Case report

Refractory to treat Helicobacter cinaedi bacteremia with bilateral lower extremities cellulitis in an immunocompetent patient

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Introduction

Helicobacter cinaedi is a Gram-negative spiral rod and was first isolated from rectum in homosexual men with proctocolitis in 1984 [1]. H. cinaedi inhabits the gastrointestinal tract of mammals. H. cinaedi has been increasingly reported to cause many types of infections, and has been isolated from both immunocompetent and immunocompromised patients. Proctocolitis is first reported [1], however, more invasive diseases such as bacteremia, cellulitis, arthritis, osteomyelitis, and meningitis have been recently reported. Cellulitis among immunocompromised patients is often multi-focal [2], however, among immunocompetent patients, multi-focal cellulitis is rare. In the literature, approximately 30–60% of patients have recurrent symptoms [3]. Longer antimicrobial treatment may be required.

We report here an immunocompetent patient with H. cinaedi bacteremia complicated with bilateral lower extremities skin and soft tissue infections which was refractory to treat and required a prolonged antimicrobial treatment.

Case report

A 54-year-old Japanese man with past medical history of hypertension presented with one month history of fever, bilateral lower extremities pain and erythema. The patient had been well until approximately one month prior to admission, when he noted fever, pain and redness in the bilateral lower extremities. He had no history of injuries. Five days prior to admission, he was seen by his primary care physician, and given a diagnosis of cellulitis in the bilateral lower extremities. He was treated with oral levofloxacin 500 mg daily was prescribed. Four days later, blood cultures turned positive for Gram-negative spiral rod. Then he was admitted to our hospital for further investigation.

On admission, he had mild pain in the bilateral lower extremities. He denied sore throat, running nose, fatigue, chills, night sweats, weight changes, abdominal pain, nausea, vomiting, diarrhea, dysuria, and frequency. He did not use illicit drugs. He denied homosexual contact, any trauma, insect bites, or contact with animals. The temperature was 36.5 °C, the blood pressure was 157/79 mm Hg, and the heart rate was 51 beats/min, respirations 16/min. He had symmetrical tenderness and erythema in the bilateral lower extremities (Fig. 1). The remainder of the physical examinations was normal. The laboratory data showed the white
blood cell count was 8200/μl, neutrophils 73%, erythrocyte sedimentation 46 mm/h, otherwise unremarkable. Immunological studies including immunoglobulin, complements were normal. Human Immunodeficiency Virus (HIV) and Human T-cell Lymphoma Virus type-1 serology were both negative. CT of the lower extremities without contrast was normal. Intravenous antimicrobial treatment with meropenem (1 g every 8 h) was started empirically for Gram-negative spiral rod. The patient’s erythema

Table 1
Previously reported Helicobacter cinaedi infections, antimicrobial agents, and duration of the therapy.

