Helicobacter fennelliae Bacteremia
Three Case Reports and Literature Review

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Abstract: Helicobacter fennelliae is a gram-negative, spiral bacillus that appears as thin-spread colonies on sheep blood agar and is similar to Helicobacter cinaedi. H fennelliae is diagnosed by genetic testing, which is not readily available in all laboratories. Therefore, H fennelliae bacteremia has only been reported sporadically, and little is known about its clinical characteristics.

We describe 3 cases of H fennelliae bacteremia with gastrointestinal symptoms, including nausea, vomiting, and diarrhea. Isolates could be differentiated from H cinaedi by biochemical reaction testing, including nitrate reduction and alkaline phosphatase hydrolysis.

INTRODUCTION

Helicobacter fennelliae was first described in 1985 as a new Campylobacter species isolated from asymptomatic, homosexual men with enteritis and proctitis.1 This organism was subsequently reorganized as a Helicobacter species based on 23S rRNA hybridization studies in 1991. 2 Helicobacter species are gram-negative, spiral bacteria that are categorized into 2 groups: gastric Helicobacter and enterohelial Helicobacter. 3 H fennelliae is an enterohelial Helicobacter that causes bacteremia and appears as thin-spread colonies on sheep blood agar. This organism is fastidious and difficult to culture, and its features are similar to Helicobacter cinaedi. In addition, H fennelliae is diagnosed by genetic testing, such as 16s rRNA sequencing, which is not readily available in all laboratories. Therefore, H fennelliae bacteremia has been reported only sporadically, and little is known about its clinical characteristics.

We report 3 cases of H fennelliae bacteremia that could be differentiated from H cinaedi by biochemical reaction testing and provide a review of the literature.

CASE PRESENTATION

Case 1
A 77-year-old Japanese female with cervical cancer and malignant pleural effusion presented at our hospital. She had a radical hysterectomy for treatment of cervical cancer 1 year prior and had received 3 courses of paclitaxel and nedaplatin. She developed bilateral lower extremity lymphedema 3 days before presentation and low back pain, nausea, and vomiting the day before. Her body temperature was 36.6 °C, heart rate was 105 beats/min, and blood pressure was 93/57 mm Hg. The physical examination revealed tenderness in the upper part of the abdomen, costovertebral angle tenderness, and pitting edema in the lower leg, but was otherwise unremarkable. Blood tests obtained on admission revealed a white blood cell count of 11,730 cells/μL with 97% neutrophils, a C-reactive protein level of 40.5 mg/dL, a blood urea nitrogen level of 58.2 mg/dL, and a creatinine level of 1.39 mg/dL. After 2 sets of blood cultures were obtained, she was treated for dehydration with 1 g of intravenous cefepime, 3 times a day. Five days later, spiral-shaped, gram-negative bacilli, a shape suggestive of Helicobacter spp, were isolated from both aerobic blood cultures. Intravenous antibiotic therapy was changed from cefepime to 2 g of ampicillin 4 times a day to treat suspected H cinaedi bacteremia. After the patient showed improvement of her general condition, intravenous ampicillin was switched to oral amoxicillin on the 12th day after admission for treatment of enteritis and bacteremia, and antibiotics were given for a total of 18 days. No recurrence was observed during the 18-month follow-up.

Case 2
A 51-year-old Japanese female with esophageal cancer, liver metastasis, and malignant pleural effusion presented at our hospital. She had received 2 courses of cisplatin and fluorouracil, and radiotherapy. Two days before hospitalization, she had developed anorexia accompanied by nausea and vomiting. Her body temperature was 36.5 °C, heart rate was 98 beats/min, blood pressure was 96/58 mm Hg, and SpO2 was 90%. The physical examination was otherwise unremarkable. Blood tests obtained on admission revealed a white blood cell count of 14,210 cells/μL with 97% neutrophils, a C-reactive protein level of 7.71 mg/dL, a blood urea nitrogen level of 22.0 mg/dL, and a creatinine level of 0.88 mg/dL. Two sets of blood cultures were obtained, and 5 days later, bacteria with a shape suggestive of Helicobacter spp were isolated from both blood cultures. The patient was administered 1.5 g of ampicillin/
sulbactam intravenously, 4 times a day. However, she died due to an underlying disease 27 days after hospital admission.

