Fatal Relapse of a Purulent Pleurisy Caused by \textit{Campylobacter fetus subsp. fetus} \footnote{Published ahead of print on 16 May 2007.}


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\textit{Campylobacter fetus} is associated with invasive disease, while other \textit{Campylobacter} species, such as \textit{C. coli} and \textit{C. jejuni}, are a common cause of bacterial diarrhea. Bacteremia has been well described, but pleurisy remains very uncommon. We report the recurrent isolation of a \textit{C. fetus} subsp. \textit{fetus} strain during two episodes of pleural effusion with a fatal outcome.

CASE REPORT

A 79-year-old man came to the emergency department of the Centre Hospitalier de Rambouillet, a general hospital in a southern suburb of Paris, France, with a 3-day history of fever and difficulty breathing. Of note in the patient’s past medical history was vascular and cardiac thrombosis as lower limb obliterative arteritis, femoral thrombosis, iliac artery stenosis, and coronary stenosis, which led to the placement of stents in the patient. The patient did not present with diabetes mellitus. Upon admission, the patient suffered from malnutrition; his medications included amiodarone, buflomedil, furosemide, acenocoumarol, acetylsalicylic acid, and ibresartan. He had been experiencing several episodes of diarrhea, fever, and chills for the previous 3 weeks. Physical examination revealed an oral temperature of 38°C, septic shock with hypotension, and hypoxemia. Lack of breath could be heard on the left side upon auscultation of the lungs. Chest X-rays revealed an important pleural effusion, which was confirmed by an ultrasound test and chest computed tomography scan. His laboratory tests returned with the following results: hemoglobin (97 g/liter), platelet count (19.3 \times 10^{10}/liter), neutrophils (16.5 \times 10^{9}/liter), serum creatinine (91 \mu mol/liter), and C-reactive protein (62 mg/liter). Purulent pleurisy complicated by septic shock was diagnosed. An antibiotic regimen administered intravenously, amoxicillin-clavulanate (1 g three times a day) and gentamicin (5 mg/kg of body weight once a day), was begun. The patient was transferred to the intensive care unit. The blood cultures drawn upon admission were negative, but the pleural fluid culture on a blood agar plate incubated anaerobically at 37°C was positive for a spiriche-like bacterium identified as \textit{Campylobacter fetus} (strain 2004/670H) by using a common routine method (Api Campy; bioMérieux, Marcy l’Etoile, France). Successive stool and blood cultures were negative. The patient’s condition steadily improved. Several new pleural drainages were required, yielding abundant purulent liquid. On the eighth day, the patient’s serum creatinine level increased significantly; gentamicin was then changed to intravenous ofloxacin (200 mg twice a day). The accumulation of fluid into the lungs stopped. The patient was discharged from the hospital after completing 21 days of intravenous antibiotic therapy.

Three months later, the same patient was hospitalized at the Centre Hospitalier de Dourdan, which is located 20 kilometers from the first hospital. He presented with respiratory distress associated with a new episode of bilateral pleural effusion that was diagnosed after ultrasound testing. This time there was no history of a prior diarrheic episode, but he showed increasing dyspnea over a 3-day period. He was admitted to the intensive care unit. His laboratory tests returned with the following results: hemoglobin (105 g/liter), platelet count (361 \times 10^{9}/liter), white blood cell count (12.9 \times 10^{9}/liter), neutrophils (10.7 \times 10^{9}/liter), C-reactive protein (62 mg/liter), and serum creatinine (84 \mu mol/liter). At the time of his admission, the possibility of endovascular infection due to \textit{C. fetus} was not considered. Therefore, antimicrobial treatment was not immediately prescribed. All bacteriological cultures were initially negative. The pleural fluid culture collected on the eighth day and incubated anaerobically on blood agar plates yielded another strain of \textit{C. fetus} (2004/667H), which was again identified by a common routine method. An antibiotic regimen of imipenem (500 mg three times a day) and amikacin (15 mg/kg once a day) was prescribed on the ninth day and administered intravenously. Nonetheless, the patient died 1 week later. Death was attributed to constrictive purulent pleurisy.

