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ORIGINAL ARTICLE

Helicobacter cinaedi-Associated Refractory Cellulitis in Patients with X-Linked Agammaglobulinemia

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Abstract

X-linked agammaglobulinemia (XLA) is characterized by severe or recurrent infections, hypogammaglobulinemia, and circulating B cell deficiency. The frequent pathogens seen in patients with XLA include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and enterovirus as well as *Campylobacter* and *Helicobacter species*. Here, we describe two patients with XLA who developed cellulitis and bacteremia caused by *Helicobacter cinaedi* even when administered an appropriate immunoglobulin replacement therapy. *H. cinaedi* may be difficult to isolate using a conventional blood culture system and could be identified by sequence analysis and mass spectrometry. *H. cinaedi* infection causes recurrent symptoms frequently, and patients require a long course of antibiotic treatment. Recently, the case of non-*H. pylori Helicobacter* (NHPH) infection such as *H. cinaedi* and *H. bilis* infection is increasing in number in patients with XLA. Systemic NHPH infection should be suspected, and extensive microbiological analysis should be performed to appropriately treat patients with XLA who present with fever and skin lesions.

Keywords Bacteremia · cellulitis · *Helicobacter cinaedi* · X-linked agammaglobulinemia

Abbreviations

GNR	Gram-negative rod
HIV	Human immunodeficiency virus
IVIg	Intravenous immunoglobulin
MS	Mass spectrometry
NHPH	Non-*Helicobacter pylori Helicobacter*
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
SCIg	Subcutaneous immunoglobulin
XLA	X-linked agammaglobulinemia

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Introduction

X-linked agammaglobulinemia (XLA) was originally described by Bruton in 1952 [1]. He reported about an 8-year-old boy with recurrent bacterial infections and hypogammaglobulinemia who was successfully treated with subcutaneous immunoglobulin (SCIg). In 1993, the causative gene for XLA was identified by two independent groups [2, 3] and named as *Bruton's tyrosine kinase* (BTK). XLA is clinically characterized by recurrent infections, hypogammaglobulinemia, and decreased number of circulating B cells [4]. The most frequent pathogens that are seen in patients with XLA include encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. These organisms cause sepsis, meningitis, cellulitis, pneumonia,

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arthritis, otitis, and/or sinusitis. Patients with XLA are possibly susceptible to encapsulated organisms because of impaired opsonization and complement activation due to IgG and IgM deficiency. Most viral infections have a normal course in these patients because they show normal T cell immunity. However, infection with a non-enveloped virus including enterovirus can cause chronic meningoencephalitis and sometimes a dermatomyositis-like syndrome. Neutralizing antibodies against enterovirus play a significant role in eradicating the infection. Infections with the non-sporulating Gram-negative rods (GNRs) *Campylobacter* and *Helicobacter* have been described to cause sepsis, gastrointestinal disease, skin lesions, pericarditis, and recurrent fever. These GNRs are colocalized in the intestinal tract, and patients with XLA demonstrate impaired intestinal defense mechanism by IgA deficiency. Gastrointestinal infection caused by the flagellate *Giardia lamblia* is also found in these patients. *Ureaplasma* and *Mycoplasma* infections may cause symptoms in the respiratory and urogenital tracts and joints.

Recent advances in immunoglobulin replacement therapy have decreased the frequency of these infections; however, some remain troublesome in patients with XLA. Here, we describe two patients with XLA who had refractory cellulitis and bacteremia caused by *H. cinaedi* infection although they were on a therapeutic dose of immunoglobulin. In addition, we reviewed the non-*H. pylori Helicobacter* (NHPH) infections in patients with XLA.

Methods

Detection of *H. cinaedi*

Blood culture was performed using an automated blood culture system (BACTEC system; Becton Dickinson, Sparks, MD). *H. cinaedi* was identified by PCR with specific primers for the 16S rRNA of *H. cinaedi* [5]. Alternatively, *H. cinaedi* was confirmed by mass spectrometry (MS) with MALDI Biotyper (Bruker, Billerica, MA) using a matrix-assisted laser desorption/ionization time-of-flight system [6].

Results

Patient Reports

Patient 1 was a 24-year-old male. At the age of 2 years, the patient was hospitalized for pneumonia and found to have hypogammaglobulinemia and a reduced number of B cells. His maternal uncle also had hypogammaglobulinemia, and the patient was suspected to have XLA. At the age of 5 years, he was definitely diagnosed with XLA because of BTK-deficient monocytes and *BTK* mutation (c.IVS 11+3G>T) [7]. Thereafter, intravenous immunoglobulin (IVIg) replacement therapy was initiated. At the age of 20 years, IVIg was switched to SCIg. The IgG trough level was maintained over 1000 mg/dL.

