td>
<td>25</td>
<td>Survived</td>
</tr>
<tr>
<td>Rechtman</td>
<td>1991</td>
<td>Abdominal abscess</td>
<td>65</td>
<td>Male</td>
<td>9</td>
<td>Survived</td>
</tr>
<tr>
<td>Moyano</td>
<td>1994</td>
<td>Endocarditis</td>
<td>26</td>
<td>Male</td>
<td>16</td>
<td>Survived</td>
</tr>
<tr>
<td>Rehany</td>
<td>1994</td>
<td>Panophthalmitis</td>
<td>13</td>
<td>Male</td>
<td>9</td>
<td>Survived</td>
</tr>
<tr>
<td>Scanlan</td>
<td>1994</td>
<td>Osteomyelitis and bacteremia</td>
<td>81</td>
<td>Male</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>Chaudry</td>
<td>2014</td>
<td>Endocarditis</td>
<td>22</td>
<td>Male</td>
<td>7</td>
<td>Survived</td>
</tr>
<tr>
<td>Edagiz</td>
<td>2015</td>
<td>Emphyema</td>
<td>60</td>
<td>Male</td>
<td>18</td>
<td>Survived</td>
</tr>
</tbody>
</table>

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 $52 \times 10^3$ 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, 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**

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