The two strains of \textit{C. fetus} taken from pleural effusion cultures performed by the two different laboratories were sent to the French National Reference Center for Helicobacter and Campylobacter. The two isolates, numbered 2004/670H and
2004/667H, were identified as *C. fetus* subsp. *fetus* by both standard bacteriological and molecular methods (13). In accordance with the Antimicrobial Committee’s recommendations for the French Society of Microbiology, the antimicrobial susceptibility pattern was established by the disc diffusion method and confirmed by determination of the MICs using Etest methodology (10). First, the two isolates as well as two unrelated *C. fetus* strains used as controls were genotyped using randomly amplified polymorphic DNA PCR (RAPD-PCR). The two control strains were (i) the type strain, CIP53.96, which was isolated from a sheep fetus; and (ii) strain 01190 referenced in our laboratory collection that had been isolated in 2001 in a human blood culture. DNA was extracted using QIAamp DNA mini kit (QIAGEN, Courtaboeuf, France) according to the manufacturer’s instructions. RAPD-PCR was performed in a 25-μl volume containing 20 ng of template DNA, 1 × PCR buffer (Promega, Charbonnieres, France), 200 μM of each deoxynucleoside triphosphate (Promega), 1.25 U of Taq DNA polymerase (Promega), and 2 μM of one of three primers. The three primers were 1290, 5'-GT GGA TGCGCA-3'; K3V16, 5'-CAC A CCTC CAG-3'; and KSV2, 5'-GGT GCG CGG AA-3' (1). The reaction was performed in a Gene Amp 9700 thermocycler (Applied Biosystems, Foster City, CA). The amplification program consisted of 1 cycle of 5 min at 94°C; 40 cycles of 30 s at 94°C, 30 s at 36°C, and 1 min 30 s at 72°C; and 1 cycle of 7 min at 72°C. Amplicons were analyzed by electrophoresis on a 1.5% agarose gel stained with ethidium bromide. We also used the *C. fetus* multilocus sequence typing (MLST) method designed at the University of Oxford and available on the website http://pubmlst.org/efetus/ as a second genotyping strategy (22). Fragments of seven housekeeping genes (*aspA, glnA, gltA, ghsA, pgm, tkt*, and *uncA*) were amplified using the primers and protocol previously described (22). Sequencing was achieved on an ABI Prism 3100 sequencer (Applied Biosystems) with BigDye Terminator v1.1 sequencing kit (Applied Biosystems) in accordance with the manufacturer’s instructions. For each sequence, an allele number was allotted after comparison with the website database. The two isolates exhibited an identical antimicrobial susceptibility pattern: they were both susceptible to ampicillin, the combination of amoxicillin plus clavulanate, gentamicin, and erythromycin, and both had an intermediate susceptibility to doxycycline. The MIC for ciprofloxacin against the two strains was 0.5 mg/liter; according to the French guidelines, they were categorized as susceptible to fluoroquinolones (10). The RAPD pattern obtained with primer 1290 showed very similar profiles between the two isolates; nevertheless, an additional band was found for the 2004/670H isolate (Fig. 1). The use of two other primers led to identical profiles for the two isolates, although insignificant differences were noted in the intensities of the bands (Fig. 1). The profiles obtained with the two unrelated control strains were different for each of the three primers. MLST applied to the two related isolates and to the *C. fetus* type strain revealed allelic identities for *aspA* (allele 1), *ghsA* (allele 2), *gltA* (allele 2), *pgm* (allele 1), and *tkt* (allele 2). According to the nomenclature proposed, the *ghsA* allele number for strain CIP 53.96 was 3, and it was 2 for the 2004/670H and 2004/667H isolates. The *uncA* allele number was 1 for strain CIP 53.96. The *uncA* allele was identical for both isolates but did not correspond to any of the 11 alleles present in the databank corresponding to 140 isolates. They were, however, very similar to allele 4, showing only a one-base difference.

