

First Report of Bacteremia Caused by *Clostridium cadaveris* in China

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Background: Bacteremia caused by *C. cadaveris* is an extremely rare infection that accounts for 0.5–2% of all positive blood cultures. *C. cadaveris* is an opportunistic agent that is highly lethal in immunocompromised or epithelial barrier disruption hosts.

Case Presentation: A 74-year-old woman was admitted to our hospital with a high fever. The patient was diagnosed with an abdominal infection after a bowel invasion and recurrence of an ovarian tumor after surgery. Blood sample culturing yielded transparent, smooth, moist, slightly raised colonies without a hemolytic ring. *C. cadaveris* was identified by gram staining and MALDI-TOF MS. 16S rRNA gene sequencing confirmed a sequence homologous to *C. cadaveris* in the GenBank database. Drug susceptibility testing showed that *C. cadaveris* was sensitive to cefoxitin, clindamycin, imipenem, meropenem, metronidazole, and vancomycin. After treatment, the patient's body temperature was normal and she was discharged from the hospital.

Conclusion: This is the first case report of bacteremia caused by *C. cadaveris* in China and also the first report of identifying *C. cadaveris* in clinical specimens by MALDI-TOF MS. This case study could increase the awareness of these infections in China.

Keywords: *C. cadaveris*, bacteremia, rapid identification, drug sensitivity test

Introduction

Clostridium cadaveris (*C. cadaveris*) is a motile, anaerobic, gram-positive straight rod bacterium that is most prominent during the decay of dead bodies. It was first reported by Klein in 1899.^{1,2} *C. cadaveris* is widely distributed in the environment and can be isolated from soil, marine sediment, and cobra venom.^{3,4} It has been found in intestinal tracts of humans and is excreted in feces.^{5,6} Pathologically, *C. cadaveris* produces toxins and is occasionally isolated from abscesses and wound infections, with extremely rare episodes of bacteremia resulting in positive blood cultures. Only a few reports of bacteremia have been reported, for example, Knight et al reported a case in Australia and Schade et al reported two cases in the Netherlands.^{7,8,15} In this article, we provide the first report of a bacteremia case caused by *C. cadaveris* in China. We analyzed the first *C. cadaveris* clinical isolate by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS) and summarized the rapid identification and results of antimicrobial susceptibility testing.

Materials and Methods

Blood Cultures and Isolates Identification of *C. cadaveris*

One strain of *C. cadaveris* was isolated from a positive blood anaerobic culture in the Department of Laboratory Medicine at the First Affiliated Hospital of Anhui

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Medical University in 2020. One drop of blood was inoculated onto Columbia blood plate medium, and the anaerobic package was added at 37°C and in a 5% CO₂ chamber. The colonies were taken for gram staining and microscopic examination for primary identification.

MALDI-TOF MS Identification

MALDI-TOF MS was performed using a Vitek MS platform by the direct smear method according to the instructions of the manufacturer. After the acquisition of the spectra, data were transferred to the analysis server, which used software algorithms to compare the generated spectrum with the typical spectra within the database.

16S rRNA Gene Sequencing Identification and Construction of a Phylogeny Tree

The original bacteria were purified and expanded to extract genomic DNA. A forward primer 27F and a reverse primer 1492R were used for PCR amplification. The sequencing was compared with the 16S rRNA gene sequencing of known bacteria in the GenBank database. The phylogenetic tree was established using the MEGA7.0 software.

In vitro Drug Susceptibility Testing

All tests were performed using the agar dilution method.

Case Report

A 74-year-old woman was admitted to our hospital with a high fever due to recurrence of an ovarian tumor following surgery. About 2 years ago, the patient had resections of the whole uterus, bilateral adnexa, greater omentum, and appendix. Postoperative pathological examinations revealed the presence of poorly differentiated adenocarcinoma with necrosis in the ovaries and cancer cells were found in the greater omentum and appendix. The patient was treated with chemotherapy. No obvious bone marrow suppression was observed following treatment, and periodic reviews were conducted. One year later, the patient had a CA125 level of 66.04U/mL and human epididymis secreted proteins 4 (HE4) level of 209.70pmol/L. CT examination suggested postoperative recurrence of ovarian cancer, and multiple cystic foci were observed in the right upper abdomen, spleen, and perispleen. Multiple metastases were considered.

