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Case report

Salmonella Enteritidis cholecystitis with chronic granulomatous disease

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A B S T R A C T

We describe a 40-year-old woman with *Salmonella* cholecystitis complicating adult-onset X-linked chronic granulomatous disease (CGD) caused by a *de novo* mutation in the paternal-origin *CYBB* gene. CGD was diagnosed by familial genetic analysis of the *CYBB* gene encoding NADPH oxidase gp91^{phox} after detection of a refractory subcutaneous abscess at the age of 28. At age 40, she began experiencing frequent fever and diarrhea over a period of 3 months that were refractory to antibacterial treatment. Cholecystitis was evident. Her symptoms improved after percutaneous trans-hepatic gallbladder aspiration puncture with stand-by cholecystectomy. *Salmonella enterica* serotype Enteritidis (*S.* Enteritidis) was detected in blood, stool, and bile acid samples. Due to her suppressed bactericidal ability caused by CGD, *S.* Enteritidis was considered to have translocated from the gut to reside in the gallbladder, causing her repeated enteritis and sepsis. When encountering CGD with recurrent salmonellosis, the possibility of cholecystitis should be considered as another infection focus.

Introduction

Chronic granulomatous disease (CGD) is a rare hereditary disorder caused by a genetic abnormality of NADPH oxidase and its related molecules, which impairs the production of superoxide and hydrogen peroxide and their associated bactericidal ability. Patients with CGD suffer from a variety of recurrent bacterial and fungal infections. Approximately 70% of CGD patients have the X-linked variant, with the remaining 30% displaying autosomal recessive inheritance [1,2]. For many years, the onset of X-linked CGD was thought to occur only in male infants. However, adult-onset female cases of X-linked CGD caused by a *de novo* mutation have recently surfaced as well [3,4]. Several reports of relapsing *Salmonella* infection in patients with CGD exist in the literature [5,6], but its pathogenesis remains incompletely understood . We herein describe an adult female with X-linked CGD caused by a *de novo* mutation in the paternal-origin *CYBB* gene complicated by relapsing *Salmonella enterica serotype Enteritidis (S. Enteritidis)* gastroenteritis complicated by bacteremia and acute cholecystitis. Patient needed antibacterials and percutaneous gall bladder aspiration followed by cholecystectomy.

Case report

A 40-year-old woman was admitted to our hospital for treatment of fever, upper abdominal pain, and diarrhea. At the age of 28, she developed a refractory subcutaneous abscess. DNA analysis of the *CYBB* that encodes gp91^{phox} demonstrated that she was heterozygous for a nonsense mutation, ^{206}Trp(TGG)/stop(TGA) and therefore, a diagnosis of adult onset X-linked chronic granulomatous disease was made, as described in a previous report [1]. Molecular biological study revealed that her disease was caused by a de novo mutation in the *CYBB* gene on the paternal-origin X-chromosome and a skewed inactivation of the normal maternal X-chromosome [1]. Stimuli-induced microbicidal reactive oxygen metabolites formation test of her neutrophils revealed that only 9.6% of the neutrophils produced H_2O_2, and nitroblue-tetrazolium slide test demonstrated about 10% positive cells [1].

Three months before being admitted to our hospital, the patient's 45-year-old husband had suffered from diarrhea due to infectious enteritis of unknown cause. Six days after husband`s symptom appeared, she presented with diarrhea and fever and was diagnosed as having bacterial enteritis, for which she received levofloxacin (500 mg/day).

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Table 1
Laboratory data on admission.

< Hematology >			< Biochemistry >					
WBC	6900	/μL	TP	7.4	g/dL	CRP	7.4	mg/dL
Neut	71.8	%	Alb	3.4	g/dL	Procalcitonin	0.1	ng/mL
Baso	0.1	%	AST	20	U/L			
Mono	3.3	%	ALT	23	U/L	< Tumor markers >		
Lymph	17.1	%	LDH	164	U/L	CEA	0.5	ng/mL
RBC	332×10^4	/μL	ALP	164	U/L	CA19-9	6	U/mL
Hb	10.6	g/dL	GGTP	22	U/L			
Platelets	18.8×10^4	/μL	T-Bil	0.5	mg/dL	< Infection >		
			BUN	8.5	mg/dL	TP-Ab	(−)	
< Coagulation >			Cre	0.53	mg/dL	HBs-Ag	(−)	
PT	12.7	sec	Na	135	mEq/L	HCV-Ab	(−)	
APTT	31.6	sec	K	3.0	mEq/L	HIV-Ab	(−)	
			Cl	105	mEq/L	Blood culture	(−)	

