

# 골수형성이상증후군 환자에서의 *Clostridium bif fermentans* 균혈증 1예

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## A Case of *Clostridium bif fermentans* Bacteremia in a Patient with Myelodysplastic Syndrome

Cases of anaerobic bacteremia are rare, and the clinical impact of clostridial bacteremia remains to be clarified. Previous clinical reports have suggested that *C. bif fermentans* is less virulent than other *Clostridia* species. This microorganism has occasionally been reported to cause septic arthritis, necrotizing pneumonia with empyema, brain abscesses, endocarditis, and metastatic osteomyelitis. Herein, we report on a case of *C. bif fermentans* bacteremia in a patient with myelodysplastic syndrome in South Korea.

**Key Words:** *Clostridium bif fermentans*, Bacteremia, Myelodysplastic syndrome

### Introduction

*Clostridia* are Gram-positive, spore-forming obligate anaerobes that are found throughout nature. There are almost 90 recognized species within the genus *Clostridium*, but less than 20 of these are associated with clinical illnesses. *Clostridium* are frequently found in the respiratory, gastrointestinal, and female genital tracts, and they are known to induce invasive cellulitis, myonecrosis, fulminant intravascular hemolysis, food poisoning, pseudomembranous colitis, botulism, and tetanus by producing exotoxins that target the nervous system [1]. The most common etiological organisms that cause *Clostridium* bacteremia are *C. perfringens*, *C. bif fermentans* and *C. septicum* [2]. Identifying different species of *Clostridium* in cases of clinical infection is important because some are indicative of the underlying bowel pathologies (*C. septicum*) [3], they require antitoxin administration (*C. tetani*), or they are reflective of increased resistance to certain antimicrobials (*C. ramosum*, *C. innocuum* and *C. clostridioforme*) [4].

Previous clinical studies have suggested that *C. bif fermentans* is less virulent than other clostridia. However, there are a few reports that *C. bif fermentans* caused intra-abdominal infections, and especially that *C. bif fermentans* is involved with bowel perforation, soft tissue infection, gas gangrene, septic arthritis, necrotizing pneumonia with empyema, brain abscess, endocarditis,

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and metastatic osteomyelitis [5]. There is also abundant evidence demonstrating the significance of the morbidity of clostridial bacteremia under specific circumstances such as cases arising in cirrhotic patients or immune-compromised patients [6]. Herein, we report on a case of *C. bifermentans* bacteremia in a patient with myelodysplastic syndrome (MDS). To the best of our knowledge, this is the first reported case of *C. bifermentans* bacteremia in South Korea.

## Case report

A 75-year-old male patient who had been diagnosed with MDS in 2008 and had received conservative care was admitted to the hospital due to fever in January 2010. He was treated for neutropenic fever with antibiotics (intravenous, 2 g cefepime every 12 hours) for 2 weeks and granulocyte colony-stimulating factor (G-CSF). Two days after the first injection of antibiotics, the patient became afebrile and the pancytopenia persisted. Thereafter, he was treated for pancytopenia with an injection of G-CSF.

After 42 days in the hospital, the patient again complained of a febrile sensation with chills. His vital signs were as follows: the blood pressure was 110/60 mm Hg, the pulse rate was 100 beats per minute, the respiratory rate was 30 breaths per minute, and the body temperature was 39.3°C. No abnormalities of the head, ears, eyes, nose, or throat were observed. The heart sounds were normal and no murmur was present. The lungs were clear on auscultation and percussion. The liver and spleen were not palpable. There was no abdominal distension or tenderness. The results of the neurological examination were normal. There was no venous access device or indwelling urinary catheter.

The white blood cell count was 1,060/mm<sup>3</sup>, of which 45.3% were neutrophils (480/mm<sup>3</sup>) and 44.8% were lymphocytes (470/mm<sup>3</sup>). The hemoglobin level was 5.6 g/dL and the platelet count was 13,000/mm<sup>3</sup>. The serum creatinine level was 0.9 mg/dL. The serum aspartate aminotransferase level was 20 U/L and the alanine transaminase level was 19 U/L. The total bilirubin level was 1.3 mg/dL. The C-reactive protein (CRP) level was 9.14 mg/dL. The chest X-ray revealed cardiomegaly and clear lung fields. The electrocardiogram was normal. Urine analysis revealed microscopic hematuria (25-50 erythrocytes per high-power field), but no pyuria. The urine culture was negative.

After 48 hours of incubation, gram-positive rods were isolated in two anaerobic bottles from three sets of blood cultures. These rods were subsequently identified as *C. bifermentans* using a Vitek2 ANI card (BioMerieux Inc., Durham, NC, USA). The clostridial

isolate was suspended in tryptic soy broth to a McFarland standard of 1 to 1.5 for the susceptibility test. According to the Clinical and Laboratory Standards Institute breakpoints, the organism was found to be susceptible to penicillin, clindamycin, imipenem, and metronidazole. Subsequently, the cefepime (2 g intravenously every 12 hours) that was being administered to the patient was replaced with ampicillin-sulbactam (1.5 g intravenously every 6 hours) and clindamycin (600 mg intravenously every 12 hours). The combination of ampicillin-sulbactam and clindamycin was used because the patient was immune-compromised and had severe pancytopenia.