Case 3
A 74-year-old Japanese female with pancreatic cancer and lymph node metastasis, who had received 2 courses of gemcitabine and nanoparticle albumin–bound paclitaxel, was admitted to our hospital due to persistent fever and a positive blood culture. One week before hospitalization, 2 sets of blood cultures were obtained, and spiral-shaped, gram-negative bacilli were isolated from one of the blood cultures after 5 days. Her body temperature on admission was 36.4 °C, heart rate was 63 beats/min, and blood pressure was 112/50 mm Hg. She had a history of diarrhea and pasty stools. Additionally, she noted mild pain in both knees, and pitting edema in the lower leg was observed; however, the physical examination was otherwise unremarkable. Initial laboratory findings included a white blood cell count of 10,800 cells/μL with 76% neutrophils, a C-reactive protein level of 8.24 mg/dL, a blood urea nitrogen level of 16.7 mg/dL, and a creatinine level of 0.77 mg/dL. She was administered 2 g of ampicillin intravenously, 4 times a day. Ampicillin was switched to oral amoxicillin on the 4th day after intravenous treatment, and antibiotics were given for a total of 6 weeks. Her follow-up blood cultures were all negative, and no recurrence had been observed at follow-ups.

Blood culture samples were processed using the Bactec FX system (Becton, Dickinson and Company, Sparks, MD). Microaerobic cultures were performed with chocolate II agar (Kyokuto Pharmaceutical, Tokyo, Japan) and Trypto soy agar II with sheep blood (Kyokuto Pharmaceutical, Tokyo, Japan) for 6 days at 37 °C in a moist microaerobic atmosphere (5% O2, 10% CO2, 0% H2, 85% N2) generated by the TE-HER CAMPYLO INCUBATOR HZC-3 (Hirasawa Works, Tokyo, Japan). *H. fennelliae* infection was suspected when blood cultures demonstrated thin-spread colonies and gram-negative spiral bacilli (Figures 1 and 2). The isolates were then identified by DNA sequencing of the 16S rRNA genes for *H. fennelliae* and were also tested for nitrate reduction and alkaline phosphatase hydrolysis using the Api campy identification system (bioMerieux Vitek, Tokyo, Japan), which can be performed in general hospitals (Table 1).

The study protocol was approved by the institutional review board of the Shizuoka Cancer Center Hospital. The patient consent requirement was waived due to the retrospective nature of the study.

**DISCUSSION**
According to a growing number of studies and advances in genetic analysis, such as 16S rRNA gene sequencing, the number of reports of *H. fennelliae* bacteremia has been steadily growing throughout the last decade. However, few reports have assessed the clinical characteristics or the treatment of patients with *H. fennelliae* bacteremia. We describe 3 cases of *H. fennelliae* bacteremia that were differentiated from *H. cinaedi* by biochemical reaction testing and provide a literature review. To the best of our knowledge, this is the first review of *H. fennelliae* bacteremia.

Clinical characteristics of *H. fennelliae* bacteremia are summarized in Table 2.

**TABLE 1. Differential Characteristics of *H. fennelliae* and *H. cinaedi***

| Taxon     | Nitrate Reduction | Alkaline Phosphatase Hydrolysis | Catalase Production | Urease Activity |
|-----------|-------------------|---------------------------------|---------------------|-----------------|
| *H. fennelliae* | –                  | +                               | +                   | –               |
| *H. cinaedi*  | +                  | –                               | –                   | +               |