*Campylobacter* species are among the top three bacteria implicated in food-borne disease, displaying an annual incidence of 12.72 cases per 100,000 inhabitants in the United States (8). The invasive propensity of some *Campylobacter* species is well documented: bacteremia, deep abscess, meningitis, cellulitis, and arthritis (2, 6, 17, 18). *C. fetus* is the main *Campylobacter* species found in invasive disease, while other *Campylobacter* species, such as *C. jejuni* or *C. coli*, are implicated in gastrointestinal infections; this could be the result of their high level of resistance to the bactericidal effect of serum (4, 17). Human *C. fetus* infections are probably underestimated, and their frequency may be increasing (5). Subjects with these infections are often immunocompromised (2, 17, 18). Pleurisy is rarely reported; *C. fetus* is the main *Campylobacter* species connected with empyema or pulmonary abscess, with the exception of one case of purulent pleurisy due to a *Campylobacter lari* strain reported in 1998 (3, 7, 12, 14, 16, 19, 21). Nevertheless, because of inappropriate standardization of biochemical tests, accurate identification of *Campylobacter* strains at the species level should include molecular methods. This is particularly true for *C. fetus*, which furthermore is divided into two different subspecies that have dramatic differences in their epidemiological and clinical implications (20).

To the best of our knowledge, this is the first reported case of recurrent pleurisy caused by accurately identified *C. fetus* subsp. *fetus* strains in a immunocompromised patient. The results obtained by antimicrobial susceptibility testing, RAPD typing, and MLST indicate the probable isolation 4 months later of the same strain from the same patient (22). Few genomic differences have been pointed out by any of the
RAPD primers. A possible explanation is that this strain evolved in vivo between the two samplings probably in relation to antimicrobial treatment. Nonetheless, the MLST pattern showed a unique ST for both isolates that had never been previously observed among the 140 strains used for the MLST database setup (22). According to the definitions of Chu et al., these two episodes could be qualified as a “relapse” (an incompletely treated primary episode that results in the emergence of the original microorganism from a protected source such as deep-tissue infection) rather than a “reinfection” (infection with a new microorganism) (9). Inadequate therapy of Campylobacter infections was clearly identified as being clinically relevant (11). Recurrent bacteremia and relapse often occur after termination of an antibiotic treatment lasting less than 3 weeks. In this particular case, antibiotic treatment failure was not due to an inadequate choice of compounds or duration of therapy, noncompliance of the patient, or an acquired resistance mechanism of the strain; a whole regimen of recommended drugs was administered intravenously during the hospital stay (21 days), and both strains were fully susceptible to all the prescribed antibiotic compounds. One other hypothesis that could be proposed is the antibiotic diffusion deficiency in a reshaped pleural membrane. Furthermore, the impact of C. fetus vascular tropism in this patient with a medical history of thrombosis is still possible. Interestingly, Neuzil et al. previously reported a case of recurrent infection 7 years after the first episode of bacteremia caused by C. fetus (15). The reasons of this relapse proposed by the authors were (i) the probable presence of a sequestered site of infection in bone, (ii) the intrinsic serum resistance of the strain, and/or (iii) the absence of specific antibody in this patient who suffered from malignant thymoma and hypogammaglobulinemia (15).

In summary, we describe the first reported case of fatal recurrent pleurisy caused by C. fetus subsp. fetus. This case report emphasizes the need to systematically consider the possibility of relapse or recurrence whenever a patient with a history of invasive Campylobacter infection presents with a new febrile episode. The completion of a 3-week antimicrobial treatment of the initial episode, however, does not exclude the possibility of a clinical relapse, which is probably linked to a deep sequestered site. An association of two antibiotics with a synergistic effect, for example, a fluoroquinolone and a β-lactam, should be used in severe cases of pleurisy as early as possible.

REFERENCES


