

Case Report

Successful treatment of recurrent *Helicobacter fennelliae* bacteraemia by selective digestive decontamination with kanamycin in a lung cancer patient receiving chemotherapy

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Introduction: *Helicobacter fennelliae* is an enterohepatic *Helicobacter* species causing bacteraemia in immunocompromised hosts. Only a few cases of recurrent *H. fennelliae* bacteraemia have been reported in Japan and there are no guidelines regarding antimicrobial treatment for *H. fennelliae* infection.

Case presentation: *H. fennelliae* bacteraemia was observed in a patient receiving platinum-based chemotherapy for lung cancer. To prevent recurrence, the patient received antibiotic therapy with cefepime, amoxicillin and doxycycline for 6 weeks, which is similar to the therapy for *Helicobacter cinaedi* bacteraemia. Bacteraemia recurred despite the long-term antibiotic therapy. We hypothesized that the *H. fennelliae* bacteraemia originated from endogenous infection in the intestinal tract due to the long-term damage of the enteric mucosa by platinum-based drugs and performed selective digestive decontamination (SDD) with kanamycin. Bacteraemia did not recur after SDD.

Conclusion: Our observations indicate that clinicians should be aware of possible recurrent *H. fennelliae* bacteraemia, which could be effectively prevented by SDD with kanamycin.

Keywords: recurrent bacteremia, lung cancer, chemotherapy; *Helicobacter fennelliae*; selective digestive decontamination, kanamycin.

Received 7 July 2016
Accepted 11 October 2016

Introduction

Helicobacter cinaedi and *Helicobacter fennelliae* are spiral-shaped Gram-negative rods that are enterohepatic *Helicobacter* species; they inhabit the colons of humans and animals, and cause bacteraemia in immunocompromised hosts, especially in patients with human immunodeficiency virus or haematological malignancies (Kemper *et al.*, 1993; Kiehlbauch *et al.*, 1995; Ng *et al.*, 1987; Hsueh *et al.*, 1999;

Rimbara *et al.*, 2013a, b; Saito *et al.*, 2016). *H. cinaedi* and *H. fennelliae* also cause bacteraemia in patients with chronic renal failure, autoimmune diseases and solid organ cancers (Nishine *et al.*, 2007; Matsumoto *et al.*, 2007; Rimbara *et al.*, 2013b; Saito *et al.*, 2016). There are several reports of recurrent *H. cinaedi* bacteraemia in immunocompromised hosts (Sullivan *et al.*, 1997; Mammen *et al.*, 1995; Kikuchi *et al.*, 2012; Uçkay *et al.*, 2006), which is treated with prolonged antibiotic therapy to prevent further recurrence (Kiehlbauch *et al.*, 1994; Tee *et al.*, 1996; Sullivan *et al.*, 1997). However, only a few cases of recurrent *H. fennelliae* bacteraemia have been reported in Japan (Saito *et al.*, 2016), and there are no guidelines regarding the choice or duration of

Abbreviations: CBDCA, carboplatin; GI, gastrointestinal; PEM, pemetrexed; SDD, selective digestive decontamination.

antimicrobial treatment and prevention of recurrence for *H. fennelliae* infection. Here, we describe a case of recurrent *H. fennelliae* bacteraemia, which occurred in a patient receiving platinum-based chemotherapy for solid organ cancer. The recurrence of *H. fennelliae* bacteraemia in this case was successfully prevented by selective digestive decontamination (SDD) with oral kanamycin.

Case report

A 73-year-old man suffering from advanced lung adenocarcinoma with multiple metastases was admitted to our hospital in Shinjuku-ku, Tokyo, for a third cycle of chemotherapy. His lung adenocarcinoma diagnosed 8 years

previously had gradually progressed despite surgical treatment, chemotherapy and radiation therapy. He also had a medical history of thyroid papillary carcinoma treated by thyroidectomy 7 years previously. The patient had received two cycles of carboplatin/pemetrexed (CBDCA/PEM) therapy within the 4 months prior to this admission.

On hospital day 2, 43 days after the second cycle of chemotherapy, the patient developed a fever (38.3 °C); however, no other symptoms, such as shaking chills, diarrhoea, abdominal pain or extremity pain, were observed. His physical parameters were almost normal. Laboratory examinations showed a white blood cell count of 8640 cells μl^{-1} , a neutrophil count of 6790 cells μl^{-1} and a C-reactive protein level of 16.2 mg dl^{-1} , indicating a strong inflammatory