*H. fennelliae = Helicobacter fennelliae, H. cinaedi = Helicobacter cinaedi*.
| Author                     | Year | Age, Sex | Background      | Clinical Features                                                                 | Diagnosis      | Antimicrobials                  |
|---------------------------|------|----------|-----------------|----------------------------------------------------------------------------------|----------------|-------------------------------|
| Skirrow et al<sup>4</sup> | 1993 | NR, male | NR              | Fever                                                                           | NR             | NR                            |
|                          |      | NR, male | Hepatitis       |                                                                                  | NR             | NR                            |
| Kiehlbauch et al<sup>5</sup> | 1995 | NR, female | NR              |                                                                                  | DNA-DNA hybridization | Ampicillin/ Sulbactam/Ceftazidime |
| Hsueh et al<sup>6</sup>   | 1999 | 48, male | Cirrhosis       | Fever, shaking drowsiness, hypotension                                         | NR             | NR                            |
|                          |      |          | diabetes mellitus |                                                                                  | Gas chromatogram | Ampicillin/ Sulbactam/Ceftazidime |
| Asahara et al<sup>7</sup> | 2008 | NR      | NR              |                                                                                  | 23S rRNA       | Imipenem                      |
| Omata et al<sup>8</sup>   | 2011 | 60, female | SLE, femoral  | Fever, lower extremity rash                                                   | NR             | Imipenem                      |
| Inui et al<sup>9</sup>    | 2011 | 46, female | None            | Fever, abdominal pain, proctitis                                               | NR             | Ceftriaxone                   |
| Smuts and Lastovica<sup>10</sup> | 2011 | NR, female | NR              |                                                                                  | 16S rRNA, rpoB | --Azithromycin                 |
|                          |      | 5, male | Diarrhea, acidosis |                                                                                  | 16S rRNA, rpoB | NR                            |
|                          |      | 6, male | Fever, gastroenteritis |                                                                                  | 16S rRNA, rpoB | NR                            |
|                          |      | 8, female | Pneumonia       |                                                                                  | 16S rRNA, rpoB | NR                            |
| Nishida et al<sup>11</sup> | 2013 | 56, male | Alcoholic liver disease | Fever, headache, stiff neck meningitis                                        | 16S rRNA       | Ceftriaxone                   |
| Otani et al<sup>12</sup>  | 2013 | 55, female | SLE, lupus nephritis | Cellulitis                                                              | NR             | Cefazolin                      |
| Nagamatsu et al<sup>13</sup> | 2013 | 73, male | Lung cancer     | Fever, recurrent bacteremia                                                      | 16S rRNA       | Ampicillin/ Sulbactam/Cefepime |
|                          |      |          | NR              |                                                                                  | Ampicillin/ Sulbactam/Cefepime | Ampicillin/Sulbactam/Ampicillin |
| Maehara et al<sup>14</sup> | 2013 | 50, male | Renal transplantation | Fever, chill abdominal pain                                           | Genetic analysis | NR                            |
|                          |      |          | Malignant lymphoma |                                                                                  | NR             | NR                            |
| Rimbaira et al<sup>15</sup> | 2013 | NR      | Malignant lymphoma |                                                                                  | 16, 23S rRNA   | NR                            |
|                          |      |          | Autoimmune disease |                                                                                  | 16, 23S rRNA   | NR                            |
| Yoshizaki et al<sup>16</sup> | 2014 | 64, male | Renal failure   | Recurrent bacteremia, bacterial pericarditis                                  | Genetic analysis | Ceftriaxone                   |
| Miyagi et al<sup>17</sup> | 2014 | 50s, male | Lymphoplasmacytic lymphoma | Fever, recurrent bacteremia                                           | 16S rRNA       | --Piperacillin 16S rRNA       |
| Clarithromycin            |      |          | NR              |                                                                                  | --Ceftazidime  Cefepime | Ampicillin/Ampicillin/Sulbactam/Ampicillin |
| Present case              | 2014 | 77, female | Cervical cancer | Low back pain, nausea, vomiting                                             | 16S rRNA       | --Ceftazidime  Cefepime | Ampicillin/Ampicillin/Sulbactam/Ampicillin |
| Present case              |      | 51, female | Esophageal cancer | Nausea, vomiting                                                               | 16S rRNA       | --Amoxicillin                |
| Present case              |      | 74, female | Pancreatic cancer | Fever, diarrhea, arthralgia                                                     | 16S rRNA       | --Amoxicillin                |

NR = not reported, SLE = systemic lupus erythematosus.
cellulitis (1 case), rash (1 case), meningitis (1 case), bacterial pericarditis (1 case), and fever (10 cases). Gastrointestinal symptoms were common; however, cellulitis was not as common in patients with H. fennelliae bacteria as it is in those with H. cinaedi bacteria.\textsuperscript{18} However, 3 cases of recurrent bacteremia have been identified in previous reports,\textsuperscript{12,16,17} which were similar to those of H. cinaedi.\textsuperscript{18,19} No deaths have been reported due to H. fennelliae bacteremia in the current or previous cases.

Detailed pathophysiology of the developing H. fennelliae infection has not yet been demonstrated. However, acute mucosal inflammation was observed in rectal biopsies from pig-tailed macaque monkeys that developed diarrhea in response to H. fennelliae infection.\textsuperscript{20} In addition, general and specific mechanisms for immune evasion and suppressor cells in H. fennelliae have been identified in previous reports,\textsuperscript{13,16,17} which were similar to those of H. cinaedi.\textsuperscript{20}

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