The patient developed acute pericarditis 9 months before admission, which subsided spontaneously. He complained of discomfort in his left leg 4 months before admission. Then, 2 months prior to admission, edema, redness, and hardness were noted on his left leg and the lesion was diagnosed as cellulitis, which was treated with oral antibiotics for 3 weeks. However, the lesion reoccurred after the cessation of the antibiotics, and the patient was treated further for 1 week. The patient suddenly complained of chest pain and tiredness. ST-segment elevation was observed on an electrocardiogram, and he was admitted to the hospital. Intravenous cefazolin administration improved pericarditis and cellulitis in 2 days. After discharge, the blood culture comprising aerobic bottles on admission was found to be positive for GNR 5 days later (Fig. S1). The patient was rehospitalized and received intravenous cefotaxime. Physical examination revealed warm erythema on his left lower leg (Fig. 1a). GNR was identified as *H. cinaedi* by MS analysis. Magnetic resonance imaging showed no evidence of osteomyelitis. *H. cinaedi* was not detected in stool by Gram staining. Cefotaxime administration was changed to intravenous ceftriaxone and oral minocycline treatment. The patient was treated for 20 days, and his symptoms disappeared. After discharge, he was treated with oral minocycline. Cellulitis recurred even with oral antibiotic administration, and the blood culture was again positive for *H. cinaedi*. He was then hospitalized and treated with intravenous ceftriaxone, which was ineffective. Therefore, the patient was treated with intravenous imipenem/cilastatin for 3 weeks and oral minocycline for 12 weeks combined with kanamycin for intestinal decontamination for 15 days. Following the combined use of antibiotics, he recovered from cellulitis and bacteremia. He was free from infection for 11 months.

Patient 2 was a 15-year-old male who was hospitalized for pneumonia and sepsis at the ages of 2 and 3 years, respectively. He was diagnosed with XLA (c.1690C>T, p.Ala520Thr), and IVIg replacement therapy was started. IgG trough level was maintained above 600 mg/dL.

He suffered from recurrent skin infection since the age of 10 years. At the age of 13 years, IVIg was switched to SCIg, and IgG trough level was increased to 1000 mg/dL because of recurrent skin infection. At the age of 15 years, the patient injured his left leg and fractured his right arm in an accident. The accident-cased scar did not heal and formed a nodule 3 months later. Skin biopsy of the nodule revealed no significant pathological findings, except inflammatory cell infiltration. Concurrently, he experienced low-grade fever accompanied by the swelling of his right arm and skin rash on his left leg (Fig. 1b), which lasted for 1 month. Blood culture comprising aerobic bottles was performed and found to be positive for GNR for 5 days, which was defined as *H. cinaedi* by gene analysis and MS analysis. The patient was treated with

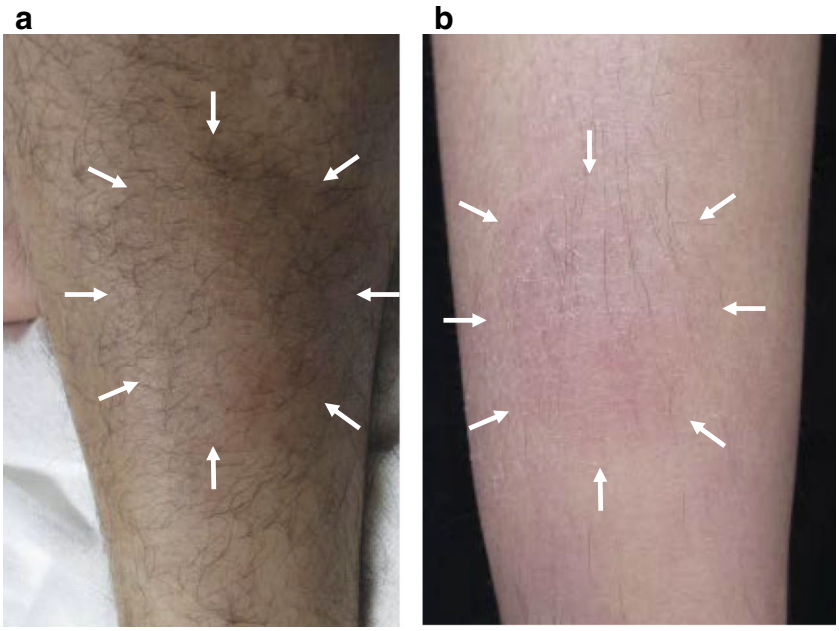

Fig. 1 Skin lesions of cellulitis caused by *Helicobacter cinaedi*. Cellulitis is salmon pink in color (surrounded by arrows). **a** and **b** depict skin lesions in the lower legs of patients 1 and 2, respectively

intravenous ceftriaxone for 4 weeks. Following oral switching to amoxicillin, the skin symptoms worsen and the blood culture was again positive for *H. cinaedi*. He was re-treated with intravenous ceftriaxone and oral minocycline for 2 weeks as well as oral minocycline for an additional 18 weeks. The skin nodule was surgically removed. He was free from infection for 14 months.