During hospitalization, the patient had a fever with an axillary temperature reaching 39.3°C. On laboratory investigations, the patient had a procalcitonin (PCT) level of

0.57 ng/mL, a CRP level of 148.42 mg/L, a WBC count of 3.76×10^9 /L, and a neutrophil percentage of 80.4%. Blood culture was conducted in aerobic and anaerobic flasks. The positive bacteria were identified as *C. cadaveris* in an anaerobic flask after 16.4 h. Considering abdominal infection due to bowel invasion caused by *C. cadaveris*, the patient was treated with imipenem and cilastatin sodium (1 g, every 8 h, iv. drip) for anti-infection and hydrocortisone sodium succinate (0.01 g, once, iv. drip) for anti-inflammation. After 2 days, the patient's body temperature was normal and she was discharged from hospital.

Results

After culturing for 48 h, gray, translucent, smooth, slightly raised colonies with a diameter of 0.5–1 mm were visible without a hemolytic ring (Figure 1). The gram staining results showed a positive bacillus (Figure 2). The MALDI-TOF MS of the isolated strain was most homologous to *C. cadaveris* with a confidence level of 99.9% (Figure 3). The PCR product was identical to the 16S rRNA gene sequencing of known *C. cadaveris*. By constructing a phylogenetic tree, it is found that that isolate was located in the same branch as *C. cadaveris* (Figure 4). The isolate was confirmed, and the entry number is NR 104695.1. The strain was sensitive to cefoxitin, clindamycin, imipenem, meropenem, metronidazole, and vancomycin. The minimum inhibitory concentration (MIC) is shown in Table 1. The MIC was defined as the concentration of the drug that completely inhibited growth or caused a marked

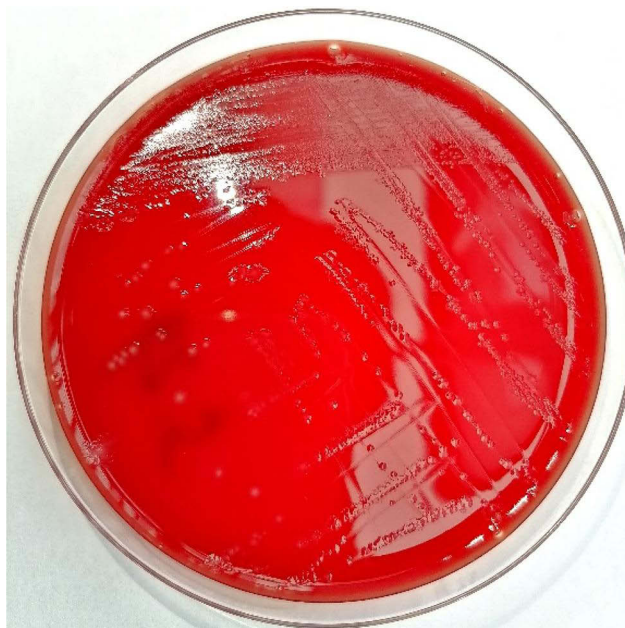


Figure 1 Result of pure culture of the bacterial isolate after 48 h.

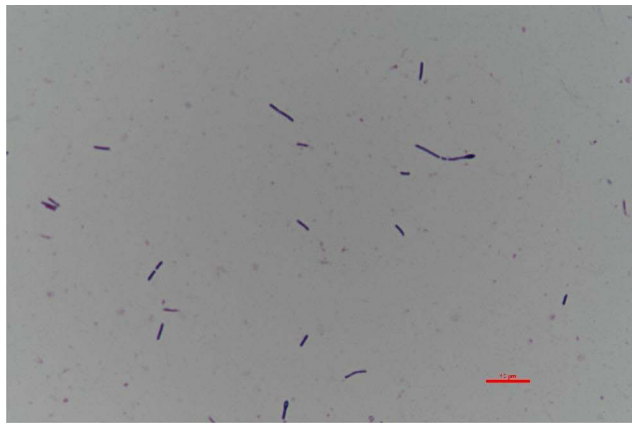


Figure 2 Gram staining of the bacterial isolate.

reduction (50% or 90%) in the presence of growth compared to the drug-free growth control.