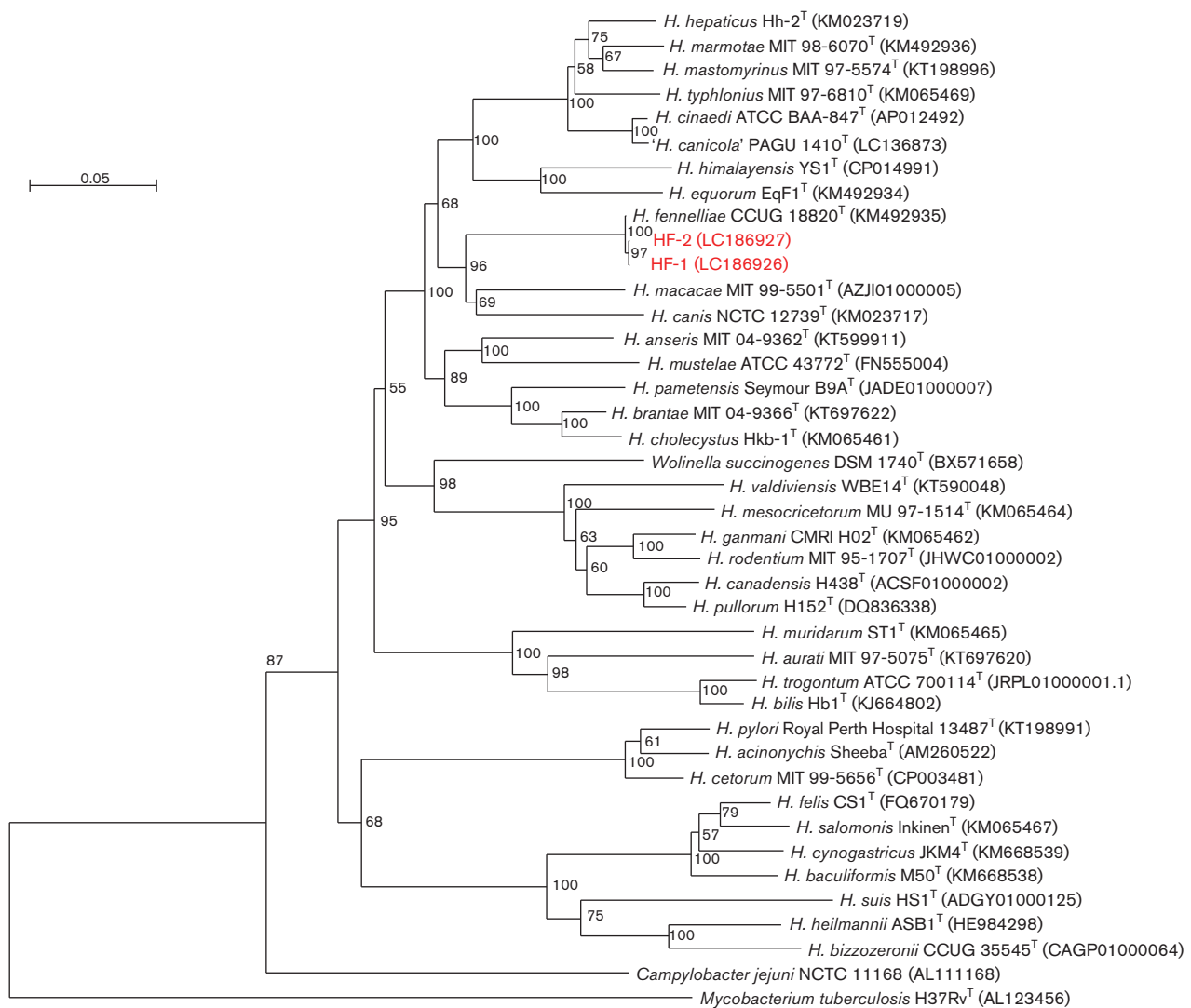


Fig. 1. Phylogenetic tree based on the GyrA protein sequences showing the position of our two isolates (HF-1 and HF-2) within the genus *Helicobacter*. GenBank/EMBL/DBJ accession numbers and type strains are indicated. The numbers at the branching points are bootstrap percentages (based on 1000 replications). The evolutionary distances were computed using the Kimura empirical model, and the phylogenetic tree was constructed using the NJplot software. The bar represents 1 inferred amino acid substitution per 100 amino acids.

Table 1. MICs of antibiotics for *H. fennelliae* isolated from the lung cancer patient and the CCUG 18820 strain

| <i>H. fennelliae</i> isolate | MIC ($\mu\text{g ml}^{-1}$) of : | | | | | | | | | | | | |
|------------------------------|------------------------------------|-------------|----------|----------|-----------|------------|----------------|-------------|-------------|-------------|---------------|--|--|
| | Ampicillin | Amoxicillin | Cefepime | Imipenem | Kanamycin | Gentamicin | Clarithromycin | Clindamycin | Doxycycline | Minocycline | Ciprofloxacin | | |
| HF-1 | 0.5 | NA | 1 | 0.031 | 0.5 | 0.25 | NA | 0.5 | 0.25 | 0.031 | 32 | | |
| HF-2 | 0.5 | NA | 1 | 0.031 | 0.5 | 0.25 | NA | 0.5 | 0.25 | 0.031 | 32 | | |
| CCUG 18820* | ND | 1 | ND | 0.031 | ND | 0.5 | 0.125 | ND | ND | 0.125 | 0.5 | | |

NA, Not attempted; ND, no data.

