INTERNAL MEDICINE

□ CASE REPORT □

Relapsing *Campylobacter Coli* Bacteremia with Reactive Arthritis in a Patient with X-linked Agammaglobulinemia

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Abstract

A patient genetically diagnosed with X-linked agammaglobulinemia repeatedly developed bacteremia due to *Campylobacter coli* (*C. coli*) for one year and seven months in spite of immunoglobulin replacement therapy. Throughout the clinical course, *C. coli* with identical genetic patterns was repeatedly isolated from both blood and stool cultures, thus indicating that the patient had latent intestinal infection. The bacteremia was always accompanied by reactive arthritis. Since the immunoglobulin level was extremely low with severe B cell deficiency, the reactive arthritis must have been induced in a humoral immunity-independent manner. Adding oral minocycline following intravenous meropenem was very effective; the stool cultures became negative and the patient has been well for more than one year without relapse of bacteremia.

Key words: *Campylobacter coli*, *Campylobacter jejuni*, bacteremia, reactive arthritis, X-linked agammaglobulinemia

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Introduction

X-linked agammaglobulinemia (XLA) is a congenital immunodeficiency due to dysfunction of Bruton's tyrosine kinase (BTK) that is indispensable for the maturation of B cells (1). Lack of B cells and immunoglobulin renders the patient highly susceptible to infectious diseases and seriously impairs the humoral immunity.

Here, we report the first case of XLA with relapsing *Campylobacter coli* (*C. coli*) bacteremia that was accompanied by reactive arthritis. We describe the clinical course, speculate the pathogenesis, and discuss the treatment.

Case Report

A 35-year-old man was admitted to our hospital because of fever sustained for one month accompanied by pain and swelling of the left ankle joint. The patient had been diagnosed with agammaglobulinemia when he was 3 years old and had been receiving gammaglobulin replacement therapy once a month. He had suffered from pneumonia several times. His elder brother had also been diagnosed with agammaglobulinemia and died of severe pneumonia at the age of 10. No other family members were diagnosed with agammaglobulinemia. The arthralgia had appeared not only in the ankle joint, but also in his right knee and left hip joint, which, however, disappeared within several days. He was treated with oral clarithromycin on an outpatient basis, but the fever and arthralgia continued. Prednisolone was then administered at small doses, 5-10 mg, to control arthralgia, but it was ineffective. About one month after the onset of the arthritic symptoms, gram negative rods were isolated from his blood. The patient was admitted to our hospital. The isolated bacteria were spiral-shaped and grew on 5% sheep blood agar at 42℃; they were positive for oxidase as well as catalase and weakly positive for hippurate hydrolysis. From these findings, they were considered to be *Campylobacter* species. To identify the isolated bacterial strain, we performed the PCR assay as described by Fermer et al (2).

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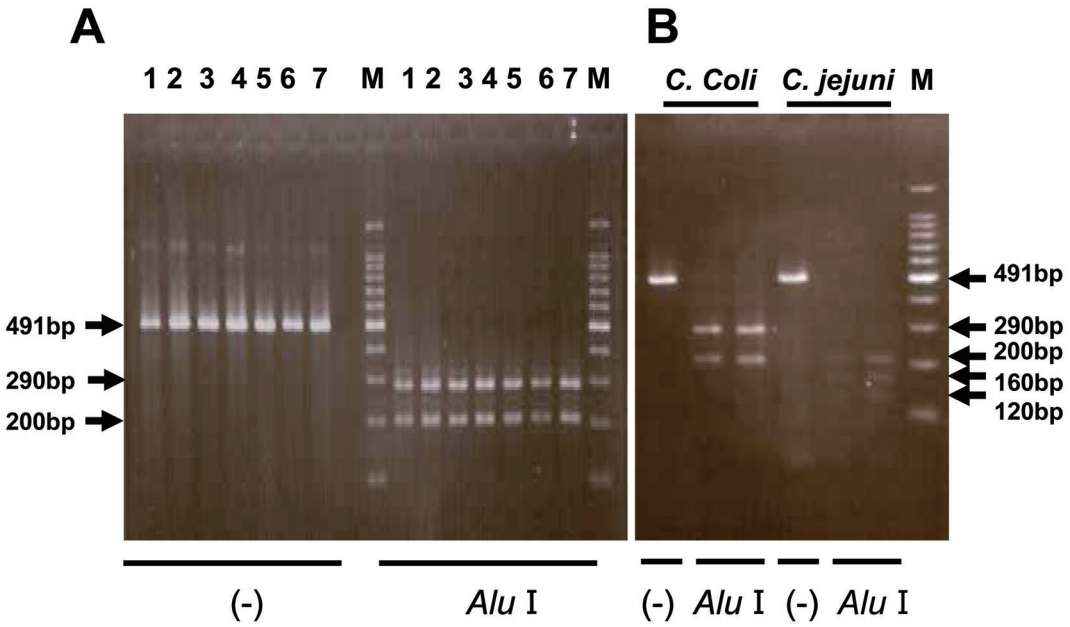

