Infective Internal Iliac Artery Aneurysm
Caused by *Campylobacter fetus*

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**Abstract**

A 67-year-old man with a persistent high fever was diagnosed to have an infective aneurysm in his left internal iliac artery. A blood culture detected a gram-negative spiral rod that was first identified as *Campylobacter fetus* subsp. *venerealis* based on a matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) analysis. However, the strain was finally confirmed to be *Campylobacter fetus* subsp. *fetus* based on a genetic analysis. The infection was successfully treated with emergency resection of the aneurysm, followed by 4 weeks of antibiotic therapy. Involvement of the peripheral artery is uncommon in cases of *C. fetus*-infective aneurysm. To figure out the epidemiology and pathogenicity of *C. fetus* infection, the accurate identification of the responsible organisms is essential.

**Key words:** bacteremia, *Campylobacter fetus* subsp. *venerealis*, infective aneurysm, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), zoonosis

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**Introduction**

Members of the genus *Campylobacter*, which are known to be classified into 17 species, are motile, gram-negative spiral rods. In humans, *Campylobacter jejuni* and *Campylobacter coli* are major gastrointestinal pathogens. On the other hand, *Campylobacter fetus* has been reported to cause systemic infection without inducing any digestive symptoms (1, 2).

Infective aneurysm is one of major infections associated with *C. fetus*. The most common site of *C. fetus*-induced infective aneurysms is the abdominal aorta (3), while the peripheral arteries are infrequently involved. We herein describe a case of infective aneurysm caused by *C. fetus* that occurred in the left internal iliac artery of an immunocompetent adult patient.

**Case Report**

A 67-year-old man visited his physician complaining of prolonged fever for the previous 5 days. His past medical history included dyslipidemia, hypertension, percutaneous coronary intervention, artificial graft replacement surgery for the right common iliac artery and coil embolization for the right iliac artery. Even after 3 days of administering intravenous ceftriaxone and oral tosufloxacin, his fever did not improve, and the patient was referred to our hospital for further consultation.

On arrival, his vital signs were as follows: blood pressure, 118/59 mmHg; heart rate, 84 bpm; and body temperature, 38.5°C. There were no gastrointestinal symptoms. Physical examination did not reveal any specific findings, but laboratory data showed signs of high inflammation (serum C-reactive protein level, 13.41 mg/dL). Echocardiography showed no evidence for infective endocarditis. Contrast-enhanced computed tomography (CECT) showed a newly formed aneurysm in his left internal iliac artery, with a maximum size of 28 mm, which was surrounded by a dirty fat sign (Fig. 1A, B). Positron-emission tomography demonstrated a high uptake in the aneurysm. Taken together, the clinical course and radiological findings strongly suggested the presence of an infective aneurysm.

Blood culture revealed gram-negative spiral-shaped organ-
isms, which was first identified as *Campylobacter fetus* subsp. *Venerealis* by means of a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis. The result of antimicrobial susceptibility testing performed by the E-test in a condition of 10% capnec incubation showed the minimum inhibitory concentrations of the pathogen to be as follows: ceftriaxone, 8 μg/mL; ceftazidime, 16 μg/mL; imipenem, 0.064 μg/mL; meropenem, 0.032 μg/mL; levofloxacin, 0.064 μg/mL; gentamicin, 0.5 μg/mL; and clarithromycin, 2 μg/mL. Treatment was initiated with the intravenous administration of cefotaxime and levofloxacin. One week later, although the fever had disappeared and the serum inflammatory reactions had also improved, follow-up CECT demonstrated the infective aneurysm to have become irregularly enlarged with deformation (Fig. 1C). As a result, an emergency operation was performed. The aneurysm strongly adhered to the surrounding tissues, but it was successfully resected. No organisms were detected from a bacterial culture of the resected arterial wall.

Antibiotic therapy with levofloxacin was continued after the surgery, and the postoperative course was stable. The patient was discharged from the hospital 2 weeks after the operation and completed a 4-week course of levofloxacin without any signs of recurrence.

**Bacterial analysis**

To reconfirm the result of the MALDI-TOF MS analysis of the pathogen, the organism was subjected to a complete 16S rRNA sequence analysis. After extracting the DNA, a 16S rRNA fragment of approximately 1,500 bps was amplified by polymerase chain reaction (PCR) using the universal primers 8UA (5'-AGA GTT TGA TC (A/C) TGG CTC AG-3') and 1485B (5'-TAC GGT TAC CTT GTT ACG AC-3'). Then, a sequencing analysis was performed by applying primers 341A (5'-CTA CGG GCA GCA GTG GTG G-3'), 519B (5'-ATT ACC GCG GC (G/T) GCT G-3') and 907A (5'-AAA CT (T/C) AAA (T/G) GA ATT GAC G-3'). Using the BLAST sequence homology search program at DDBJ (DNA Data Bank of Japan, http://dndbj.nig.ac.jp/blast/blastn?lang=ja), the organism was confirmed to be homologous with the published sequences of either *Campylobacter fetus* subsp. *fetus* or *C. fetus* subsp. *venerealis*. However, the results did not allow us to differentiate among the subspecies of the strain.