 *Rimbara *et al.* (2013b).

response without neutropenia. Chest X-ray findings were the same as in previous tests. The patient was treated empirically with ampicillin/sulbactam (3 g twice a day) for 2 days without clinical improvement, and then with cefepime (2 g twice a day), after which the fever gradually subsided.

After the initiation of ampicillin/sulbactam therapy, two sets of aerobic and anaerobic blood cultures were performed using BACTEC Plus Aerobic/F culture vials and BACTEC Plus Anaerobic/F culture vials (Becton, Dickinson), respectively. On hospital day 7, one of the two aerobic cultures became positive after 6 days of incubation in BACTEC 9240 medium (Becton, Dickinson), whereas both anaerobic cultures remained negative. Gram staining of the positive culture revealed spiral-shaped Gram-negative rods. Subsequent subculturing on Nissui sheep blood agar plates and Nissui modified Skirrow's medium EX plates (Nissui Pharmaceutical) revealed thin film-forming colonies and scanty transparent colonies, respectively, after 7 days of incubation at 35 °C in a microaerobic atmosphere (6–12 % O₂, 5–8 % CO₂). *H. cinaedi* was suspected based on the colony characteristics and the biochemical properties of the isolate were tested by the API Campy system (bioMérieux).

The isolate was initially identified as *H. fennelliae* (microcode 4401064) with a relatively low probability level of 80.2 %. However, the biochemical characteristics of nitrate reduction, alkaline phosphatase production and esterase activity were different from those of *H. cinaedi*. To confirm the identification, the *gyrA* gene of the isolate was sequenced (2450 bp) and the deduced protein sequence (811 residues) used to determine the phylogenetic relationship with the GyrA protein of *H. fennelliae* CCUG 18820^T, whose sequence was obtained from a public database (Ménard *et al.*, 2016; Kawamura *et al.*, 2016). In the phylogenetic analysis based on GyrA sequences, the isolate (HF-1; accession no. LC186926) was identified as *H. fennelliae* (Fig. 1). Antimicrobial susceptibility was determined by the agar dilution method (Rimbara *et al.*, 2012). Our experiments revealed low MICs of ampicillin, cefepime and doxycycline for our *H. fennelliae* isolate; however, the MIC of ciprofloxacin was much higher than that for *H. fennelliae* CCUG 18820^T (Table 1), which is consistent with previous findings (Rimbara *et al.*, 2013b).

The patient was treated with cefepime for 15 days, and then with the oral antibiotics doxycycline (100 mg twice a day) and amoxicillin (500 mg three times a day) for 24 days. The long-term antibiotic therapy we used was similar to that used for *H. cinaedi*. The patient received the third cycle of chemotherapy on hospital day 15 and was discharged on hospital day 21.

After 6 weeks of oral antibiotic therapy, the patient was admitted again for a fourth cycle of CBDCA/PEM therapy. On day 7 after chemotherapy, he showed a high-grade fever (39.8 °C) and malaise with no other symptoms. Laboratory tests revealed no neutropenia. *H. fennelliae* bacteraemia was considered, and the patient was treated empirically with

cefepime after two sets of blood cultures were performed. One aerobic blood culture was positive after 5 days of incubation, demonstrating spiral-shaped Gram-negative rods. Subcultures, phenotypic tests, gene sequence determination and phylogenetic analysis of the GyrA protein were performed as described above. This isolate (HF-2; accession no. LC186927) was identified as *H. fennelliae* and was the same as the HF-1 strain (Fig. 1). HF-2 showed an antimicrobial susceptibility similar to that observed in the HF-1 strain. Antibiotic therapy with cefepime continued for 14 days and the patient defervesced.

H. fennelliae bacteraemia recurred in spite of the long-term oral antibiotic therapy. The patient was still being treated with CBDCA/PEM and was at risk of recurrence. We assumed that the primary source of blood infection was the gastrointestinal (GI) tract, which is known as a common reservoir for *H. cinaedi* (Imafuku *et al.*, 2016; Uçkay *et al.*, 2006), and prescribed SDD with oral kanamycin monosulfate (500 mg four times a day) for 2 weeks. The patient did not have any further episodes of *H. fennelliae* bacteraemia during chemotherapy after completing the SDD.