Figure 1. **PCR assay was performed to identify the bacterial strain isolated from blood and stool. The products were electrophoresed with or without being digested by *Alu* I (A). The control PCR products of *Campylobacter coli* and *Campylobacter jejuni* are also shown with their specific sizes indicated (B). Lanes in (A): 1, Blood in 1st ; 2, Stool in 2nd ; 3, Blood in 2nd ; 4, Blood in 3rd ; 5, Stool in 3rd ; 6, Stool in 4th ; 7 , Blood in 4th hospitalization, respectively. *C. coli*: *Campylobacter coli*, *C. jejuni*: *Campylobacter jejuni*, M: Size Marker.**

As shown in Fig. 1 (Lane 1), the strain was determined as *C. coli* by the specific size of its PCR product.

On admission, his body temperature was 37.2℃, blood pressure was 124/62 mmHg, and his pulse rate was 72 per minute. On physical examination, his left ankle and knee were swollen and accompanied by sedentary pain. Hepatomegaly was also observed. He had not complained of any abdominal symptoms including pain and diarrhea. Laboratory findings on admission revealed a slight liver dysfunction. RA factor was negative. His HLA haplotype was not examined. Analysis of peripheral blood lymphocytes by flow cytometry revealed that the number of B lymphocytes in his peripheral blood was 21/μl. His serum IgG was 156 mg/dl, and neither IgA nor IgM was detectable, even though he had been receiving gammaglobulin replacement therapy once a month. From the clinical course and family history, X-linked agammaglobulinemia was suspected. In order to confirm the diagnosis, his peripheral blood was obtained for flow cytometric analysis to examine the expression of BTK. Flow cytometric analysis of intracellular BTK expression in monocytes was performed as described previously (3). As shown in Fig. 2, BTK expression was negligible in his peripheral blood monocytes. In addition, we performed genetic examination of *BTK* gene as described previously (4). Both the BTK mutation analysis and flow cytometric analysis were performed after informed consent had been obtained. A deletion was detected in the 15th exon (coding for the tyrosine kinase domain) of *BTK* gene. The deletion leads to a frameshift and generates a premature stop codon. Thus, the patient was genetically diagnosed with XLA with the BTK deficiency. After admission, we started intravenous administration of ceftazidime, to which the isolated *C. coli* was sensitive. They were resistant to erythromycin. Gammaglobulin was also administered. The fever and the arthritis were resolved shortly after starting ceftazidime and his blood culture turned negative on the 7th hospital day. Although we did not perform aspiration of joint fluid, we concluded that the arthritis was reactive according to the diagnostic criteria defined in the previous report (5): the development of synovitis in a previously asymptomatic joint within the first two months after development of symptoms of bacteremia. In addition, its rapid disappearance after defervescence supported the diagnosis. Although his stool was repeatedly obtained for culture during the first hospitalization, it was consistently negative for *C. coli*. Thus, the source of bacteremia could not be identified. After intravenous ceftazidime had been changed to oral administration of minocycline, to which the bacteria was also sensitive, the patient was discharged on the 30th hospital day. Minocycline was administered for one week.

