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CASE REPORT

Recurrent *Campylobacter lari* Bacteremia in X-Linked Agammaglobulinemia: A Case Report and Review

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SUMMARY X-linked agammaglobulinemia (XLA) is a primary immune deficiency disease with a B-cell defect. We present the first XLA patient who had recurrent *Campylobacter lari* bacteremia. High dose intravenous immunoglobulin combined with azithromycin once per week, and a complete avoidance of bacterial reservoirs may be helpful for the prevention of *C. lari* bacteremia.

X-linked agammaglobulinemia (XLA) is a primary immune deficiency disease (PID) with low counts of circulating B-cells and serum immnoglobulins (Ig). Bacterial infections are the major clinical presentations.[1] *Campylobacter lari* is a gram negative rod whose main reservoirs are poultries and domestic mammals. Although it is infrequently isolated from humans, there were reports of *C. lari* gastroenteritis,[2] permanent pacemaker infection,[3] and prosthetic joint infection,[4] mainly in immunocompromised hosts but occasionally also in immunocompetent hosts. To date, bacteremia due to *C. lari* was reported in only 10 patients worldwide.[2-5] Furthermore, a *C. lari* bacteremia in an XLA patient has never been reported. We present the first XLA patient with recurrent *C. lari* bacteremia.

CASE REPORT

A 15-year-old male has been diagnosed with XLA since 9 years of age. He had a history of frequent upper and lower respiratory tract infections (RTI). There was no family history of such infections. An immunologic work up revealed undetectable serum Igs (IgG, IgM, IgA). A lymph node biopsy was negative for lymphoid follicles or germinal centers. DNA analysis showed a mutation at codon 261 of exon 9 on *Bruton's tyrosine kinase (BTK*) gene. He had been well with a treatment of 400 mg/kg of intravenous immunoglobulin (IVIG) treatment every 4 weeks. The trough IgG level was maintained at 400 mg/dl.

At 15 years of age, he was hospitalized due to fever, cough, dyspnea and headache (Table 1). A computerized tomography (CT) scan of the paranasal sinus showed chronic sinusitis. The bacterial culture and PCR for enterovirus in the cerebrospinal fluid (CSF) were negative. Blood cultures were positive

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for *C. lari* on two occasions and the organism resisted to all cephalosporins and quinolones but was sensitive to aminoglycosides. The *in vitro* sensitivity to macrolides was not performed. He was treated with one dose of IVIG (600 mg/kg) plus gentamicin and ceftazidime for 14 days. The blood culture became negative three days after the treatment. After this episode the dose of monthly IVIG was set at 600 mg/kg.

Five months later, he presented with fever and headache (Table 1). The bacterial culture and PCR for enterovirus of the CSF were negative. The blood cultures were positive for *C. lari* in three different specimens and the organism was sensitive to aminoglycosides, amoxicillin/clavulanate, cefepime, and carbapenem, but resistant to amoxicillin, quinolone, co-trimoxazole, first, second and third generation cephalosporins. The bacterial sensitivity to macrolides was not performed. The trough IgG level was 559.5 mg/dl. One dose of 600 mg/kg of IVIG plus 14 days of cefotaxime and amikacin were given. The blood culture became negative after 13 days of treatment. The echocardiogram was normal. Exploration of environmental risk factors revealed a poultry farm in his neighborhood and he was moved to the university dormitory to avoid further exposure. Azithromycin (500 mg) was given once/week as prophylactic treatment and the monthly IVIG was maintained at 600 mg/kg.

Eight months after the second episode, he was hospitalized for worsened sinusitis (Table 1). His blood culture was positive for *C. lari* despite azithromycin, monthly IVIG and avoidance of bacterial reservoirs. In this episode, *C. lari* was sensitive to amoxicillin/clavulanate, aminoglycosides, imipenem, fourth generation cephalosporins and piperacillin/tazobactam. One dose of 600 mg/kg of IVIG and amoxicillin/clavulanate for 14 days were given. The blood culture became negative three days after the treatment. Thereafter the dose of azithromycin was increased to 750 mg once/week along with 600 mg/kg of monthly IVIG. The patient was followed for 4 months before the dose of monthly IVIG was decreased to 400 mg/kg due to financial problems.

Fifteen months after the 3rd episode, the patient was found to have worsened sinusitis again (Table 1). He was treated with one dose of 400 mg/kg of IVIG plus 2 weeks of oral amoxicillin/clavulanate. The trough IgG level was 492 mg/dl. His blood culture was positive for *C. lari* but no sensitivity test was performed. At the two-week-follow up, the blood culture was negative. Since then, the dose of monthly IVIG was increased to 600 mg/kg or adjusted to keep the trough IgG level around 600 mg/dl. The patient was still on 750 mg/week of azithromycin. At the time of this report, he is being followed for 9 months after this last episode without *C. lari* bacteremia.

