**Helicobacter cinaedi-associated Vertebral Osteomyelitis in an Immunocompetent Patient**

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**Abstract**

A 56-year-old previously healthy man was hospitalized due to a 10-day history of neck pain and an elevated C-reactive protein level. Gram-negative spiral bacilli were isolated from his blood, and *Helicobacter cinaedi* was confirmed using 16S rRNA sequencing. The infectious focus was not identified by initial cervical magnetic resonance imaging (MRI); however, repeated MRI demonstrated prominent high signal intensity in the entire region of the C6-C7 vertebrae and C6/C7 disc space. Furthermore, fluorodeoxyglucose-positron emission tomography/computed tomography showed no significant uptake, other than in the C6-C7 region. The patient was successfully treated with ceftriaxone for six weeks without sequelae.

**Key words:** *Helicobacter cinaedi*, vertebral osteomyelitis, spondylodiscitis, immunocompetent

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**Introduction**

Vertebral osteomyelitis is an infection of the vertebrae and adjacent intervertebral discs which requires long-term treatment (1). Back pain is present in most patients with vertebral osteomyelitis, whereas a fever is frequently absent, and the diagnosis of vertebral osteomyelitis may be delayed or missed in clinical practice (2, 3).

*Staphylococcus aureus* is the most common causative bacteria of non-tuberculosis vertebral osteomyelitis, accounting for half of all cases caused by coagulase-negative *Staphylococci* and *Streptococci* (1, 2). *Enterobacteriaceae* are also important microorganisms in cases of vertebral osteomyelitis; however, other Gram-negative bacilli are rarely identified as causative pathogens of this disease (4).

*Helicobacter cinaedi*, previously described as a *Campylobacter*-like organism type-I (CLO-1), is a microaerophilic Gram-negative spiral rod (5) that is colonized in the intestines in humans and other mammals (6-11). *H. cinaedi* infection has been recognized as an infectious pathogen in immunocompromised hosts for the past three decades (12, 13).

We herein report a case of *H. cinaedi*-associated vertebral osteomyelitis in an immunocompetent patient.

**Case Report**

A 56-year-old previously healthy Japanese man presented at our general internal medicine clinic with a 10-day history of severe neck pain. He had no chronic diseases, except for bronchial asthma, and had received no prescriptions for immunosuppressive drugs. He had no history of travel or close contact with animals, including pets, and reported no preceding symptoms, such as a fever, diarrhea or newly developed skin rashes.

On the initial physical examination, the patient’s temperature was 35.8°C, his heart rate was 84 beats/min, his blood pressure was 150/72 mmHg, his respiratory rate was 18 breaths/min and his oxygen saturation was 98%. A chest examination revealed no murmurs, and both heart and respiratory sounds were clear to auscultation bilaterally. No rigidity

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or rebound tenderness of the abdomen was noted. In contrast, the patient exhibited tenderness along the lower cervical vertebrae with numbness over the right shoulder and upper limb, although neither abnormal deep tendon reflexes nor motor weakness was detected. Blood tests revealed mild leukocytosis (10,800/μL with 59% neutrophils) and an elevated serum C-reactive protein level (8.1 mg/dL). The results of the HIV antigen/antibody combination test were negative. Enhanced computed tomography of the neck and trunk did not show any specific findings suggestive of bacterial infection. The patient was therefore admitted for a close examination of the neck pain and received ceftriaxone empirically after two sets of blood cultures were obtained. MRI performed on day 5 showed vertebral osteophyte formation in addition to a protruded intervertebral disc, canal stenosis and increased signal intensity, suggesting marrow edema, predominantly below the C6/C7 vertebral endplates (Fig. 1A). However, these findings were inconclusive for vertebral osteomyelitis.

Five days after blood culture incubation using the BD BACTEC FX System (Becton, Dickinson and Company, Tokyo, Japan), a positive signal was obtained from one aerobic bottle, with no signals from the anaerobic bottles. Direct Gram staining showed Gram-negative spiral bacilli, and an aerobic bottle of the blood samples was subcultured on 5% horse blood agar (Becton, Dickinson and Company), under moist, microaerobic conditions. After two days of incubation, we observed transparent, file-like colonies with a positive reaction for nitrate reductase. Therefore, a possible diagnosis of H. cinaedi was reported to the clinicians.

We repeated the MRI examination on day 19 in order to obtain a more precise diagnosis, as H. cinaedi bacteremia had been confirmed and the patient’s neck pain persisted. The MR images demonstrated a prominent high signal intensity in the entire region of the C6-C7 vertebrae and C6/C7 disc space compared with that observed on the initial MRI scans (Fig. 1B), indicating the existence of severe inflammatory changes. In an attempt to identify other sites of infection, we performed fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), which showed no significant uptake, other than in the C6-C7 7 region (Fig. 2). In addition, transthoracic echocardiography did not disclose any sites of vegetation. We ultimately made a diagnosis of pyogenic vertebral osteomyelitis, with H. cinaedi considered to be the causative pathogen. The patient was subsequently treated with ceftriaxone for six weeks and discharged on day 43. His neck pain had resolved at discharge and he experienced no recurrence of symptoms during the follow-up period.