However, the *C. coli* bacteremia accompanied by arthritis relapsed three times, 10, 16, and 18 months later, even though serum IgG was kept above 500 mg/dl by replacement of gammaglobulin. The arthritis occurred at different joints at these relapses, at the left knee at the 1st and 2nd relapses, and at the right sternoclavicular joint at the 3rd relapse. His stool still remained negative during the 2nd hospitalization at the 1st relapse in spite of repeated examination. As shown in Fig. 1, however, *C. coli* were isolated not only from the blood but also from the stool during the 3rd

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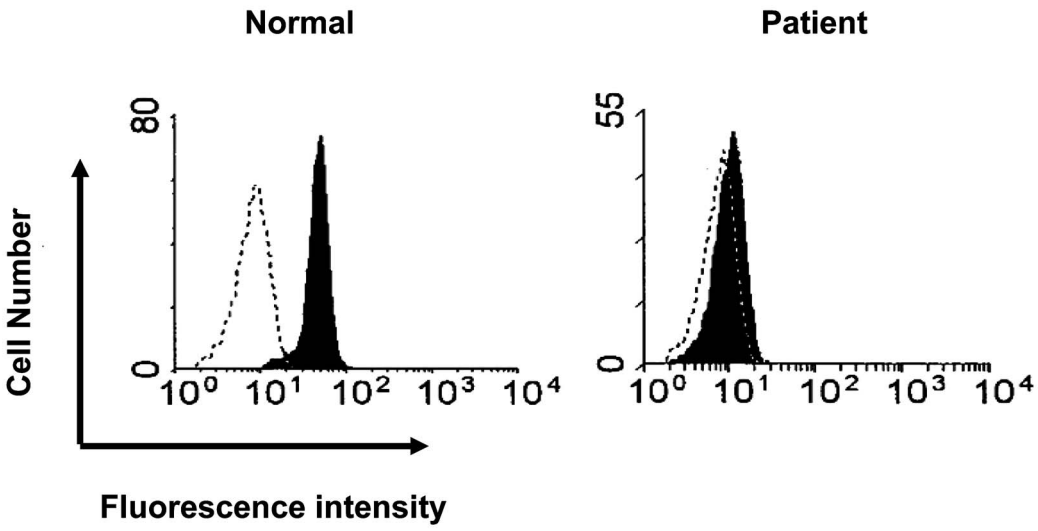

Figure 2. **Flow cytometric analysis was performed to examine the Bruton's tyrosine kinase (BTK) expression in monocytes from a normal donor and from the patient. The filled areas and those outlined with dotted lines indicate staining with anti-BTK antibody and control IgG monoclonal antibody, respectively.**

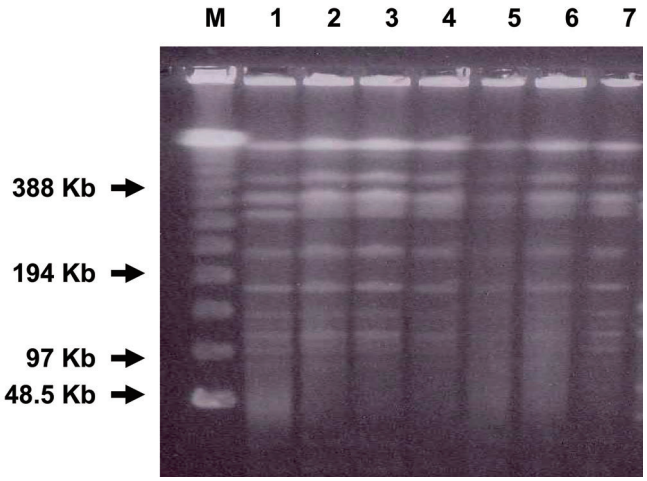

Figure 3. **Pulsed field gel electrophoresis was performed to determine the DNA patterns of isolated *Campylobacter coli*. DNA samples obtained from blood or stool cultures throughout the clinical course. Lanes: 1, Blood in 1st; 2, Stool in 2nd; 3, Blood in 2nd ; 4, Blood in 3rd ; 5, Stool in 3rd ; 6, Stool in 4th; 7 , Blood in 4th hospitalization, respectively. M:Size Marker.**