NHPH Infection in Patients with XLA

We searched NHPH infection in patients with XLA in PubMed using the terms "Flexipira" or "Helicobacter" and "X-linked agammaglobulinemia." A part of *Helicobacter cinaedi* and some *Helicobacter* spp. was previously known as "*Flexispira rappini*" strains [8]. *H. cinaedi* infection has been reported in 6 patients with XLA [9–14] and *H. bilis* infection in 5 patients [15–18]. Furthermore, infection with other NHPH, except *H. cinaedi* and *H. bilis*, has been reported in 3 patients [19–21]. The age of the patients ranged from 15 to 54 years, with an average age of 28.6 years. Among 14 patients, 7 patients (50%) presented with cellulitis and 4 patients (30%) with pyoderma gangrenosum. Although one patient did not fully respond to the treatment [12], 12 (92%) out of 13 patients showed clinical improvement through long-term antimicrobial treatment (6 weeks to 9 months). Table 1 summarizes NHPH infection in patients with XLA.

Discussion

H. cinaedi, a Gram-negative spiral bacillus, was one of the NHPH species that were first isolated from the rectum sample of a male who had sex with another male in 1984 [22]. Before 2000, *H. cinaedi* was frequently isolated from immunocompromised hosts such as human immunodeficiency virus (HIV)-positive individuals [23–28]. Since then, an increasing number of *H. cinaedi* infections have been reported, particularly in HIV-negative immunocompromised hosts [29, 30]. *H. cinaedi* colonizes in the intestinal tract not only of human but also of hamsters, rats, cats, dogs, foxes, and monkeys. However, no clear evidence of infection between humans and these animals was noted.

H. cinaedi infection causes various symptoms including fever, abdominal pain, gastroenteritis, proctitis, diarrhea, erysipelas, cellulitis, arthritis, meningitis, and bacteremia. Intriguingly, bacteremia caused by *H. cinaedi* has been described more frequently than that caused by other *Helicobacter* species. This may be because the organism could easily translocate from the intestinal tract to the vascular system [30–32]. This idea may be supported by a study that the pulse-field gel electrophoresis patterns of the blood-derived strains of *H. cinaedi* were consistent with those of the stool-derived strains [33].

H. cinaedi is mainly isolated from blood samples, and, to a lesser extent, from stool samples. It is a slow-growing organism, and relatively prolonged incubation time (4–10 days) is required for obtaining positive results for culture bottles. Therefore, once the culture test is finished within 3–4 days, *H. cinaedi* may not be detected. Regarding automated blood culture systems, the VersaTREK system can detect *H. cinaedi* within 3 days with both aerobic and anaerobic bottles, whereas the BacT/ALERT system may take a longer incubation period (usually 4–10 days) with only an aerobic bottle [32, 34]. When patients were suspected to have *Helicobacter*

Table 1 Non-*Helicobacter pylori Helicobacter* infection in XLA patients

No.	Species	Age (years)	Infection type	Antibiotics	Tx length	Tx response	Year	Reporter
1	*H. bilis*	36	Cellulitis	IPM + GM	5 months	Good	2000	Cuccherini et al. [15]
2	*H. bilis*	21	Pyoderma gangrenosum	IPM + GM → MEPM	9 months	Good		
3	*H. cinaedi*	54	Cellulitis	IPM + GM	6 weeks	Good	2004	Simons et al. [9]
4	*H. bilis*	17	Pyoderma gangrenosum	MEPM + TOB	ND	Good	2010	Murray et al. [16]
5	Urease-negative *Helicobacter* spp.	28	Cellulitis	AMPC + GM →IPM + FOS → RFP + DOXY	40 weeks iv → ND po	Good	2010	Schwarze-Zander et al. [19]
6	*H. equorum* like	35	Pleuritis	PAMP/BP + CAM	2 months	Good	2011	Funato et al. [20]
7	*H. fennelliae*	25	Pyoderma gangrenosum	ND	ND	ND	2011	Sharp [21]
8	*H. cinaedi*	26	Pyoderma gangrenosum	AMK + MEPM → DOXY + MEPM → DOXY + ERT	3 months	Good	2012	Dua et al. [10]
9	*H. bilis*	15	Cellulitis	ERT + LVFX + AZM	12 months	Good	2012	Turvey et al. [17]
10	*H. cinaedi*	19	Cellulitis	IMP → MINO	2 weeks → 2 months	Good	2016	Toyofuku et al. [11]
11	*H. cinaedi*	38	Cellulitis	ND	ND	Fair	2017	Sugimoto et al. [12]
12	*H. cinaedi*	48	Cellulitis	DOXY	4 months	Good	2017	Matsumoto et al. [13]
13	*H. bilis*	20	Cholangitis	CTRX + MNZ + DOXY → MFLX → AZM	2 months → 22 days	Good	2017	Degand et al. [18]
14	*H. cinaedi*	18	Fasciitis	MEPM + DOXY	6 weeks	Good	2018	Hill et al. [14]

