

## *Clostridium bifermentans* Bacteremia with Metastatic Osteomyelitis

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**Osteomyelitis caused solely by an anaerobic organism is uncommon. We report a case of recurrent *Clostridium bifermentans* bacteremia resulting in metastatic osteomyelitis involving the sacrum, spine, and ribs. The emergence of resistance of this organism to imipenem and metronidazole is noteworthy because of the usual susceptibility of clostridial species to these antibiotics.**

Anaerobic organisms are becoming more common isolates from bone in polymicrobial infections. However, purely anaerobic osteomyelitis resulting from hematogenous spread is rare (2). The most frequent anaerobic isolates from bone cultures are various *Bacteroides* species or gram-positive cocci (3, 12). Osteomyelitis caused solely by a clostridial species is uncommon (4, 9, 13). We report a patient with metastatic osteomyelitis due to *Clostridium bifermentans*.

**Case report.** An 81-year-old man with a history of recurrent localized oropharyngeal lymphoma was admitted to the hospital with lower back pain. He had received the cyclophosphamide-mechlorethamine-ovocovin-procarbazine-prednisone regimen 6 weeks prior to admission and developed severe lumbosacral pain refractory to narcotics. He had a history of myocardial infarction 2 years previously and urinary retention for several months.

Initial physical examination revealed an elderly white male with a temperature of 101°F (about 38°C), a blood pressure of 120/80 mm Hg, a pulse rate of 88 beats per min, and a respiratory rate of 20/min. The physical examination was remarkable for an enlarged right pharyngeal soft tissue mass measuring approximately 2 by 2 cm, as well as a small, nontender left anterior cervical lymph node. The cardiac examination revealed an irregularly irregular rhythm. No murmur was heard. Bibasilar lung rales were present. There was no abdominal tenderness, masses, or hepatosplenomegaly. There was no tenderness in response to palpation over the spine. There were no lesions on the extremities or the skin. The neurologic examination was normal. There was no venous access device nor indwelling urinary catheter.

Hemoglobin was 8.7 g/dl, hematocrit was 26.7%, and leukocyte count was 3,000/mm<sup>3</sup> with 51% segmented neutrophils, 29% bands, 9% lymphocytes, 9% monocytes, 1% basophils, and 1% nucleated erythrocytes. The platelet count was 40,000/mm<sup>3</sup>. The blood urea nitrogen was 30 mg/dl, and the serum creatinine was 1.1 mg/dl. The total bilirubin was 1.2 mg/dl, serum aspartate aminotransferase was 104 U/liter, serum alanine aminotransferase was 113 U/liter, alkaline phosphatase was 489 U/liter, albumin was 3.2 g/dl, and the lactate dehydrogenase was 963 U/liter. The prothrombin time and partial

thromboplastin time were normal. The urine analysis showed 25 to 50 erythrocytes, 5 to 10 leukocytes, and a few bacteria per low-power field. The peripheral blood smear showed no evidence of hemolysis. A chest radiograph was unremarkable. Lumbar spine films showed evidence of osteopenia and degenerative joint disease. Urine cultures were negative. After 48 h, three sets of blood cultures grew gram-positive rods, subsequently identified as *C. bifermentans* (confirmed by D. Citron, R. M. Alden Research Laboratories, Santa Monica Medical Center, Santa Monica, Calif.) which, by the disk elution method, was initially reported as resistant to low doses of penicillin (2 U/ml) and cefotetan (18 µg/ml) but susceptible to high doses of penicillin (10 U/ml), cefoxitin (18 µg/ml), clindamycin (1.6 µg/ml), chloramphenicol (12 µg/ml), erythromycin (3 µg/ml), metronidazole (16 µg/ml), ampicillin-sulbactam (4 µg/ml), and imipenem (2 µg/ml).