Discussion

Accurate identification of obligate anaerobic, gram-positive bacilli is difficult as they are small, fastidious, and biochemically inert. In the past, it has been particularly challenging to isolate *C. cadaveris* from clinical samples. Recently, MALDI-TOF MS has become widely established in clinical microbiology laboratories as an effective method to identify bacteria and fungi^{12,13} with an accuracy of 90% or higher. In this report, MALDI-TOF MS was used to identify an

isolated strain of *C. cadaveris* with a confidence of 99.9%. This is the first report of *C. cadaveris* in China and also the first report of identifying *C. cadaveris* in clinical specimens by MALDI-TOF MS technology. 16S rRNA gene sequencing and MALDI-TOF MS were both performed on the strain. A phylogenetic tree was constructed to confirm the correctness of the pathogen. The results of 16S rRNA gene sequencing and MALDI-TOF MS were consistent, and both achieved high accuracy.

C. cadaveris is an opportunistic pathogen that causes infection problems in immunocompromised patients.^{9,10} *C. cadaveris* infection is usually associated with a poor physical condition, underlying malignancy, and severe immune suppression. *C. cadaveris* has been found in the human intestinal tract and is the source of infection in most abdominal bacteremia cases.¹¹ In this report, the patient had recurrent ovarian cancer and intestinal invasion resulting in abdominal infection and bacteremia. Knight et al reported a case of a 19-year-old man who had *C. cadaveris* bacteremia with associated superior mesenteric vein thrombus. Following treatment with intravenous metronidazole, piperacillin/tazobactam, and oral vancomycin, and the patient demonstrated a gradual clinical improvement and resolution of symptoms.⁸ Citron et al evaluated the in vitro activity of glycolipopeptide antibiotics (Ramoplanin, Teicoplanin, and Vancomycin)

