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The first case of *Odoribacter splanchnicus* bacteremia isolated from a patient in China☆

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ABSTRACT

Background: Odoribacter splanchnicus is an extremely rare pathogen of human infection. This case reports bacteremia infection of *O. splanchnicus*, which is highly likely to result in misdiagnosis if inappropriate diagnostic method are used.
Case presentation: A 29-year-old Chinese male patient with no underlying disease was hospitalized twice for injuries caused by a car accident. During the second hospitalization, abdominal surgery was performed and high fever developed after the surgery. A strain of *O. splanchnicus* was isolated from the blood and confirmed by MALDI-TOF-MS and 16S rRNA gene analysis. Finally, the patient recovered successfully by using antibiotics, fluid replacement and albumin input.
Conclusions: This is the first case of *O. splanchnicus* bacteremia in China. We present a brief review of the cases concerning *O. splanchnicus* infection in humans. *O. splanchnicus*, as part of the normal intestinal flora, is well known for its anti-tumor and immune regulating properties, it is rarely isolated from clinical samples. This case illustrates the potential of *O. splanchnicus* as a pathogen and suggests attention to the use of new and advanced methods like MALDI-TOF MS and 16S rRNA gene sequencing to identify rarely isolated species from clinical samples.

1. Introduction Background

Odoribacter splanchnicus is a non-spore forming, non-motile, gram-negative anaerobe bacterium normally found in the intestines. It is known for its anti-tumor and immune regulatory activities [1–5], but relatively little is known about its pathogenicity in humans, and only a few cases of human infection have been reported [9–11]. Here, we report a case of postoperative *O. splanchnicus* infection in the bloodstream of a patient with intestinal perforation.

2. Case report

A 29-year-old Chinese male patient with no underlying disease was admitted to the emergency department due to an open abdominal injury caused by a car accident. After emergency surgery (splenic arteriography and embolization of diseased vessels were selected) , the patient was hospitalized for five days, during which he did not develop fever and was not given antibiotics. Although

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the patient's condition improved slightly and recovery was not complete , he insisted on automatic discharge.

Two days after the discharge, the patient was re-admitted due to persistent lower abdominal pain. His body temperature was 36.8 °C, blood pressure was 135/67 mmHg, and physical examination showed total abdominal tenderness, especially the lower abdomen, with rebound pain and muscle tension. In the second hospitalization, laboratory tests showed white blood cell count of 16.62 $x10^9$/L and neutrophils of 87.80 %. Computed tomography (CT) showed intestinal perforation, peritonitis, high density shadow in the ascending colon, and thickening and swelling of the long segments of the ascending colon and ileum, suggesting fecal obstruction and local inflammatory edema of the ascending colon. After the diagnosis of intestinal perforation, emergency surgery was performed immediately involving resection of the necrotic small intestine, small intestine ostomy, and surgical removal of the abdominal abscess, which was sent for conventional bacterial culture. The patient received one-time intravenous infusion of cefoperazone-sulbactam(2g) prior to surgery as empirical treatment. On the first day after surgery, the patient's body temperature rose to 39.3 °C, white blood cell count was 22.68 $x10^9$/L, neutrophils of 94.1 %, and anti-infection therapy was changed to intravenous infusion of imipenem-cilastatin (1g every 6h) sodium and Linezolid(0.6g every 12h) after bilateral double sets of blood culture. The blood culture bottles were incubated in a BacT/Alert system (Becton Dickinson, New Jersey, US). On the fourth postoperative day, bilateral anaerobic blood culture bottles reported positive (the positive time was 65.5h and 78.5h respectively) and Gram staining confirmed presence of gram-negative bacteria under the microscope. Because the double anaerobic blood culture bottles were positive, the specimen extracted from the bottles were inoculated onto common blood agar plate and cultured with 35 °C anaerobic conditions. The colony appeared slow growth, with moist, gray-white bacteria colonies growing on day 3 (Fig. 1). The isolated strain was not identified with VITEK 2 Anaerobic and Corynebacteria identification card (VITEK 2 ANC Test Kit, Merier, France), but matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) Biotyper (Library BDAL-11897-4274 Version 12, Bruker Daltonics, Bremen, Germany) identified *O. splanchnicus* with a score of 2.110 (Fig. 2). Because of the discrepancy between the results of these two analytical methods, 16S rRNA sequencing was adopted for further verification. The BLAST software (MEGA software version 10) was used to conduct homology analysis of the gene sequences of the isolated strain and those in the GenBanK database. The isolated strain showed a 100 % match to the 16S rRNA of *O. splanchnicus* (GenBank No.NR_074535.1), was in the same clade as *O. splanchnicus* and belonged to the same species (Fig. 3).