DISCUSSION

XLA is characterized by a B lymphocyte differentiation defect resulting in blocking the B-cell precursor differentiation at the pre-B cell stage. Peripheral B lymphocytes are almost always absent,

Table 1 Summary of clinical manifestations, investigations and treatments

	1st episode	2nd episode	3rd episode	4th episode
Clinical manifestations	Fever, cough, dyspnea headache	Fever, headache	Fever, coughs, worsened sinusitis	Worsened sinusitis no fever
Trough IgG	Not available	559.5 mg/dl	650 mg/dl	492 mg/dl
Hemoculture	*C. lari*, 2 specimens	*C. lari*, 3 specimens	*C. lari*, 1 specimen	*C. lari*, 1 specimen
CSF culture	No growth	No growth	Not done	Not done
Stool culture	No growth	No growth	No growth	Not done
Treatment	Ceftazidime + gentamicin x 14 days	Cefotaxime + amikacin x 14 days	Amoxicillin/clavulanate x 14 days	Amoxicillin/clavulanate x 14 days
Prophylaxis	No	Azithromycin 500 mg once a week	Azithromycin 750 mg once a week	Azithromycin 750 mg once a week

leading to extremely low serum Ig. The defective gene is identified as *BTK* gene on Xq21.3. About one-third of XLA cases are sporadic. In this patient, clinical symptoms of multiple RTI, undetectable Ig counts, absence of lymphoid follicles/germinal centers on biopsy, and the *BTK* mutation helped to differentiate XLA from other B cell disorders. Replacement therapy with IVIG at 350-600 mg/kg every 3-4 weeks is recommended.

Bacteremia can be found in 10% of XLA patients.[1] *Campylobacter* spp. is increasingly recognized as a human pathogen. Among the four species of clinical relevance, *C. jejuni* is the most common pathogen in humans, followed by *C. coli*.[3] Both species are recognized as common causes of diarrhea, but extraintestinal infections including bacteremia were so far only rarely described.[6-7] *C. fetus* is occasionally reported as cause of bacteremia and systemic illness.[5,8] Bacteremia due to *C. lari* was reported in only 10 patients worldwide so far.[2-5] One of these patients was a 25-day-old neonate,[2] three patients were elderly,[3-5] and four patients were immunocompromised (one with multiple myeloma,[3] one with AIDS,[3] two with unidentified immunocompromised conditions[3]). Two patients were considered normal hosts.[3] To our knowledge, this is the first case of a *C. lari* bacteremia in XLA.

Although it is believed that the reservoir for *C. lari* bacteremia is in the gastrointestinal tract, only one-third of the patients with *Campylobacter* bacteremia have diarrhea, and stool cultures are positive in only 66% of them. For patients without diarrhea, only 16% have positive stool cultures.[9] Our patient had *C. lari* bacteremia on three separate occasions without either diarrhea or presence of *C. lari* in the stool. The optimal antimicrobial regimen and duration of treatment for *Campylobacter* bacteremia has not been well defined. Macrolides were once recommended as the drug of choice and fluoroquinolones were considered as an alternative therapy. However, several reports have shown increasing resistance of these organisms to both antibiotics.[10] In Thailand, ciprofloxacin resistance among *Campylobacter* species increased from 0% in 1987 to 84% in 1995.[11] From 2002-2003, resistance rates of *Campylobacter* were: cephalothin-100%, co-trimoxazole-90%, quinolones-82%, ampicillin-34%, erythromycin-6%, tetracycline-60%, nalidixic acid-78%.[10] Of note, most *Campylobacter* species in Thailand are susceptible to macrolides (88% for erythromycin[10] and 85-93% for azithromycin[11]). *C. lari* isolated from our patient was sensitive to aminoglycosides, amoxicillin/clavulanate, and carbapenem, but was resistant to ciprofloxacin. There have been reports of successful treatments for *C. lari* bacteremia with various antimicrobial regimens such as amoxicillin/clavulanate,[3] erythromycin with or without netilmycin,[2,3] and imipenem with gentamicin.[3] The duration of the antibiotic therapy for *Campylobacter* bacteremia has been reported from one to four weeks.[9,12] Our patient responded well to a two-week course of effective antibiotics.

Although the majority of patients with *Campylobacter* bacteremia were immunocompromised hosts or in an extreme age group, recurrent bacteremia was unusual, with a rate of 1.7% and the mortality was 2.5-10.5%.[9] In our case, we believe that the recurrent bacteremia was due to a relapse of the organism within the host, given the inability of the host to produce any antibody to fight the pathogen and the fact that recurrences occurred even after the patient moved away from the contaminated environment. The antibody titer in a regular dose of IVIG may not be high enough to suppress this infection and we postulate that higher IgG levels may be effective. There have been reports of patients with recurrent *Campylobacter* bacteremia who remained in remission with long-term clarithromycin suppression therapy.[13] We used azithromycin because of the longer half life, in addition to an increased dose of 600 mg/kg IVIG in this patient. However, at the third episode, a breakthrough occurred even with a trough IgG level of 650 mg/dl and concurrent azithromycin prophylaxis. Therefore, a higher dose of azithromycin was started. This combination, together with strict avoidance of the bacterial reservoir, seemed to prolong the relapse time for *C. lari* bacteremia. The fourth episode of bacteremia happened when the trough IgG level dropped to 492 mg/dl. This episode could be explained by either the lower level of trough IgG or the resistance of *C. lari* to azithromycin. Since *Campylobacter* species have the potential to develop resistance to many antibiotics, a sensitivity test to antibiotics especially to macrolides should be done from all cultures positive for *C. lari* to provide an appropriate antibiotic treatment plan and suppressive therapy in the future.

In conclusion, we reported the first case of an XLA patient with four episodes of *C. lari* bacteremia. High dose IVIG combined with high dose azithromycin once/week, and complete avoidance of the bacterial reservoir may have been helpful for the prevention of further *C. lari* bacteremias in this patient.

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