hospitalization at the 2nd relapses. In order to identify the genetic patterns of the isolated bacteria, pulsed field gel electrophoresis (PFGE) was performed as modifying the method described by Steele et al (6). In brief, bacteria suspensions were solidified with 1.6% InCert agarose gel and digested with 20 U of *Sma* I. Then PFGE was performed with a 1% PFGE-grade agarose gel by the CHEF DR-II system (Bio-Rad Laboratories, Richmond, CA, U.S.A) with initial and final pulse times of 1 and 35 seconds, respectively for 18.5 hours. Interestingly, as shown in Fig. 3, *C. coli* isolated from his blood or stool showed the same genetic pattern at initial bacteremia and later relapses. Thus, we concluded that the patient had the latent intestinal infection with *C. coli*, which gave rise to the recurrent bacteremia. Cefepime was effective for the bacteremia at these relapses. After discontinuation of cefepime, we did not add oral administration of antibiotics at the 1st and 2nd relapses. Stool culture remained positive for *C. coli* after leaving the hospital after the 2nd relapse, and the bacteremia relapsed again. Meropenem was effective for the bacteremia at the 3rd relapse, and also made stool cultures negative for *C. coli*. The patient was discharged after the therapy was changed from intravenous administration of meropenem to oral administration of minocycline. Minocycline was administered for two weeks and discontinued. His stool has been obtained for culture periodically. It has been negative for *C. coli* and the patient has been well for about one year without relapse of bacteremia.

Discussion

Although 10 cases have been reported for *Campylobacter* bacteremia with XLA (Table 1), this is the first reported case of XLA that developed *C. coli* bacteremia with reactive arthritis. The definitive diagnosis of XLA was made by confirming the BTK deficiency by flow cytometry. In addition, a deletion mutation was detected in the region coding for the SH1 domain by sequencing the *BTK* gene (4). Various types of mutation of *BTK* gene have been reported, and it has been known that there is no correlation between the genotype and the phenotype of XLA patients (4). In the present patient, the mutation resulted in negligible expression of BTK and severe deficiency of humoral immunity.

Campylobacter is a gram negative rod bacterium which

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Table 1. Reported Cases of XLA with *Campylobacter jejuni/coli* Bacteremia

Case	Age/Sex	Clinical findings	Stool culture	Effective treatment	Infection	Reference
1	24/M	Bacteremia Diarrhea	(+)	Sulfamethoxazole/trimethoprim Fradiomycin (p. o.) Gentamicin (i. v.) Doxycycline (p. o.)	NE	13
2	25/M	Bacteremia Cellulitis	(-)	ND	ND	14
3	11/M	Bacteremia	(+)	Piperacillin (i. v.) Erythromycin (p. o.)	E	15
4	7/M	Bacteremia Cellulitis	(+)	Ciprofloxacin (p. o.) with maternal plasma	E	16
5	32/M	Pericarditis Bacteremia	(+)[a]	Ceftazidime (i. v.) Erythromycin (i. v.)	NE	17
6-9	ND	Bacteremia	ND	ND	ND	8
10	34/M	Bacteremia Cellulitis	(+)	Panipenem/betamipron (i. v.) Kanamycin (p. o.)	E	12

Case 1-9: *Campylobacter jejuni*, Case 10: *Campylobacter coli*, ND: Not described, E: Eradicated, NE: Not eradicated, [a]: colon biopsy

latently infects intestines of cattle and can be a pathogen of colitis in human beings. Among *Campylobacter* species, *C. fetus* can be a cause of systemic infections including bacteremia. On the other hand, *C. coli* and *C. jejuni* (which is closely related to *C. coli*) predominantly induce colitis and rarely cause bacteremia except in immunodeficient individuals (7). Interestingly, van der Hilst et al reviewed 49 adult patients with hypogammaglobulinemia and indicated that patients with XLA were more susceptible to *C. jejuni* than those with common variable immunodeficiency (CVID) (8). In addition, Woodbridge and Ketley reported that the susceptibility was closely correlated with the IgA level in CVID (9). The extremely low level of IgA in this patient might have allowed the latent intestinal infection with *C. coli* leading to the recurrent bacteremia.

