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Case report

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

Yuichi Shimizu [a], Harumi Gomi [b,*], Haruhiko Ishioka [b], Momoko Isono [a]

[a] Department of General Internal Medicine, Mito Kyodo General Hospital, University of Tsukuba, Japan
[b] Center for Global Health, Mito Kyodo General Hospital, University of Tsukuba, 3-2-7 Miyamachi, Mito, Ibaraki 310-0015, Japan

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ABSTRACT

Helicobacter cinaedi is known to cause bacteremia with multi-focal cellulitis, usually, among immunocompromised patients. We report here a 54-year-old Japanese man who was found to have bacteremia complicated with bilateral lower extremities cellulitis due to *H. cinaedi*. This patient did not have any immunocompromised conditions including Human Immunodeficiency Virus infection. In this patient, the cellulitis was multi-focal which is rare among immunocompetent patients. In addition, interestingly, the cellulitis was symmetrically on the both sides on the lower dorsal part of the extremities. The patient was treated with meropenem, which was considered as one of the best available agents, however, he required a prolonged antimicrobial treatment. During the admission, he underwent colonoscopy which was unremarkable, and his stool culture was also negative while on meropenem. Subsequently, he developed recurrent symptoms of the right lower extremity twice and each time he was treated with intravenous meropenem followed by oral minocycline. After the total of 12 weeks of antimicrobial treatment, his symptoms subsided. Clinicians should be aware of this organism when treating multi-focal, or symmetrical cellulitis even if the patients are immunocompetent.

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. Two sets of blood culture were obtained and 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 dorsal part of the extremities (Fig. 1). The remainder of the physical examinations was normal. The laboratory data showed the white

* Corresponding author. Tel.: +81 29 231 2371; fax: +81 29 221 5137.
E-mail address: hgomi-oky@umin.org (H. Gomi).

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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	Cefepime, cefotiam, minocycline	18 days
5	Ishibashi R	2015	47	Female	Type 2 diabetes	Bacteremia, cellulitis	Cefazolin, cefdinir	Not reported
6	Unosawa S	2015	79	Male	Hypertension	Infected abdominal aortic aneurysm	Ampicillin/sulbactam, gentamicin + ceftriaxone, sultamicillin	4 months
7	Kakuta R	2014	64	Male	Hypertension, hyperlipidemia	Infected abdominal aortic aneurysm	Ceftriaxone + levofloxacin, doripenem+ vancomycin, ampicillin/sulbactam +minocycline, amoxicillin + minocycline	More than 6 weeks (not reported)
8	Kakuta R	2014	59	Male	None	Infected abdominal aortic aneurysm	Piperacillin/tazobactam, faropenem, piperacillin/ tazobactam, amoxicillin, minocycline	More than 5 weeks (not reported)
9	Kakuta R	2014	62	Male	Myocardial infarction	Infected abdominal aortic aneurysm	Doripenem, amoxicillin, minocycline	More than 4 weeks (not reported)
10	Bartels H	2014	71	Male	Polymyalgia rheumatica, aortic stenosis	Endocarditis	Amoxicillin/ clavulanate + gentamicin, ceftriaxone + gentamicin	6 weeks
11	Sugiyama A	2014	34	Female	Marfan syndrome, schizophrenia	Meningitis	Vancomycin + ceftriaxone, meropenem	3 weeks
12	Kikuchi H	2012	31	Female	Systemic lupus erythematosus, rheumatoid arthritis, necrotizing fasciitis	Bacteremia, cellulitis	Cefazolin + clindamycin, pazufloxacin, aztreonam, relapse, aztreonam, minocycline	18 days, relapse, 6 weeks
13	Kim SK	2012	71	Male	Status post splenectomy, immune hemolytic anemia, aplastic anemia	Bacteremia	Piperacillin/ tazobactam + levofloxacin	20 days
14	Holst H	2008	61	Male	None	Bacteremia, cellulitis	Dicloxacillin, penicillin, relapse, rifampicin	2 weeks, relapse, 2 weeks
15–25	Kitamura T	2007	22–79	2 male and 9 female	After the orthopedic surgery	Bacteremia, cellulitis	Sultamicillin, imipenem, cefotiam	Not reported
26	Uçkay I	2006	53	Female	Malignant lymphoma	Bacteremia	Ceftriaxone + gentamycin, clarithromycin, levofloxacin, relapse, ceftriaxone + doxycycline, amoxicillin, metronidazole, doxycycline	9 weeks, relapse, 3.5 months
27	Lasry S	2000	20	Male	None	Bacteremia, synovitis	Ciprofloxacin + rifampicin	12 weeks
28	Burman WJ	1995	26	Male	Human immunodeficiency virus infection	Bacteremia	Oxacillin/dicloxacillin, oxacillin + gentamicin, ciprofloxacin	31 days
29	Burman WJ	1995	39	Male	Acquired immune deficiency syndrome	Bacteremia	Ciprofloxacin	21 days
30	Burman WJ	1995	56	Female	Alcoholism	Bacteremia	Cefotetan, clindamycin + gentamicin, amoxicillin/clavulanate	18 days
31	Burman WJ	1995	27	Female	Human immunodeficiency virus infection	Bacteremia	Erythromycin, ciprofloxacin, doxycycline	53 days
32	Burman WJ	1995	36	Male	Acquired immune deficiency syndrome	Bacteremia	Cephalexin, ciprofloxacin, doxycycline, ceftriaxone/ cefixime	34 days
33	Burman WJ	1995	34	Male	Acquired immune deficiency syndrome	Bacteremia	Ciprofloxacin	10 days
34	Burman WJ	1995	28	Male	Acquired immune deficiency syndrome	Bacteremia	Ceftriaxone, ciprofloxacin, doxycycline	42 days

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

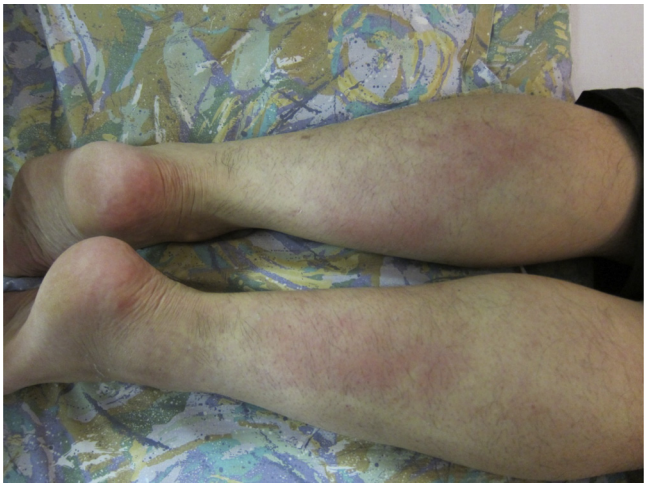

Fig. 1. Symmetrical erythema in the bilateral lower dorsal part of the extremities.

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 esophagogastroduodenoscopy 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.

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