Based on the above examination, the patient was diagnosed with post-operative bacteremia. On the third day after surgery, the patient's body temperature returned to normal, white blood cell count was 13.92$x10^9$/L, neutrophils of 89.3 %, and after blood culture identification results were obtained, antibiotic treatment was changed from imipenem-cilastatin and Linezolid (for 3 days) to cefoperazone-sulbactam (2g every 12h, for 8 days) again. And the abdominal abscess was incubated at 35 °C under aerobic conditions for 24 hours to grow moist, white and large colonies, which were identified as *Klebsiella pneumoniae* by MALDI-TOF MS with a score of 2.210. The *K.pneumoniae* colonies were sensitive to cefoperazone sulbactam, imipenem and other antibiotics(VITEK 2 GN Test Kit, Merier, France). Although the patient had a normal temperature after 3 days of antiinfective treatment with imipenem-cilastatin, he continued to receive antiinfective therapy with cefoperazone-sulbactam for 8 days due to the long delay in the course of the disease and the high inflammatory index. At the same time, the patient was given supportive treatment, such as forbidden drinking and fasting, active fluid replenishment, and human blood albumin input, etc. Therefore, the patient recovered and was discharged 14 days after the operation. During the subsequent month of outpatient follow-up, the patient did well with no complications.

Fig. 1. A colony of *Odoribacter splanchnicus* seen on a common blood agar plate(Cultured 3 days).

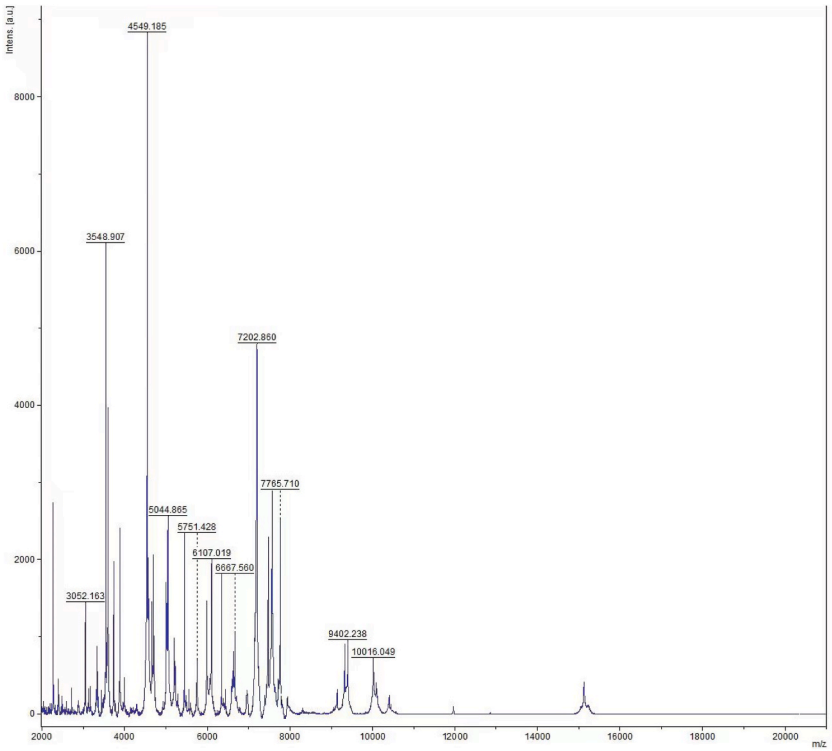

Fig. 2. The isolated strain was identified *Odoribacter splanchnicus* with a score of 2.110.