| Case number | Author       | Year | Age (year) | Sex   | Medical history                                                                 | Site of infection                                      | Antimicrobial agents                                                                 | Duration of treatment |
|------------|--------------|------|------------|-------|---------------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------|
| 1          | Murata S     | 2015 | 56         | Male  | Bronchial asthma                                                                | Vertebral osteomyelitis and bacteremia                  | Ceftriaxone                                                                          | 6 weeks              |
| 2          | Haruki Y     | 2015 | 64         | Male  | None                                                                            | Bacteremia, spondylitis, diskitis                      | Cefazolin + fosfomycin                                                                | 8 weeks              |
| 3          | Mishima K    | 2015 | 48         | Male  | Hepatitis C virus infection induced liver cirrhosis, diabetes mellitus, hypertension | Bacteremia, cellulitis                                  | Cefazolin, relapse, cefazolin, ciprofloxacin, minocycline                           | 7 days, relapse, 4 months |
| 4          | Ishibashi R  | 2015 | 76         | Female| Slowly progressive type 1 diabetes, rheumatoid arthritis                        | Bacteremia                                             | Ceftepime, cefotiam, minocycline                                                    | 18 days              |
| 5          | Ishibashi R  | 2015 | 47         | Female| Type 2 diabetes                                                                  | Bacteremia, cellulitis                                  | Cefazolin, cefdinir                                                                   | Not reported 4 months |
| 6          | Unosawa S    | 2015 | 79         | Male  | Hypertension                                                                     | Infected abdominal aortic aneurysm                     | Ciprofloxacin + levofloxacin, doripenem + vancomycin, amoxicillin + sulbactam + minocycline | More than 6 weeks (not reported) |
| 7          | Kakuta R     | 2014 | 64         | Male  | Hypertension, hyperlipidemia                                                     | Infected abdominal aortic aneurysm                     | Piperacillin/tazobactam, faropenem, piperacillin/tazobactam, amoxicillin, minocycline | More than 5 weeks (not reported) |
| 8          | Kakuta R     | 2014 | 59         | Male  | None                                                                            | Infected abdominal aortic aneurysm                     | Ceftriaxone                                                                          | Not reported 6 weeks |
| 9          | Bartels H    | 2014 | 71         | Male  | Polymyalgia rheumatica, aortic stenosis                                         | Endocarditis                                           | Amoxicillin + clavulanate + gentamicin, ceftriaxone                                 | More than 4 weeks (not reported) |
| 10         | Sugiyama A   | 2014 | 34         | Female| Marfan syndrome, Ehlers-Danlos syndrome, rheumatoid arthritis, necrotizing fasciitis | Meningitis                                             | Ceftriaxone                                                                           | 3 weeks              |
| 11         | Kikuchi H    | 2012 | 31         | Female| Systemic lupus erythematosus, rheumatoid arthritis, necrotizing fasciitis       | Bacteremia, cellulitis                                  | Ceftriaxone                                                                           | 18 days, relapse, 6 weeks |
| 12         | Kim SK       | 2012 | 71         | Male  | Status post splenectomy, immune hemolytic anemia, aplastic anemia, None          | Bacteremia                                             | Piperacillin/tazobactam + levofloxacin                                               | 20 days              |
| 13         | Holst H      | 2008 | 61         | Male  | Myocardial infarction                                                            | Infected abdominal aortic aneurysm                     | Dicloxacillin, penicillin, relapse, rifampicin, amoxicillin + sulbactam, imipenem, minocycline | 2 weeks, relapse, 2 weeks |
| 14         | Kitamura T   | 2007 | 22-79      | 2 male and 9 female                  | After the orthopedic surgery                          | Bacteremia, cellulitis                                  | Ciprofloxacin                                                                         | Not reported |
| 15–25      | Uğur I       | 2006 | 53         | Female| Malignant lymphoma                                                               | Bacteremia                                             | Piperacillin + rifampicin, Oxacillin/dicloxacillin, oxacillin + gentamicin, ciprofloxacin | 9 weeks, relapse, 3.5 months |
| 27         | Lasty S      | 2000 | 20         | Male  | None Human immunodeficiency virus infection                                      | Bacteremia, synovitis                                  | Ciprofloxacin                                                                         | 12 weeks             |
| 28         | Burman WJ    | 1995 | 26         | Male  | Acquired immune deficiency syndrome                                              | Bacteremia                                             | Ciprofloxacin                                                                         | 31 days              |
| 29         | Burman WJ    | 1995 | 39         | Male  | Alcoholism                                                                       | Bacteremia                                             | Cefotetan, clindamycin + gentamicin, amoxicillin + clavulanate, doxycycline           | 21 days              |
| 30         | Burman WJ    | 1995 | 56         | Female| Human immunodeficiency virus infection                                           | Bacteremia                                             | Erythromycin, ciprofloxacin, doxycycline                                              | 53 days              |
| 31         | Burman WJ    | 1995 | 27         | Female| Acquired immune deficiency syndrome                                              | Bacteremia                                             | Cephalexin, ciprofloxacin, doxycycline                                               | 34 days              |
| 32         | Burman WJ    | 1995 | 36         | Male  | Acquired immune deficiency syndrome                                              | Bacteremia                                             | Ciprofloxacin                                                                         | 10 days              |
| 33         | Burman WJ    | 1995 | 34         | Male  | Acquired immune deficiency syndrome                                              | Bacteremia                                             | Ceftriaxone, ciprofloxacin, doxycycline                                              | 42 days              |
| 34         | Burman WJ    | 1995 | 28         | Male  | Acquired immune deficiency syndrome                                              | Bacteremia                                             | Ceftriaxone, ciprofloxacin, doxycycline                                              | 42 days              |
improved on the second day of admission. On the sixth day of admission, the organism was identified as *H. cinaedi* by polymerase chain reaction. The susceptibility testing showed as follows: Ampicillin, imipenem, and gentamicin were susceptible. Clarithromycin and levofloxacin were resistant. Stool culture obtained while he was on meropenem on the 10th day of admission was negative. Abdominal ultrasound and esophagogastrroduodenoscopy showed no significant abnormalities. Colonoscopy showed mild proctitis, however, biopsy specimen showed non-specific inflammation. Transthoracic echocardiogram showed no vegetation. Intravenous meropenem 1 g every 8 h was administered for 14 days. The erythema and pain improved and he was discharged home. Nineteen days after discharge, the patient came back with right lower extremity erythema and pain. He was re-admitted and meropenem 1 g every 8 h was restarted. Blood cultures and stool cultures on admission were both negative. His symptoms improved immediately after the initiation of treatment. Intravenous meropenem was administered for four weeks and then switched to oral minocycline 100 mg twice daily. However, two weeks later, he was re-admitted due to the recurrent right lower extremity pain. Repeated blood cultures this admission were negative. Three week courses of intravenous meropenem was administered followed by oral minocycline 100 mg twice daily for 3 weeks. After the two episodes of recurrence and subsequent prolonged treatment, his symptoms subsided.