After therapy with imipenem was begun, the patient became afebrile within 48 h. A noncontrast computerized tomography scan of the chest and abdomen revealed linear atelectasis, fatty changes in the liver, an inflamed bladder with a filling defect, a left renal cyst, and dilatation of the small bowel and colon. A hepatobiliary diisopropyl iminodiacetic acid-labelled scan was consistent with acute cholecystitis. To eradicate the potential source of *C. bifermentans*, the patient underwent a cholecystectomy. Cultures of the gall bladder were negative; pathology was consistent with cholelithiasis and chronic cholecystitis. Subsequent blood cultures were negative. The patient was treated with imipenem (500 mg intravenously every 6 h for 9 days) and then cefoxitin (2 g intravenously every 8 h for 12 days). One week after cessation of antibiotics, the patient developed an acute myocardial infarction with pulmonary edema. He again became febrile to 102°F (about 39°C). Repeat blood cultures grew *C. bifermentans* reported as resistant to penicillin (2 U/ml), cefoxitin (18 µg/ml), chloramphenicol (12 µg/ml), metronidazole (16 µg/ml), and imipenem (2 µg/ml) but susceptible to clindamycin (1.6 µg/ml), cefotetan (18 µg/ml), and ampicillin-sulbactam (4 µg/ml). Treatment with clindamycin (900 mg intravenously every 8 h) was begun. An abdominal-pelvic computerized tomography scan revealed loss of trabecular pattern involving the left sacrum with minimal endosteal scalloping, as well as a small focus of air overlying the left sacrum. Magnetic resonance imaging confirmed these findings. A bone scan showed multiple areas suspicious for metastatic infection, including T11 through L5 and several ribs. The erythrocyte sedimentation rate was 151 mm/h.

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The patient underwent computerized-tomography-guided aspiration of the left sacral alar bone, from which hemorrhagic, turbid fluid was obtained. The gram stain of the fluid showed a few polymorphonuclear cells and erythrocytes, but no organisms were seen. Cultures after 72 h grew *C. bifermentans*. Colonoscopy and ileoscopy revealed only a 1-cm-diameter sessile polyp, which was removed.

The blood cultures became negative 2 days after clindamycin therapy was begun. The patient received a total of 6 weeks of intravenous clindamycin therapy; he did well and was discharged to a rehabilitation center.

**Discussion.** Clostridia are gram-positive, spore-forming obligate anaerobes that are ubiquitous throughout nature. *C. bifermentans*, first isolated in 1902 by Tissier and Martelly (6), is found in soil, sewage, and the normal intestinal flora of humans. Occasionally, it has been reported to cause septic arthritis, necrotizing pneumonia with empyema, brain abscess, and endocarditis (5, 6, 10, 11). The association between clostridial infection, particularly with *C. septicum*, and colonic and hematologic malignancies is well recognized (7). Metastatic *C. septicum* osteomyelitis has been previously described in a patient with rectal adenocarcinoma (9). This is the first reported case of metastatic osteomyelitis caused by *C. bifermentans*.

Our patient had multiple blood cultures positive for *C. bifermentans* and a positive bone culture from his sacrum. His bone scan demonstrated additional lesions on the vertebrae and ribs, consistent with metastatic osteomyelitis resulting from hematogenous spread of the organism. Clinical signs of clostridial sepsis (shock, jaundice, and intravascular hemolysis) were not evident during the protracted bacteremia. Although there were no signs or stigmata of subacute bacterial endocarditis, the prolonged bacteremia suggested an intravascular infection.

Improved anaerobic culture techniques have shown that the incidence of osteomyelitis caused by anaerobic bacteria is greater than has been previously recognized (3). In the review by Hall et al. of 182 cases of osteomyelitis, only nine patients (5%) were found to have a single anaerobic organism. Moreover, these patients were older, had a shorter interval between the onset of symptoms and treatment, and had a foreign body, in contrast to the patients with mixed aerobic-anaerobic infections (3). Anaerobic osteomyelitis occurs mostly as a result of direct extension from an adjacent focus of infection. It is rarely a complication of bacteremia. Osteomyelitis is seldom caused by a *Clostridium* species in pure culture. Chronic osteomyelitis caused by *C. clostridiiforme*, vertebral osteomyelitis caused by *C. difficile*, and metastatic osteomyelitis caused by *C. septicum* are among the few previously reported cases (4, 9, 13).