Infection with *Campylobacter* species, including *C. coli*, is known to be frequently accompanied by reactive arthritis. A population-based study by Hannu et al revealed that 7% or 13% of patients infected with *C. jejuni* or *C. coli*, respectively, had reactive arthritis, although no control subject that was selected from the registry had such symptoms (5). The pathophysiology for development of the reactive arthritis remains to be clarified. Concerning *C. jejuni* infection, it is well known that molecular mimicry between the bacterial antigen and human tissue might cause autoimmune disorders including Guillain-Barre syndrome (10). The patient reported here, however, developed the reactive arthritis associated with *C. coli* infection in spite of very low levels of gammaglobulin in his blood. Furthermore, Locht et al reported that *Campylobacter* bacteremia patients with or without arthritis showed no difference in anti-*Campylobacter* antibody level (11). These observations imply that *Campylobacter* infection likely causes reactive arthritis through mechanisms independent of humoral immunity.

In spite of susceptibility to *Campylobacter* (8), there are only 10 reported cases of *Campylobacter* bacteremia with XLA as shown in Table 1. Case 10 is a boy with XLA who developed *C. coli* bacteremia with relapsing cellulites of the right lower leg (12). The other nine patients, Cases 1 to 9, developed bacteremia due to *C. jejuni* (8, 12-17). Thus, the present patient represents the second reported case of XLA that developed *C. coli* bacteremia. In four of the patients (Cases 3, 4, 5, and 10), bacteremia developed in spite of gammaglobulin replacement therapy. Although the serum levels of immunoglobulin were not described in these reports, the replacement therapy was seemingly ineffective in preventing the development of bacteremia of *Campylobacter* species in these patients. In five patients (Cases 1, 3, 4, 5, and 10), including the patient with *C. coli* bacteremia (Case 10), the source was considered to be the intestine, because stool cultures were also positive for the *Campylobacter* species. Interestingly, none of these patients had abdominal symptoms, such as pain or diarrhea. It is also noteworthy that bacteremia relapsed after recovery from the first episode of systemic infection in four of five patients (Cases 1, 4, 5 and 10). At the relapse of bacteremia, the bacteria were also isolated from fecal specimens in these patients. Case 4 still remained positive for *C. jejuni* in the fecal specimen after the 1st bacteremia was cured. In the case with *C. coli* bacteremia (Case 10), stool cultures turned negative, but bacteremia due to the same strain relapsed more than five years later. These patients might have the latent intestinal infection with the *Campylobacter* species. These findings indicate that it is difficult to eradicate *C. coli/jejuni* in XLA patients. However, in Case 10, bacteremia was finally controlled by intravenous administration of panipenem/betamipron followed by additional oral administration of kanamycin for 2 weeks. In addition, the bacteremia of other patients (Cases 3

and 4) was controlled successfully by orally administrated antibiotics, erythromycin and ciprofloxacin, respectively. Although erythromycin has been used as the 1st choice drug for *Campylobactor* infection, its resistance rate in *Campylobacter* is increasing (18). Actually the bacteria isolated from the present patient were resistant to erythromycin. He was treated by intravenous administration of meropenem followed by oral administration of minocycline for 2 weeks according to the results of *in vitro* susceptibility testing. The bacteria might have been eradicated from the intestine because his stool has been negative for *C. coli* for more than one year. From these observations, it is speculated that additional oral administration of the antibiotics to which the isolated bacteria are sensitive may play a crucial role in control of *C. coli/jejuni* in XLA patients. However, minocycline was also administered, though only for a week, at the 1st development of bacteremia without successfully eradicating the presumptive latent intestinal infection. Periodical bacterial examination should be performed after discontinuing administration of antibiotics to confirm eradication and to determine the appropriate duration of oral administration.

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