We then additionally performed another genetic investigation to differentiate the pathogen by a multiplex PCR assay based on previous reports (4, 5). Specific primers named MG3F (5'-GAT GGC AGC AGC TGC TAA GAT 3'-), MG4R (5'-TAG CTA CAA TAA CGA CAA CT-3'), nC1165g4F (5'-AGG ACA CAA ATG GTA ACT GG-3'), MG4R (5'-TAG CTA CAA TAA CGA CAA CT-3'), and nC1165g4R (5'-GAT TGT ATA GCG GAC TTT GC-3') were used for the analysis. The primer MG3F/MG4F amplifies a product of the *cstA* gene (764 bps) that *C. fetus* universally possesses (6), and the primer nC1165g4F/nC1165g4R amplifies a product of the *virB11* gene (233 bps), which is present only in *C. fetus* subsp. *venerealis* (7). The PCR protocol was set as follows: 35 cycles of denaturation (95°C for 30 seconds) after an initial denaturation at 95°C for 180 seconds, primer annealing at 53°C for 30 seconds, and primer extension at 72°C for 60 seconds. A final extension step was set at 72°C for 180 seconds. To visualize the PCR products, electrophoresis with 1.2% agarose gel was carried out. As a result, the organism was finally identified as *C. fetus* subsp. *fetus*, and not *C. fetus* subsp. *venerealis* (Fig. 2).

**Discussion**

*C. fetus* causes the onset of infective aneurysm, mostly in the abdominal aorta (3). According to our literature review, there was only one case each of a *C. fetus*-infected bilateral deep femoral artery (8) and bilateral internal iliac artery aneurysm (9). Our case is thus considered to be relatively rare. Although it is known that *C. fetus* is resistant to complement-dependent immunity (10) and it also has a tropism for the human vascular endothelium leading to endovascular infections (11), the reason for the frequent occurrence of aortic infection is unclear.
Precisely how our patient became infected remains unclear. Although the patient regularly ate yoghurt made from cow milk obtained at a domestic farm, the relevance of this to the infection is unknown.

In conclusion, we herein reported a rare case of an infective aneurysm occurring at the left internal iliac artery that was caused by a genetically confirmed strain of *C. fetus* subsp. *fetus*. The MALDI-TOF MS analysis is generally a reliable method, but it may be unsuitable for differentiating the subspecies of *C. fetus*. To obtain a better understanding of the epidemiology and pathogenesis of *Campylobacter* species, the organisms should therefore be accurately identified at clinical laboratories.

The authors state that they have no Conflict of Interest (COI).

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**Figure 2.** Multiplex polymerase chain reaction findings for differentiating between the subspecies of the *Campylobacter* strain. M: size marker, Lane 1: the patient’s strain. *Campylobacter fetus* universally possesses *cstA* gene (764 bps), while *virB11* gene (233 bps) is only present in *C. fetus* subsp. *venerealis* (7). In our case, there was only one band at 764 bps, thus suggesting the isolate to be *C. fetus* subsp. *fetus*.

*Campylobacter* is classified into two subspecies: *C. fetus* subsp. *fetus* and *C. fetus* subsp. *venerealis*. *C. fetus* subsp. *fetus* is a well-known pathogen in humans that frequently causes bacteremia and infective aneurysms. In contrast, *C. fetus* subsp. *venerealis* is a sexually transmitted organism occurring most frequently in livestock, such as cattle. The causative pathogen in our case was first determined to be *C. fetus* subsp. *venerealis* by a MALDI-TOF analysis, but it was finally identified to be *C. fetus* subsp. *fetus* by means of genetic investigations. A literature review showed that, although there has been one report of *C. fetus* subsp. *venerealis* isolated from a human specimen (12), human cases of *C. fetus* subsp. *venerealis* disease have never been reported. Therefore, we performed a molecular analysis to confirm the identity of the organism.

The classification of *Campylobacter* species is complicated, and the accurate identification of the organism is difficult. A MALDI-TOF MS analysis is a currently established technique for bacterial identification with high accuracy (13). Although this method can yield rapid results, it sometimes cannot differentiate between species and thus can misidentify the organism. The accuracy of this method for identifying *C. fetus* is reported to be reliable; namely, the concordance rate was 100% in 40 strains (14). However, for the differentiation of *C. fetus* subspecies, there are still no reliable data. In fact, the MALDI-TOF MS result in our case was incorrect. It is therefore possible that *C. fetus* subsp. *venerealis* infections have been underreported because of inadequate methods. Even in a large clinical case series (183 episodes of *Campylobacter* bacteremia) (1), the subspecies were not determined genetically. As a result, whether or not *C. fetus* subsp. *venerealis* can cause human infection still remains to be elucidated.
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