Tx, treatment; *IPM*, imipenem; *GM*, gentamicin; *MEPM*, meropenem; *TOB*, tobramycin; *ND*, no data; *AMPC*, amoxicillin; *FOS*, fosfomycin; *RFP*, rifampicin; *DOXY*, doxycycline; *iv*, intravenous; *po*, per oral; *PAMP/BP*, panipenem/betamipron; *CAM*, clarithromycin; *AMK*, amikacin; *ERT*, ertapenem; *LVFX*, levofloxacin; *AZM*, azithromycin; *MINO*, minocycline; *MNZ*, metronidazole; *MFLX*, moxifloxacin

infection, clinicians request the microbiology laboratory to incubate culture bottles for a longer period. Recently, 16S rRNA gene analysis has been one of the most common approaches for investigating bacterial strains. In patient 2, *H. cinaedi* was identified by detecting16S rRNA amplicon specific for *H. cinaedi.* In addition, electrospray ionization/time-of-flight MS can be performed to detect multiple bacteria species that may be present in a culture or clinical specimen. In fact, MS could identify *H. cinaedi* in the culture bottle of both patients.

No definite recommended guidelines have been described for the susceptibility testing and treatment of *H. cinaedi* infection. *H. cinaedi* strains generally show low minimum inhibitory concentration values for carbapenems, aminoglycosides, and tetracycline, and moderate values for penicillin and cephalosporins. However, they have resistance to macrolides and fluoroquinolones. Both patients were first treated with cephalosporins but had recurrent bacteremia. It has been reported that 30–60% of patients showed recurrent symptoms [25, 29, 35]. A long-term therapy of 2–6 weeks is recommended [25]. Both patients were successfully treated with a long-term carbapenem or cephalosporin therapy combined with oral minocycline therapy. Overall, antimicrobial therapy was performed for 10 weeks in patient 1 and for 20 weeks in patient 2. We recommend that such patients should be treated with antimicrobial therapy for ≥ 6 weeks with close monitoring. The first treatment failure of minocycline therapy for patient 1 may be due to the inappropriate drug administration time because it should be taken between meals. It has been reported that digestive decontamination with kanamycin could prevent recurrent *H. cinaedi* infection [36]. According to this concept, patient 1 was treated with digestive decontamination with kanamycin, which may be effective.

Patients with XLA are fundamentally treated with immunoglobulin replacement therapy (IVIg or SCIg). This therapy reduces the frequency and severity of infections and can lower the morbidity and mortality rate. An IgG trough level of 500 mg/dL has been considered the minimum target. A meta-analysis showed that pneumonia risk could be progressively reduced by higher IgG trough levels up to at least 1000 mg/dL [37]. Both patients were treated with SCIg, and their IgG trough levels were maintained over 1000 mg/dL. However, they developed refractory cellulitis and bacteremia caused by *H. cinaedi*. Currently, most patients with XLA are being treated with higher IgG trough levels, and the number of cases of severe bacterial and enterovirus infections has

reduced. However, the number of cases of NHPH infections including *H. cinaedi* and *H. bilis* infection is increasing. NHPH has a strong ability to translocate from the intestinal mucosa to the vascular system. IgA may play a significant role in protecting bacterial translocation; however, patients with XLA showed no or few IgA even administered the adequate immunoglobulin replacement therapy.

In conclusion, patients with XLA are susceptible to infections with NHPH including *H. cinaedi*. They typically experience bacteremia with these organisms, although the bacteria may be difficult to grow in a conventional culture system. Gene analysis and MS analysis may help in their bacteria detection. This technology was useful in the identification of a difficult-to-grow *Helicobacter* organism. However, the treatment is difficult and several patients present with recurrent bacteremia. They could be treated with long courses of antibiotics. If patients with XLA present with ambiguous skin lesion and fever, they should be considered to have an NHPH infection.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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