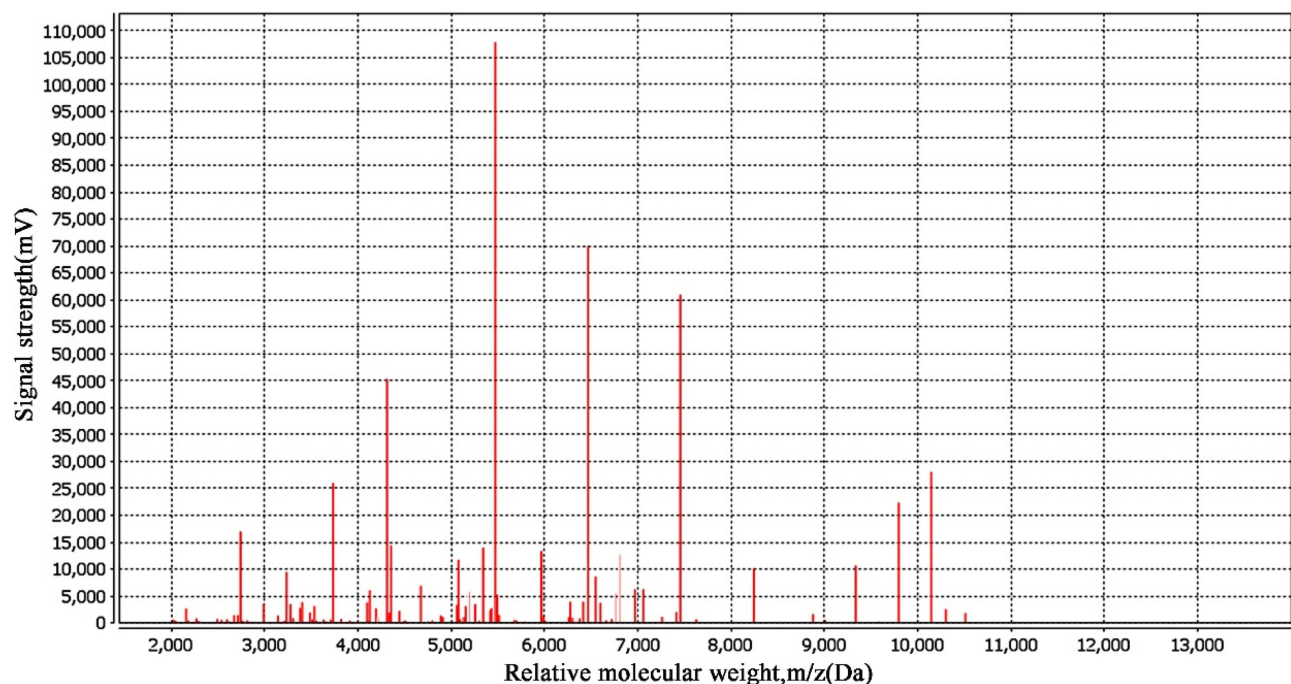


Figure 3 Mass spectra of the bacterial isolate.

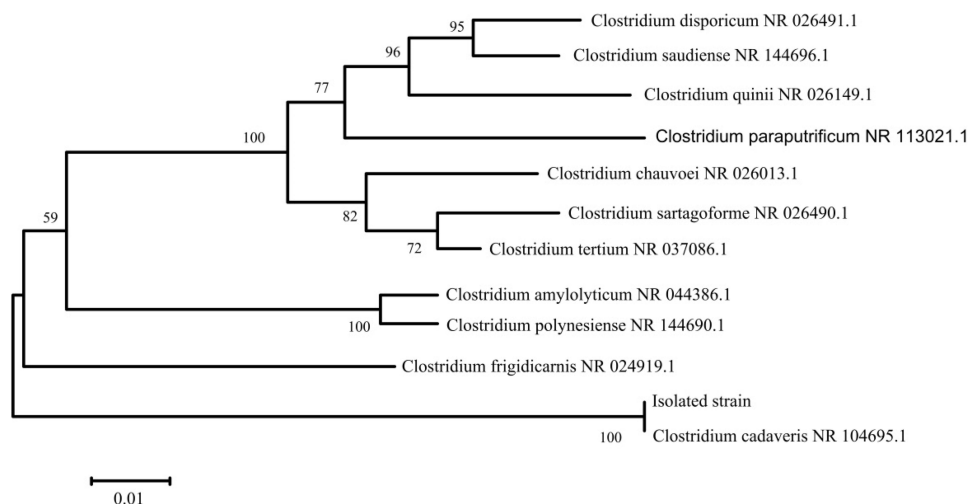


Figure 4 Phylogenetic tree of the bacterial isolate.

using an agar dilution method to identify drugs that were active against *C. cadaveris*.¹⁴ In this report, susceptibility testing was performed according to the reference agar dilution method and the MIC results of cefoxitin, clindamycin, imipenem, meropenem, metronidazole, and vancomycin were consistent with Goldstein's results. The drugs exhibited potent activity against *C. cadaveris*. In the case of our patient, imipenem and cilastatin sodium were chosen as antibiotics and the patient showed a strong clinical response.

Conclusions

In this report, one strain of *C. cadaveris* was isolated and identified by MALDI-TOF MS and 16S rRNA gene sequencing as a rapid and accurate detection method that was performed within 24 h. After treatment with imipenem and cilastatin sodium, the patient's body temperature returned to normal. Accurate diagnosis and selection of effective treatments are of particular importance in cases involving rare bacteria.

Table I Drug Sensitivity Results of Bacterial Isolate

Antibiotics	MIC (mg/L)	50%	90%
Cefoxitin	2	0.5	1
Clindamycin	2	0.5	1
Imipenem	4	1	2
Meropenem	4	1	2
Metronidazole	0.5	0.125	0.25
Vancomycin	4	1	2

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Disclosure

The authors have no conflicts of interest to declare.

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