Information on susceptibility testing for anaerobic organisms is often not available until long after treatment is initiated. Knowledge of the usual susceptibility pattern of an organism is important in the choice of therapy. *C. bifermentans* has been uniformly susceptible (in vitro) to penicillin and clindamycin, drugs commonly used in the treatment of infections caused by

anaerobes (2). In our patient, *C. bifermentans* initially resistant to a low dose of penicillin also became resistant to imipenem and metronidazole in vitro. This was significant in that these antimicrobial agents are usually active against all anaerobes (1). The mechanism of  $\beta$ -lactam resistance in clostridia is unknown.

In summary, we present a patient with *C. bifermentans* bacteremia resulting in metastatic osteomyelitis. Osteomyelitis is unusual with a clostridium as the sole infecting organism and rarely occurs as a result of bacteremia (12). The apparent emergence of imipenem and metronidazole resistance of this organism when the second bacteremia was documented is interesting because of the usual susceptibility of clostridial species to these antibiotics. Variability among the susceptibility patterns of clostridia is not well recognized, as most of these organisms are not known as primary pathogens in clinical infections (8).

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#### REFERENCES

1. Finegold, S. M., and the National Committee for Clinical Laboratory Standards Working Group on Anaerobic Susceptibility Testing. 1988. Susceptibility testing of anaerobic bacteria. *J. Clin. Microbiol.* **26**:1253-1256.
2. Gorbach, S. 1992. *Clostridium perfringens* and other clostridia, p. 1587-1596. In S. L. Gorbach, J. G. Bartlett, and N. R. Blacklow (ed.), *Infectious diseases*. The W. B. Saunders Co., Philadelphia.
3. Hall, B. B., R. H. Fitzgerald, and J. E. Rosenblatt. 1983. Anaerobic osteomyelitis. *J. Bone Joint Surg.* **65**:30-35.
4. Incavo, S. J., D. L. Muller, M. H. Krag, and D. Gump. 1988. Vertebral osteomyelitis caused by *Clostridium difficile*. A case report and review of the literature. *Spine* **13**:111-113.
5. Jonsson, D., J. Claridge, and E. J. Young. 1983. Necrotizing pneumonia and empyema caused by *Bacillus cereus* and *Clostridium bifermentans*. *Am. Rev. Respir. Dis.* **127**:357-359.
6. Kolander, S. A., E. Cosgrove, and A. Molavi. 1989. Clostridial endocarditis: report of a case caused by *Clostridium bifermentans* and review of the literature. *Arch. Intern. Med.* **149**:445-456.
7. Kornbluth, A. A., J. B. Danzig, and L. H. Bernstein. 1989. *Clostridium septicum* infection and associated malignancy. Report of 2 cases and review of the literature. *Medicine* **68**:30-37.
8. Musial, C. E., and J. E. Rosenblatt. 1989. Antimicrobial susceptibilities of anaerobic bacteria isolated at the Mayo Clinic during 1982 through 1987. Comparison with results from 1977 through 1981. *Mayo Clin. Proc.* **64**:392-399.
9. Neimkin, R. J., and J. B. Jupiter. 1985. Metastatic nontraumatic *Clostridium septicum* osteomyelitis. *J. Hand Surg.* **10A**:281-283.
10. Nolan, B., W. D. Leers, and J. Schatzker. 1972. Septic arthritis of the knee due to *Clostridium bifermentans*. *J. Bone Joint Surg.* **54**:1275-1277.
11. Pencek, T. L., and K. J. Burchiel. 1986. Delayed brain abscess related to a retained foreign body with cultures of *Clostridium bifermentans*. Case report. *J. Neurosurg.* **64**:813-815.
12. Raff, M. J., and J. C. Melo. 1978. Anaerobic osteomyelitis. *1978. Medicine* **57**:83-103.
13. Spitzer, R. D., and K. R. Ratzan. 1991. Chronic osteomyelitis due to *Clostridium clostridiiforme*. *South. Med. J.* **84**:671-672.