Genotypic identification of H. cinaedi was performed using a DNA sequence analysis of the 16S rRNA gene (776 bp) with the ABI PRISM BigDye Terminator Cycle Sequencing Kit v3.1 (Applied Biosystems, Foster City, USA). The consensus sequence had the highest similarity (774/776 bp, 99% match) to the 16S rRNA gene of H. cinaedi strain ATCC BAA-847 (GenBank accession number AP012492). The minimum inhibitory concentrations (MICs) against the isolated H. cinaedi strain were measured using the Epsilon susceptibility test (Etest, SYMEX bioMérieux, Tokyo, Japan) according to the manufacturer’s instructions, with the following results: 2 μg/mL for ampicillin, 2 μg/mL for ceftriaxone, 0.032 μg/mL for minocycline, ≥512 μg/mL for clarithromycin and ≥24 μg/mL for levofloxacin.

Multilocus sequence typing (MLST) was performed with seven housekeeping genes (23S rRNA, ppa, aspA, aroE, atpA, tkt, cdtB) as previously described (14). Consequently, the current isolate was found to belong to sequence type (ST) 10 [allelic profile: 23S rRNA (4), ppa (2), aspA (2), aroE (2), atpA (2), tkt (1), cdtB (2)].
Discussion

To the best of our knowledge, there has been no previous case report indicating an association between *H. cinaedi* and vertebral osteomyelitis in the English literature. *H. cinaedi* is considered to be more invasive than other *Helicobacter* species (5) and can cause cellulitis (15, 16), enteritis (17), graft infection (18), renal cystic infection (19), meningitis (20) and arthritis (21). In this case report, none of these manifestations were observed and an extravertebral infection was not detected on FDG-PET/CT imaging. Therefore, the vertebral and the intervertebral disc were considered to be the primary sites of infection in this case.

Much of the pathophysiology of *H. cinaedi* infection remains unclear due to the rarity of the disease. In early reports of *H. cinaedi* infection, the pathogen was recognized to be the cause of an opportunistic infection, primarily among HIV-positive or immunosuppressive patients (13, 22), and a relationship with animal contact has also been reported (23). Recently, several immunocompetent cases with *H. cinaedi* infection have been identified (15, 20), and nosocomial infections have been repeatedly reported in Japan (14, 17, 24); ST10 and ST11 were recently detected in the blood of several patients in the same ward during a short period (14). In the current case, the ST pattern (ST10) was the same as that of the previous outbreak strains in Japan, although the patient did not have a history of recent hospitalization. In addition, he had no evidence of an immunocompromised condition, treatment with immunosuppressive therapy or animal contact. Arakawa et al. reported that more than half of all cases with *H. cinaedi* bacteremia have *H. cinaedi* colonization in their stools (17). We did not perform a stool culture with the modified Skirrow’s medium because several days had passed after the initiation of antimicrobial treatment when the diagnosis of *H. cinaedi* bacteremia was made. It is therefore possible that the preceding colonization in the gastrointestinal tract might exist and be associated with the current infection, however, we could not identify the route of infection in this case.

Identifying *H. cinaedi* is important due to its characteristic antimicrobial susceptibility pattern. *H. cinaedi* is known to be resistant to quinolones as a result of a mutation in DNA gyrase (14) and exhibits a higher MIC for cephalosporins than other bacteria, the mechanisms of which have not been clarified (5). Hence, the administration of an adequate dose of intravenous beta-lactams, in addition to obtaining the susceptibility profiles, is required in order to properly treat *H. cinaedi* infection.

Matsumoto et al. reported that, in their study, *H. cinaedi* was isolated from 0.1% of all blood culture bottles (25). In addition, *H. cinaedi* infection has been reported to be frequently missed using routine microbiological identification methods and displays a high rate of recurrence (17). Moreover, *H. cinaedi* infection may occur in patients without established risk factors, as in our current case; therefore, the possible presence of *H. cinaedi* infection should be kept in mind in daily practice, especially in Japan.

Source identification is crucial for appropriate antimicrobial selection, particularly in cases involving cerebrospinal fluid or bone infection, due to the low penetration rate of antimicrobial agents (26, 27). Currently, cellulitis and enteritis are considered to be the main sites of *H. cinaedi* infection, while the infectious source is not identified in more than half of all *H. cinaedi* bacteremia cases, which are classified as primary bacteremia (17).

Vertebral osteomyelitis is a difficult infectious disease to diagnose, and its identification is frequently delayed, even in recent practice (1, 2). In addition, the incidence of this pathogen remains underestimated, as indicated in a case series of pneumococcal vertebral osteomyelitis (28). MRI has a high sensitivity and specificity for the detection of such cases (29, 30); however, the findings may be non-specific in the early phase of the disease (31) and the existence of the microbe is often clarified on repeated MRI (32). These observations are consistent with that observed in the present case and may be applicable in future cases of *H. cinaedi* bacteremia with symptoms suggestive of vertebral osteomyelitis.

There are some limitations associated with this study. The main limitation is that we did not perform any invasive procedures for the diagnosis or treatment. Therefore, while it was highly possible that *H. cinaedi* may have been the causative pathogen of the vertebral osteomyelitis according to both the blood culture and advanced imaging findings, the presence of *H. cinaedi* in the vertebral site could not be definitively proven in this report.

In conclusion, we experienced a case of vertebral osteomyelitis complicated by *H. cinaedi* bacteremia. The potential for vertebral osteomyelitis should be considered in patients with *H. cinaedi* bacteremia, especially those presenting with neck or back pain.

Author’s disclosure of potential Conflicts of Interest (COI).

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