Pararenal Lymphatic Cyst Infection Caused by *Helicobacter cinaedi*

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**Abstract**

A 43-year-old man was referred to our hospital for an acute-onset fever and left flank pain. He had been previously diagnosed with lymphangioma, and abdominal computed tomography showed pararenal cysts with fat stranding around the left kidney, of which infection was subsequently confirmed on magnetic resonance imaging. Gram-negative spiral bacilli were isolated from two sets of blood cultures, and *Helicobacter cinaedi* was identified using 16S rRNA sequencing. The patient was successfully treated with ceftriaxone therapy without recurrence. A multilocus sequence typing analysis indicated the current *H. cinaedi* strain differed from previous strains isolated in Japan.

**Key words:** *Helicobacter cinaedi*, lymphangioma, bacteremia


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**Introduction**

*Helicobacter cinaedi*, formerly named *Campylobacter cinaedi*, is a Gram-negative spiral rod that has been isolated from stool cultures in humans (1, 2), cats (3), dogs (3, 4), monkeys (5), hamsters (3, 6) and other rodents (7). *H. cinaedi* has been recognized to be an infectious pathogen since the 1980’s (8), with the first infection in Japan reported in 2003 (9).

The clinical characteristics of *H. cinaedi* infection remain largely unknown due to the difficulty of identifying the pathogen, and such infections have been reported to be frequently missed during the normal incubation period (10). Previous studies and case series have demonstrated that most *H. cinaedi* infections are classified as primary bacteremia, cellulitis or gastroenteritis (8, 10-14). Other manifestations are extremely rare, with only two reported cases of meningitis (15, 16), one case of graft infection (17) and one case of joint infection (18).

We herein report a case of pararenal lymphatic cyst infection with *H. cinaedi* bacteremia that was identified using 16S rRNA sequencing.

**Case Report**

A 43-year-old previously healthy Japanese man was referred to our hospital for an evaluation of a three-day history of fever, constant left flank pain and hematuria. He was obese (weight: 87.4 kg, body mass index: 30.2 kg/m²) and had been previously diagnosed with pathologically confirmed lymphangioma at another hospital. The lymphatic cysts extended from the left perirenal space to the inguinal region. The kidney function was normal, and he had no previous history of urinary tract infections. In addition, an annual health check-up had not revealed any chronic diseases, except the lymphangioma. The patient denied any family history of lymphangioma or diabetes mellitus (DM) or re-
cent contact with dogs, cats, hamsters or other animals and did not experience any other preceding symptoms, such as diarrhea or skin rashes.

During the initial evaluation, the patient was found to be febrile (38.5°C) and hemodynamically stable (heart rate: 102 beats/min; blood pressure: 110/70 mmHg) with moderate tenderness on the left lower flank. No remarkable skin lesions indicating either cellulitis or erysipelas were observed. Blood tests showed significant leukocytosis (white blood cell count: 28,500/μL) and elevated C-reactive protein (29.1 mg/dL) and creatinine (1.6 mg/dL) levels. The hemoglobin A1c value was 9.7%, which had not been previously examined. The results of a urinalysis were normal, with no hematuria or pyuria. A serological test for human immunodeficiency virus (HIV) was negative. In order to identify the origin of the infection, we performed computed tomography (CT), which revealed multiple cysts surrounding the left kidney with fat stranding, and tentatively diagnosed the patient with a pararenal lymphatic cyst infection based on the radiological findings and clinical manifestations. He was subsequently hospitalized after collecting two sets of blood and urine cultures. Upon admission, the laboratory data improved with the administration of ceftriaxone (1 g/day), although the treatment did not resolve the pyrexia.

Six days after incubation of the blood cultures with the BacT/Alert 3D system (Sysmex bioMérieux, Tokyo, Japan), positive signals were obtained from both aerobic bottles (124 and 134 hours). In contrast, no positive signals were detected in the anaerobic bottles and we were unable to grow any bacteria in the urine culture using conventional microbiological identification methods. Direct Gram staining showed Gram-negative spiral bacilli, and we subcultured aerobic bottles of the blood samples on 5% sheep’s blood agar under moist, microaerobic conditions with hydrogen. After 72 hours of incubation, we observed transparent film-like colonies on the 5% sheep’s blood agar. *H. cinaedi* was suspected based on the Gram staining and colony findings, and genotype identification was performed using a DNA sequence analysis of the 16S rRNA gene (776bp) with an ABI PRISM BigDye Terminator Cycle Sequencing Kit v3.1 (Applied Biosystems, Foster City, USA). The consensus sequence exhibited the highest similarity (99% match) to *Helicobacter cinaedi* (GenBank accession number AP 012492).

The minimum inhibitory concentrations against the isolated *H. cinaedi* strain were measured using the Epsilometer test (Etest, Sysmex bioMérieux), with the following results: 0.75 μg/mL for ampicillin, 0.94 μg/mL for ceftriaxone, 0.023 μg/mL for minocycline, 8 μg/mL for clarithromycin and ≥64 μg/mL for levofloxacin.