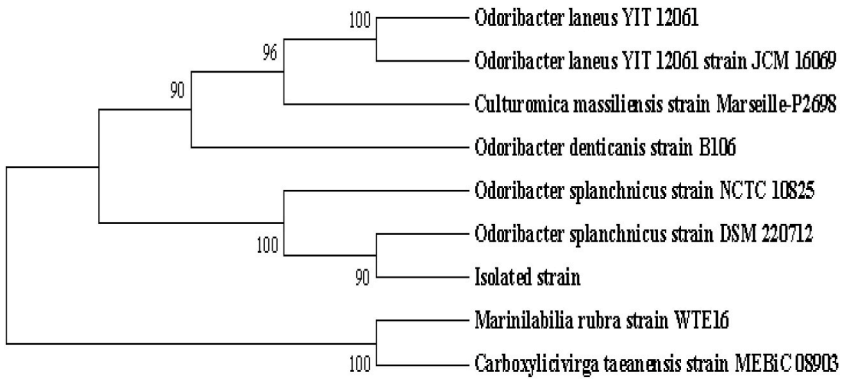

Fig. 3. Phylogenetic tree based on 16S rRNA gene sequences showing the relationships between the isolated strain and related bacterial species (MEGA software version 10). The branching pattern was generated using the maximum maximum-likelihood method based on 1000 replications. Bar, 0.01 substitutions per nucleotide position.

3. Discussion and conclusions

O. splanchnicus was formerly assigned to the genus *Bacteroides* and was originally isolated from human fecal specimens and abdominal abscesses [1]. In 2008, *O. splanchnicus* was reclassified to the genus *Odoribacter* with more data obtained from 16S rRNA gene sequencing technology [2]. The generic name derives from the Latin noun odor meaning smell and the Neo-Latin word bacter meaning a rod, referring to a rod of bad smell. The species epithet is derived from the Greek plural noun splanchna meaning innards, referring to the internal organs as the site of isolation. *O. splanchnicus* grows well at 37 °C, is strictly anaerobic and is able to ferment fructose, glucose, arabinose, galactose, mannose and lactose but does not utilize rhamnose, sucrose, salicin trehalose or trehalose [1]. *O. splanchnicus* is a common member of the human gut microbiome [3]. It can produce short-chain fatty acids to maintain the balance of the intestinal microecology and can play an anti-inflammatory and immune regulatory role in the intestinal tract [4,5]. The abundance of *O. splanchnicus* is associated with a variety of diseases such as non-alcoholic fatty liver, cystic fibrosis, inflammatory bowel disease, colorectal cancer and so on [6–8].