Discussion

Here, we report a case of recurrent *H. fennelliae* bacteraemia during platinum-based chemotherapy. Based on the clinical course observed in the patient, we can draw three important conclusions. First, *H. fennelliae* bacteraemia could recur during platinum-based anticancer chemotherapy. Our patient had advanced lung adenocarcinoma, progressing despite chemotherapy. He developed a fever without neutropenia or any other symptoms 43 days after the second cycle of chemotherapy. The portal of *H. fennelliae* entry and the cause of bacteraemia episodes in our case were unknown. It has been reported that *H. fennelliae* could be recovered from stool cultures (Burnens *et al.*, 1993; Smuts & Lastovica, 2011). CBDCA is a platinum-based anticancer chemotherapeutic agent, which sometimes causes chemotherapy-induced mucositis in the GI tract. In some cases, mucosal inflammation can persist for a long time after chemotherapy because of GI dysfunction due to enteric neuropathy associated with the platinum-based agents (Stojanovska *et al.*, 2015). Therefore, we assumed that the *H. fennelliae* bacteraemia in our case originated from endogenous infection in the GI tract due to damage of the enteric mucosa caused by chemotherapy, and that persisting mucosal damage could result in the recurrence of bacteraemia.

Second, recurrent *H. fennelliae* bacteraemia could be prevented by SDD. We chose cefepime, amoxicillin and doxycycline for the treatment based on previous reports (Rimbara *et al.*, 2013b; Kiehlbauch *et al.*, 1995), and the isolate demonstrated high sensitivity to these antibiotics as evidenced by low MICs (Table 1). It should be noted that the MIC of cefepime for *H. fennelliae* has not been reported previously and that cefepime was clinically effective for our patient. However, *H. fennelliae* bacteraemia recurred despite

a 6 week antibiotic therapy. Given that *Helicobacter* spp. had not been isolated in specimens from other patients in the same ward either before or after our patient's admission, we considered it to be a recurrence rather than nosocomial infection. Recurrent bacteraemia caused by '*Helicobacter rappini*' (now classified as *Helicobacter bilis*) after antibiotic therapy has been reported in a patient with X-linked (Bruton's) agammaglobulinaemia. In addition, it was reported that in a case of recurrent *H. cinaedi* bacteraemia, SDD with oral kanamycin monosulfate could prevent recurrence (Imafuku *et al.*, 2016). Given that the MICs of aminoglycosides for *H. fennelliae* are low (Kiehlbauch *et al.*, 1995; Rimbara *et al.*, 2013b; Ng *et al.*, 1987) and that the MIC of kanamycin for our isolate was $0.5 \mu\text{g ml}^{-1}$, we prescribed oral kanamycin. Following SDD, no side effects, including renal dysfunction, were observed and bacteraemia did not recur despite repeated courses of chemotherapy. As kanamycin is rarely absorbed from the intestinal tract (Hewitt & Finegold, 1958), this observation also indicates that the infection originated from the GI system. Our results suggest that SDD with oral kanamycin can be used to prevent the recurrence of *H. fennelliae* bacteraemia. However, this is, to the best of our knowledge, the first case report of SDD used to treat recurrent *H. fennelliae* bacteraemia and large-scale studies are required to comprehensively investigate the application of kanamycin for SDD in such situations.

Third, fluoroquinolones may be clinically less effective for *H. fennelliae* infection. No standardized antimicrobial susceptibility tests are currently available for *H. cinaedi* and *H. fennelliae*. A recent study has examined a broth microdilution method, which revealed high MICs of fluoroquinolones for *H. cinaedi* isolated in Japan (Tomida *et al.*, 2013). Although ciprofloxacin demonstrated low MICs for *H. fennelliae* CCUG 18820^T and another previously described isolate (Hsueh *et al.*, 1999), Rimbara *et al.* (2013b) have reported high MICs of ciprofloxacin for Japanese patients infected with *H. fennelliae*, which is consistent with our case and may be attributed to gene mutations. Although antimicrobial susceptibility breakpoints for *H. fennelliae* are yet to be determined, our isolates may be considered resistant to ciprofloxacin (Mégraud & Lehours, 2007), suggesting that at least in Japanese patients infected with *H. fennelliae*, fluoroquinolones, including ciprofloxacin, should be avoided.

In conclusion, our report describes a case of recurrent *H. fennelliae* bacteraemia in a patient with solid organ cancer undergoing platinum-based chemotherapy. Our observations indicate that clinicians should be aware of possible recurrent *H. fennelliae* bacteraemia, which could be effectively prevented by SDD with kanamycin.

Acknowledgements

We thank Hideki Araoka, Toranomon Hospital in Tokyo, Japan, for the consultation regarding SDD therapy. This work was supported by grants from the National Center for Global Health and Medicine (25-114 and 26-101). This report is in accordance with the

Declaration of Helsinki (1975, as revised in 2008) and the regulations of the Japanese Ministry of Health, Labour and Welfare.

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