INTERNAL MEDICINE

□ CASE REPORT □

Helicobacter cinaedi Bacteremia Mimicking a Flare of Systemic Lupus Erythematosus

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Abstract

A 40-year-old woman with systemic lupus erythematosus (SLE) presented with high-grade fever and severe thrombocytopenia. Acalculous cholecystitis and thrombocytopenia were initially suspected to be complicated with SLE and vasculitis. Contrary to our expectation, however, the patient was finally diagnosed with *Helicobacter cinaedi* bacteremia. SLE patients show various symptoms, especially when their condition is complicated with vasculitis, which mimics *H. cinaedi* bacteremia. It is therefore difficult to provide a definite diagnosis. Physicians should be mindful of the presence of *H. cinaedi* infection.

Key words: *Helicobacter cinaedi*, bacteremia, systemic lupus erythematosus, acalculous cholecystitis, thrombocytopenia

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Introduction

Helicobacter cinaedi has come to be recognized as an important organism, especially among immunocompromised patients. *H. cinaedi* grows slowly and is difficult to isolate in culture. *H. cinaedi* sometimes causes cellulitis but the main symptom is only fever without any focal findings in most cases. Furthermore, unlike most other infectious diseases, the clinical course is not acute. For these reasons, it is difficult to accurately diagnose.

When an SLE patient becomes febrile, we should determine whether there has been an exacerbation of SLE itself or whether the condition is a complication of an infectious disease. This is vital because opposite strategies are used in the treatment of SLE and infectious diseases. In the present case, *H. cinaedi* bacteremia occurred in a patient with SLE, who initially only showed fever. This was followed by atypical symptoms, including severe thrombocytopenia and acalculous cholecystitis. These symptoms mimicked a flare of the disease, which led us initiate the bolus administration of methylprednisolone.

Case Report

A 40-year-old woman was diagnosed with SLE at 20 years of age. Her symptoms included a typical rash, severe multiple organ failure, consciousness disturbance and retinal vasculitis. A laboratory analysis revealed reduced C3, C4 and CH50 levels (20 mg/dL, 7 mg/dL and 10 U/mL, respectively) and anti-nuclear antibody positivity (640×, homogenous, speckled), and anti-DNA antibody negativity. She was in a severe condition and was refractory to the initial treatment of prednisolone (1 mg/kg/day). Plasmapheresis, high-dose methylprednisolone (1 g bolus for 3 days) and an increased dose of prednisolone (1.3 mg/kg/day) were necessary to achieve remission from SLE. After the initial therapy, her condition remained stable with the administration of prednisolone (10 mg/day) for more than 10 years. A regular blood examination showed a gradual increase in the patient's C-reactive protein (CRP) level from 3 months before her admission, which had previously been normal. At first, an exacerbation of SLE was suspected and the amount of prednisolone was increased to 15 mg/day. One month before the admission, she suffered from a high grade fever (39℃) at

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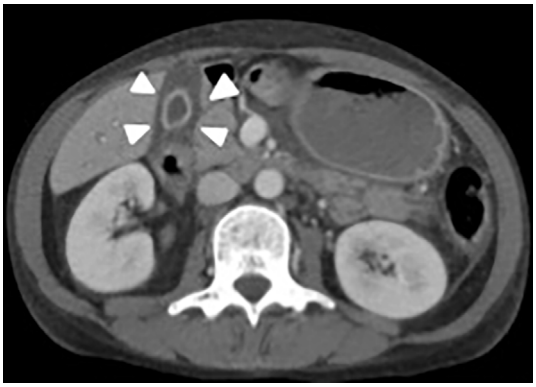


Figure 1. Abdominal CT on admission showing the thickness of the gallbladder wall (white arrowheads). There were no gallstones.