So far, *O. splanchnicus* has rarely been reported to cause human disease. In 1977, Labbe et al. reported a case of pelvic peritonitis and bacteremia in a patient with asymptomatic uterine fibroids caused by *O. splanchnicus* [9]. Subsequently, Bennion et al. reported that *O. splanchnicus* was found in 12 out of 30 peritoneal fluid, appendix tissue, and pus from patients with perforated or gangrenous appendicitis [10]. More recently, Kanematsu et al. reported a case of bacteremia in patients with appendicitis caused by *O. splanchnicus* [11]. Our report is the first documented case of *O. splanchnicus* induced bacteremia in mainland China. Göker et al. suggested that *O. splanchnicus* might become an opportunistic pathogen [3]. Manfredi et al. reported the detection of the iron capture system (ICS) gene from *O. splanchnicus*, which may be an important virulence factor in this bacterium [12]. Hardham et al. believes that *O. splanchnicus* is a potential pathogen causing periodontitis [2]. *O. splanchnicus* potentially harbors only pentaacylated lipid A, which is 100-fold less toxic compared to the *E. coli* LPS and *O. splanchnicus* is a nonadherent gut commensal with innocuous impact on the epithelial monolayer integrity [4]` [13]. However, CT in this example and the cases reported by Kanematsu et al. [11] indicate fecal obstruction and intestinal inflammation. In this case, the patient also underwent intestinal surgery, so the barrier function of the patient's gut is weakened, and the gut is impaired, and there is a possibility that *O. splanchnicus* could enter the blood from the damaged intestine. In terms of the whole course of the disease, the patient developed high fever after the second operation. After 3 days of blood culture, two bottles of blood culture reported positive results. All of the above indicated that *O. splanchnicus* was the pathogen that caused the postoperative bacteremia of the patient. In terms of the use of antibiotics, both this case and the case reported by Kanematsu et al. [11] used *β*-lactamase inhibitors antibiotics. Conversely in this case, the patient was treated with imipenem-cilastatin sodium, which is more effective against anaerobes. *O. splanchnicus* has previously been reported to be resistant to kanamycin, colistin and vancomycin [2] and is susceptible to lincomycin, tetracyclines, erythromycin, rifampicin and clindamycin (MIC values less than 0.5 μg/ml). Cephalosporins, chloramphenicol and penicillins show bacteriostatic activity (5–40μg/ml) [1,3]. However, in general, there have been few pathogenic reports about *O. splanchnicus* so far, so its specific pathogenic effects in intestinal and bloodstream infections remain to be further studied.

It is well-known that brucella blood agar is the recommendation to culture anaerobic bacteria, but in this work we use blood agar instead of brucella blood agar that it would be better to observe the growth process of the colonies. In our study, the bacterial cultures showed a raised, smooth and grayly-white colony morphology for *O. splanchnicus*, Kanematsu et al. [11] also reported the same colony morphology and misidentification as *Porphyromonas gingivalis* by using the API system. Hardham et al. [2] use *O. splanchnicus* and *P. gingivalis* test for N-Acetylglucosaminidase, arginine, indole, urea, α-arabinosidase, hydrolysis of leucyl-glycine, glycine, proline generated the same results [2], but α-Fucosidase,α-Galactosidase, Pyrrolidony are different [2], which may lead to misidentification due to the similarity of their biological phenotypes. The VITEK 2 ANC Test Kit, which based on the biochemical method in this case, also could not identify *O. splanchnicus* (probably to the lack of database entries with this strain) and MADLI-TOF MS was required [11], with final confirmed by 16S rRNA sequencing. Thus, MALDI-TOF MS is a more reliable identification method for *O. splanchnicus* than Automated biochemical bacteria identification system [11]. However, most clinical laboratories, especially those in developing countries, continue to rely on automatic identification systems to identify bacteria. As a result, *O. splanchnicus* induced infections may have been under-reported.

In conclusion, we report the first case of *O. splanchnicus* bacteremia identified by MALDI-TOF MS and confirmed by 16S rRNA in China. With the development of newer identification techniques, especially MALDI-TOF MS and 16S rRNA sequencing, *O. splanchnicus* will be more frequently identified in laboratories. Meanwhile, a better understanding of the pathogenesis of this bacterium will help in future diagnosis.

Data availability statement

The data that support the findings of this study are available in Mendeley Data V2 at https://doi.org/10.17632/gjhvhmnvxy.2.

Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study because all medical and laboratory procedures are routinely carried out and do not affect decisions concerning treatment. All participants/patients provided informed consent for the publication of their anonymised case details and images.

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CRediT authorship contribution statement

Hualiang Xiao: Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chunjiao Song:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zongyao Chen:** Software, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Miaomiao Jian:** Writing – original draft, Software, Resources, Investigation, Data curation, Conceptualization. **Chengliang Yuan:** Writing – review & editing, Writing – original draft, Resources, Data curation. **Yiman Li:** Writing – original draft, Investigation, Data curation. **Yanjiao Zou:** Writing – original draft, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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