In order to confirm the pararenal cyst infection, we performed abdominal magnetic resonance imaging (MRI) on day 7 (Fig. 1b) and compared the findings with the previous images obtained two years earlier (Fig. 1a). Consequently, MRI showed the intensity of most of the left pararenal cysts to be intermediate to high on T1-weighted fat suppression and T2-weighted images. The radiological findings improved on the follow-up MRI images obtained on day 42 (Fig. 2) along with the clinical improvement; therefore, we finally diagnosed the patient with a pararenal lymphatic cyst infection associated with *H. cinaedi* bacteremia. Drainage therapy was considered for the abscess; however, the patient refused this intervention and we continued the ceftriaxone regimen after discharge on day 8. We administered ceftriaxone for seven weeks, with a clinical response. There were no signs of recurrence during the follow-up period after the completion of therapy.

The *H. cinaedi* isolate was sent to the Department of Bacteriology II, National Institute of Infectious Diseases, and multilocus sequence typing (MLST) was performed as previously described (19). Briefly, seven housekeeping genes (23S rRNA, ppa, aspA, aroE, atpE, tkt, cdtB) were amplified and DNA sequencing was conducted to determine the allele number. Alignment was carried out with the ATGC version 6 software program (Genetyx Corporation, Tokyo Japan). The allele number and sequence type (ST) were defined according to the *H. cinaedi* MLST database (http://pubmlst.org/hicinaedi/). Consequently, the current isolate was typed as ST 18 [allelic profile; 23S rRNA (6), ppa (3), aspA (6), aroE (3), atpA (3), tkt (1), cdtB (3)], with a different sequence pattern than previous isolates identified in Japan (19).

**Discussion**

Previous studies have reported that *H. cinaedi* infection occurs primarily in immunosuppressed patients (8, 10, 13, 20). Contact with potential animal reservoirs is a suggested risk factor (15), and nosocomial infections have been reported in Japan (10, 12, 14). However, the present patient did not have a previous history of animal contact, recent hospitalization or immunosuppressive therapy. While no significant associations between *H. cinaedi* infection and DM have been found in previous studies (10, 20), undiagnosed diabetes mellitus was the only possible risk factor observed in this case. In addition, the MLST pattern differed from that of other isolates in Japan, and we were unable to identify the probable route of infection in this case.

The current patient had been previously diagnosed to have lymphangioma. Lymphangiomas are benign cystic tumors considered to be developmental abnormalities, originating from malformations with inadequate drainage of lymphatic tissue (21, 22). Although the neck and axilla are the most common sites of lymphangioma, this condition sometimes occurs in the retroperitoneal space (21). The risk of bacterial infection has not been analyzed due to the low incidence of the disease, although there are various reported cases of abdominal or retroperitoneal lymphangioma infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica* serovar Enteritidis and...
**Figure 1.** Magnetic resonance images (MRI) obtained two years before admission (a) and on day 7 of the current hospitalization (b). (a) shows the variable size of the pararenal cysts around the left kidney. The cysts display low intensity on a T1-weighted fat suppression image (a-1: white asterisks) and high intensity on a T2-weighted image (a-2, black asterisks). The intensity changed to high on a T1-weighted fat suppression image (b-1, white arrows) and heterogeneous on a T2-weighted image (b-2, black arrows).

**Figure 2.** Magnetic resonance images obtained on day 42. (a) A T1-weighted fat suppression image, (b) a T2-weighted image.

*Mycobacterium tuberculosis* based on a previous literature review (23). To the best of our knowledge, pararenal lymphatic cyst infection associated with *H. cinaedi* has not been previously described, and there is only one case of renal cyst infection noted in a recent report (24). Therefore, the current case suggests that pararenal lymphatic cysts may be possible infectious sites of *H. cinaedi*.

We successfully treated the current patient with long-term ceftriaxone therapy. Nevertheless, the appropriate antimicrobial agents and duration of *H. cinaedi* infection have not been determined. We initially considered the use of fluoroquinolones due to the favorable drug concentration achieved in renal cysts (25); however, the current strain showed good sensitivity for beta-lactams and minocycline and resistance to levofloxacin. A recent review (26) demonstrated that *H. cinaedi* exhibits low minimum inhibitory concentration (MIC) values for tetracycline, aminoglycosides and carbapenems, moderate MIC values for penicillins and resistance...
to macrolides and fluoroquinolones, with resistance genes having been detected in all isolates evaluated in a recent study in Japan (19). Hence, fluoroquinolones are not a therapeutic option, while beta-lactams are considered to be the first choice of treatment if antimicrobial susceptibility testing cannot be performed.

_H. cinaedi_ infection is also known to cause recurrent infections. Araoka et al. reported that 24% (15/63) of their patients developed recurrent bacteremia after the initial infection (10), and Kiehlbauch et al. indicated that prolonged therapy (two to six weeks) may be beneficial for _H. cinaedi_ bacteremia (20). Moreover, current guidelines recommend the long-term use of antimicrobial therapy for renal cyst infections (27). Therefore, we consider long-term ceftriaxone therapy to be valid in the current case.

There is one limitation associated with our present findings. Namely, we were unable to aspirate any pus from the paranephral lymphatic cysts. As a result, the presence of _H. cinaedi_ in the cyst was not confirmed, and it is possible that the patient had a mixed infection (28).

In summary, we experienced a case of paranephral lymphatic cyst infection associated with _H. cinaedi_ bacteremia in a patient with lymphangioma, the isolate of which exhibited a novel MLST sequence type, ST18.

**Author’s disclosure of potential Conflicts of Interest (COI).**
Kiyoko Tamai: Employment, Miroku Medical Laboratory. Yuji Yaguchi: Employment, Miroku Medical Laboratory.

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**References**