Blood culturing was performed after 10 days and no organism growth was observed. However, fever reappeared and the patient complained of pain in his right lower leg around the previous peripheral line insertion site after 7 days. Physical examination revealed swelling and redness with purulent discharge in the right pretibial area. The CRP level was elevated from 15.95 mg/dL to 27.92 mg/dL. Cultures of the discharge from the wound produced methicillin-resistant *Staphylococcus aureus*. Therefore, the patient was given teicoplanin (200 mg intravenously every 24 hours), clindamycin (600 mg intravenously every 12 hours), and meropenem (1 g intravenously every 12 hours).

Despite the 5-day antibiotic therapy, the fever persisted and the patient's mental status decreased. He developed tachycardia and tachypnea. However, the patients' family refused to approve any further medical treatment. The next day, the patient experienced sudden cardiac arrest and expired.

## Discussion

*C. bifermentans* was first isolated in 1902 by Tissier and Martelly [7], and this organism is found in soil, sewage, and among the normal intestinal flora of humans. The recovery of *C. bifermentans* from infected wounds following lawnmower injury, eye injury with a soil-contaminated foreign body, or blunt abdominal trauma is not a surprising result as this anaerobic organism is part of the soil flora [8, 9]. Clostridial species are the second most frequently isolated organism, after *Bacteroides fragilis*, in most studies of anaerobic bacteremia in cancer patients [10]. Neoplastic, infectious, and gastrointestinal diseases are the most common underlying diseases in anaerobic bacteremia patients in South Korea [11]. Hematologic, gastrointestinal and genitourinary tract malignancies were the most common underlying malignancies in cancer patients with clostridial bacteremia. This finding is not surprising since clostridial species are normal inhabitants of the

gastrointestinal track and genitourinary tract [10]. The overall survival rate of cancer patients with clostridial bacteremia is 58% [10].

The presentation and outcome of clostridial infection depends on both the underlying host defenses and the species causing the infection. The clinical presentation of bacteremia caused by clostridial species can range from asymptomatic individuals in whom the organism can be isolated from blood samples, to syndromes involving the rapid onset of shock and death. In immune-compromised patients, infection with anaerobic bacteria shows unusual clinical manifestations [10]. These patients are unable to mount an adequate inflammatory response; hence, local signs of infection may be minimal or absent [10]. A study of clostridial bacteremia in rural areas demonstrated that these cases arose from a gastrointestinal source. These cases of clostridial bacteremia frequently occurred in patients with serious underlying medical conditions (especially hematologic malignancies), and rarely it was the result of traumatic farm accidents [12].

In our case report, the patient was elderly and he had been previously diagnosed with MDS. Infection is a major cause of morbidity in patients with MDS [13]. Furthermore, he showed evidence of severe pancytopenia. The infection rates are higher in patients with 1,000 neutrophils/ $\mu$ L or less compared to the patients with more than 1,000 neutrophils/ $\mu$ L [13]. Severe pancytopenia results in a poorer prognosis of infection, and particularly for cases of *Clostridium* bacteremia. The in-hospital mortality rate of anaerobic bacteremia is 34.2% and neutropenia at the time of blood culture is the only statistically-significant factor associated with mortality [11]. Empirical therapy is necessary for neutropenic patients due to the rapid progression of untreated infection. Furthermore, if the physician suspects a clostridial infection, then prompt therapy is clearly indicated because of the high potential for rapid mortality.

*C. bifermentans* is uniformly susceptible (*in vitro*) to penicillin and clindamycin, and these 2 drugs are commonly used to treat infections caused by anaerobes [5]. However, the susceptibility of clinically-isolated anaerobes is changing. For example,  $\beta$ -lactamase production has been described in some non-*C. perfringens* species of clostridia [14]. Metronidazole, clindamycin and cefoxitin resistance have also been reported in cases of clostridia not associated with *C. perfringens* [14]. The presence of penicillin-resistant anaerobic organisms may require the use of agents that are effective against these types of bacteria. These antimicrobials include clindamycin, metronidazole, carbapenem, cefoxitin, chloramphenicol or the combination of penicillin and a  $\beta$ -lactamase inhibitor [8]. Synergy between trovafloxacin and metronidazole or clindamycin has been observed for *C.*

*bifermentans* [2]. It may be prudent to initiate therapy with a combination of antibiotics to maximize the clinical effectiveness and then to modify the regimen once the antibiotic susceptibilities of the infecting organism have been determined. In the present case, the infectious organism was susceptible to penicillin, clindamycin, imipenem, and metronidazole. Thus, we treated the patient with ampicillin-sulbactam and clindamycin, which successfully eradicated his bacteremia.

Species identification and routine susceptibility testing are also very important for selecting the appropriate antimicrobials. Unfortunately, rapid diagnostic tests for clostridial infection are not yet available and the existing tests for speciation and susceptibility require significant periods of time. Thus, the patients are at risk of dying before the testing results are available.

In conclusion, anaerobic bacteremia has recently reemerged as a significant clinical problem due to an increased number of patients with complex underlying diseases such as malignancies, liver disease, and diabetes mellitus [15, 16]. We should not fail to consider anaerobic organisms as a cause of bacteremia in immune-compromised patients. Prompt administration of the appropriate antibiotics is important in high-risk individuals with *Clostridium* sepsis.

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