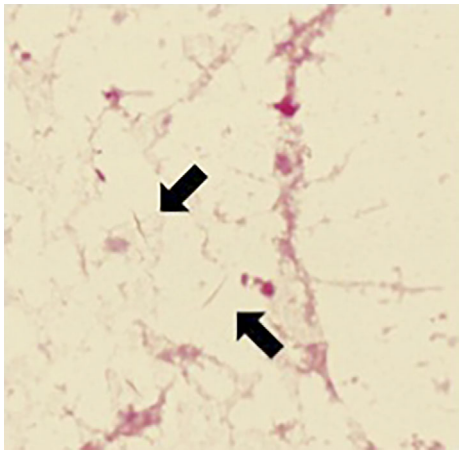


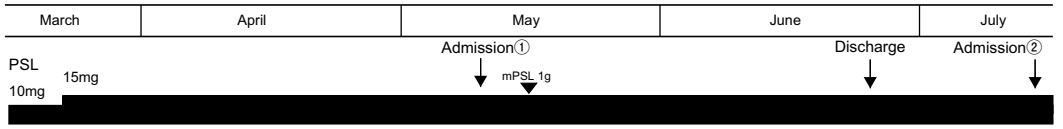
Figure 2. The Gram-negative spiral bacterium in the blood culture (black arrows).

night with shivering, chills and mild nausea. She was admitted to our hospital to undergo further examination. Her consciousness was clear, without diarrhea, cellulitis or arthritis. On admission, a complete blood cell count revealed anemia (Hb, 7.3 g/dL) with an increase in the number of fragmented red blood cells, leukocytosis (WBC, 18,880/μL) with neutrophilia (93.5%), and severe thrombocytopenia (platelet count, 37,000/μL). The patient's CRP level was elevated (14.95 mg/dL). Tests for anti-nuclear antibodies and anti-DNA antibodies were negative and the patient's complement values were normal (C3, 87 mg/dL, C4, 24 mg/dL, and CH50, 51 U/mL). An interferon-γ release assay TB was negative and no vegetation was observed by transthoracic echocardiography. Computed tomography showed significant thickening of the patient's gallbladder wall (Fig. 1) and the values of alkaline phosphatase and γ-glutamyltranspeptidase were also elevated; however, she had no abdominal pain. After admission, her high fever lasted and her anemia and thrombocytopenia advanced rapidly. The patient's blood cultures being negative, and the focus of infection had not been detected on the fourth day of admission. We were therefore forced to start methylprednisolone (1,000 mg/day) due to suspected acalculous cholecystitis which was thought to have occurred due to a flare of SLE or a complication of vasculitis. The next day, the patient's blood cultures were found to be positive (after 5 days of incubation) and microscopy showed gram-negative spiral bacteria (Fig. 2). The isolate was finally identified as *H. cinaedi* by a PCR and 16S rRNA gene sequencing. We considered that the patient's thrombocytopenia had been caused by *H. cinaedi* bacteremia, and stopped the bolus administration of methylprednisolone; prednisolone was reduced to the maintenance dose. With the administration of meropenem, the patient's temperature decreased and there was an improvement in her laboratory data with regard to her platelet count, CRP level, and the number of fragmented red blood cells. The clinical course is shown in Fig. 3. The antibiotic was changed and de-escalated to ampicillin, which caused a systemic drug eruption. Doripenem was administered for 3 weeks; thus, the total duration of treatment reached 5 weeks, at which point, the antibiotics were stopped due to pancytopenia. One month after the treatment, the *H. cinaedi* bacteremia relapsed with a high-grade fever and cellulitis (Fig. 4). Meropenem was administered intravenously for another 2 weeks, and 6 weeks of oral minocycline were given, no relapse occurred after this treatment.

Discussion

H. cinaedi is a gram-negative spiral bacterium that belongs to the Helicobacteriaceae family. It is hypothesized that *H. cinaedi* infection occurs via the oral route. In some reports, the possibility of zoonotic transmission from animal feces to humans has been discussed. However, the patient had no pets and no contact with animals. The infection route was unclear in this case. It grew slowly and required a more time to be isolated in blood cultures. The median time for *H. cinaedi* to become positive in blood cultures is 5 days (2-12 days), and the positive ratios from 5 to 7 days were only 55% and 87%, respectively (1). In order to successfully detect *H. cinaedi* bacteremia, at least 7 days of incubation should be necessary, although only 1-3 days are sufficient for most other organisms.