**Discussion**

We reported a patient with bacteremia with multi-focal skin and soft tissue infections caused by *H. cinaedi* in an immunocompetent patient which was refractory to treat with multiple recurrent episodes. An increasing number of cases of *H. cinaedi* infection among immunocompromised patients has been reported during the last few decades, and it often causes bacteremia and cellulitis [4]. Recently, *H. cinaedi* infections among immunocompetent patients are increasingly reported especially from Japan [5]. Cellulitis is often multi-focal among immunocompromised patients [2], however, among immunocompetent patients, multi-focal cellulitis is rare. *H. cinaedi* resides in the gastrointestinal tract of mammals, and has an ability to invade vascular systems [3], then causes bacteremia and multi-focal cellulitis. Among patients with community-acquired *H. cinaedi* bacteremia, more than 83.3% of the patients had apparent cellulitis, while patients with healthcare associated *H. cinaedi* bacteremia, only 43.8% of the patients had cellulitis (p = 0.078) [6]. On the basis of the previously reported case series [1–6], clinical manifestations and severities are determined by the balance between the host’s immune status and virulence of the organism. The differences of the incidence of cellulitis above could be explained by that the local infiltration of lymphocytes and neutrophils might be inhibited in the immunocompromised patients. That is, if patients with decreased immune systems may have less symptoms including none or solitary cellulitis lesions. To the contrary, patients with decreased immune systems tend to develop severe cellulitis, while the competent immune systems can prevent cellulitis to be multi-focal. The precise pathophysiology of *H. cinaedi* bacteremic infection is not very well understood.

There are currently no standardized treatment in the literature in selection and the duration of antimicrobial treatment for *H. cinaedi* infection (Table 1). Approximately 30–60% of patients have recurrent symptoms [3]. Carbapenems, aminoglycosides, and tetracyclines showed low minimum inhibitory concentration (MIC) values. Penicillins and cephalosporins showed moderate MIC values. Macrolides, and quinolones showed high MIC values [3]. The U.S. Centers for Disease Control and Prevention recommends the two to six weeks of antimicrobial treatment, however, recurrence can be seen with these treatment. In addition, patients who were treated with fluoroquinolones may have more recurrent episodes than those who were treated with other antimicrobial agents [5]. This could be explained by the higher MICs of fluoroquinolones. In our case, recurrent symptoms were observed in spite of the use of meropenem for several weeks; therefore, we re-treated him for intravenous meropenem and oral minocycline for a total of 12 weeks. Further study is needed to determine the appropriate antimicrobial agent, the duration of the antimicrobial treatment, and the pathogenesis of this infection and its recurrence needs to be investigated.

In conclusion, clinicians should be aware of this microorganism when treating patients with bilateral or multi-focal skin and soft tissue infections even if he or she is immunocompetent.

**Conflict of interest**

All authors do not have any conflicts of interests.

**Ethical approval**

In this study, ethical approval was not required.

**References**

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