The other characteristics of *H. cinaedi* bacteremia are nonspecific symptoms and a tendency of relapse. It has been hypothesized that *H. cinaedi* infection is associated with cellulitis, arthritis and gastroenteritis (2-4); however, fever is the only symptom in many cases. Actually, in ten cases of *H. cinaedi* bacteremia that were observed in our hospital in the eight years from 2007 to 2014, the only symptom was fever in five cases. The four cases of ten showed skin lesions; however, these were very mild in all of the cases. It might be a result of the lower virulence of *H. cinaedi*. The appropriate antimicrobial agents and the duration of the treatment for *H. cinaedi* infection have not been established. Carbapenems, tetracycline, aminoglycosides and penicillins are generally effective (4). Although we treated the patient for a sufficient length of time (5 weeks), she nevertheless relapsed.



WBC	5,180	5,410	18.360	18,880	8,440	1,250	9,660
Hb	9.2	7.9	8.1	7.3	7.0	10.9	12.4
PLT	27.2	23.9	10.2	3.7	6.4	12.5	5.1
AST	39	22	34	21	40	41	31
ALT	44	23	26	20	38	34	22
ALP	454	488	781	963	1,468	650	403
CRP	6.12	7.39	10.99	14.95	1.52	0.26	3.79
C3/C4	140/26	132/23	143/25			92/19	

Figure 3. **The clinical course of the present case. PSL: prednisolone, mPSL: methylprednisolone, MEPM: meropenem, ABPC: ampicillin, IPM/CS: imipenem/cilastatin, AZM: azithromycin, DRPM: doripenem, WBC: white blood cell (/μL), Hb: hemoglobin (g/dL), PLT: platelet (×10^3/μL), AST: aspartate aminotransferase (U/L), ALT: alanine aminotransferase (U/L), ALP: alkaline phosphatase (U/L), CRP: C-reactive protein (mg/dL), closed triangle: positive blood culture, open triangle: negative blood culture**

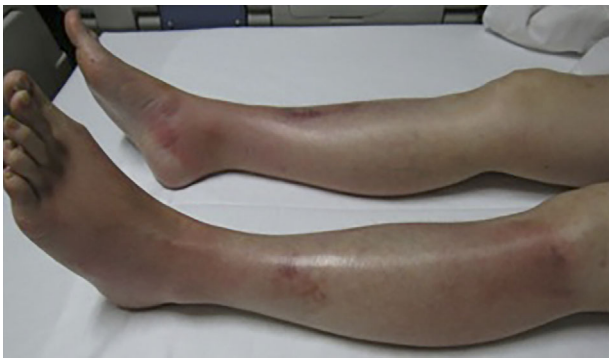


Figure 4. **Cellulitis complicated with secondary bacteremia was seen on both extremities and the patient's back.**

H. cinaedi bacteremia cases are usually reported in immunocompromised patients such as those with HIV infection, hematological disorders, malignancies, alcoholism and receiving immunosuppressive therapy (5, 6). Some other infectious diseases have been reported to mimic SLE or a flare of SLE, human parvovirus B19, cytomegalovirus, visceral leishmaniasis, which is only in endemic area, and so on (7, 8). Some bacterial infections may mimic a flare of SLE, and *H. cinaedi* might be one of them. However, as far as we are aware, reported cases on *H. cinaedi* bacteremia with SLE are very rare (9).

We finally diagnosed gallbladder thickening and thrombocytopenia, which were associated with *H. cinaedi* infection itself, not with a flare of SLE. Although the association with hepatobiliary diseases and enterohepatic *Helicobacter* species have been mentioned, most cases were caused by *H. bilis* or *H. hepaticus* (10), and not *H. cinaedi* or *cinaedi,* there have been only a few reports on hepatobiliary diseases in animals (11) and only one report on hepatobiliary diseases in humans. Our case might represent a possible presentation of the hepatobiliary infections caused by *H. cinaedi* in humans.

In conclusion, we should be mindful of the presence of *H. cinaedi* bacteremia, especially when we see febrile immunocompromised patients such as patients with SLE. *H. cinaedi* takes longer to diagnose, the most popular symptom is only fever and it is sometimes associated with various symptoms. Once an *H. cinaedi* infection is diagnosed, it is necessary to treat the patient with antibiotics for more than one month due to the tendency to relapse.

The authors state that they have no Conflict of Interest (COI).

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