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; Bas, basophils; BUN, blood urea nitrogen; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Cre, creatinine; CRP, C-reactive protein; GGTP, gamma-glutamyltranspeptidase; Hb, hemoglobin; HBs-Ag, hepatitis B virus S antigen; HCV-Ab, hepatitis C virus antibody; HIV-Ab, human immunodeficiency virus antibody; LDH, lactate dehydrogenase; Lymph, lymphocytes; Mono, Monocytes; Neut, neutrophils; PT, prothrombin time; RBC, red blood cells; T-Bil, total bilirubin; TP, total protein; TP-Ab, treponema pallidum antibody; WBC, white blood cells.

Although her symptoms subsided, the diarrhea and fever soon recurred and required hospitalization. *S.* Enteritidis was identified in blood and stool specimens, leading to a diagnosis of enteritis and sepsis caused by *S. Enteritidis*. She was given intravenous ceftriaxone (2 g/day) and her symptoms once were again relieved. She was discharged 10 days after admission. However, she developed fever, diarrhea, and upper abdominal pain 2 weeks after discharge and was referred and admitted to our hospital.

Her past medical history included meningitis (20 years old), dysmenorrhea (30 years old), and migraines (30 years old). She was taking lansoprazole, rebamipide, sulfamethoxazole/trimethoprim, tizanidine hydrochloride, diclofenac sodium, and norethisterone/ethinyl estradiol. She did not smoke or drink. She had a fever of 38 degrees Celsius. Abdominal examination revealed slight tenderness at the epigastrium without guarding or rigidity. On admission, serological examination revealed elevated C-reactive protein of 7.4 mg/dL and elevation of neutrophils (Table 1). Neither elevation of hepatobiliary enzymes nor abnormal renal function was observed (Table 1). Procalcitonin was not elevated (0.1 ng/mL) and blood culture was negative (Table 1). H_2O_2 producing rate of her neutrophils was 23%.

Since she revealed upper abdominal pain, we performed the abdominal ultrasonic examination. It showed a distended gallbladder, thickening of the gallbladder wall, and biliary sludge (Fig. 1). Sonographic Murphy's sign was positive. Abdominal contrast CT examination disclosed edematous change of the gallbladder, early patchy enhancement of the liver, and edematous change of the small intestine (Fig. 2). She was diagnosed as acute cholecystitis and acute enteritis complicating CGD.

Since her high fever persisted despite intravenous levofloxacin of 500 mg/day, percutaneous trans-hepatic gallbladder aspiration puncture (PTGBA) was performed on hospital day 2 to collect 120 mL of purulent bile (Fig. 3). *S.* Enteritidis was detected in bile and fecal cultures. Her inflammation and clinical symptoms of fever and diarrhea improved promptly after PTGBA. Colonoscopy on hospital day 7 revealed no abnormal findings suggestive of enteritis, such as mucosal edema, redness, erosion, bleeding, or ulcer. She was discharged on hospital day 12. Bile cultures at the time of elective laparoscopic cholecystectomy 2 months after discharge were negative, and there have been no additional recurrences of enteritis to date.

Discussion

This is the case report of a young woman with adult-onset X-linked CGD caused by a *de novo* mutation in the paternal-origin *CYBB* gene with recurring *S. Enteritidis* infection over a short period of time. CGD is a rare inherited disease, occurring approximately once in every 250,000 individuals [2]. Due to a complete lack of or significant decrease in the production of microbicidal reactive oxygen metabolites owing to defective phagocytic NADPH-oxidase, CGD patients are prone to a variety of recurrent bacterial and fungal infections [2]. The NADPH-oxydase enzyme is composed of five subunits ($gp91^{phox}$, $p22^{phox}$, $p47^{phox}$, $p67^{phox}$, and $p40^{phox}$). Roughly 70% of CGD cases are X-linked and caused by mutation of $gp91^{phox}$ in *CYBB*. The remaining 30% of patients harbor a mutation in *CYBA* encoding $p22^{phox}$, *NCF1* encoding

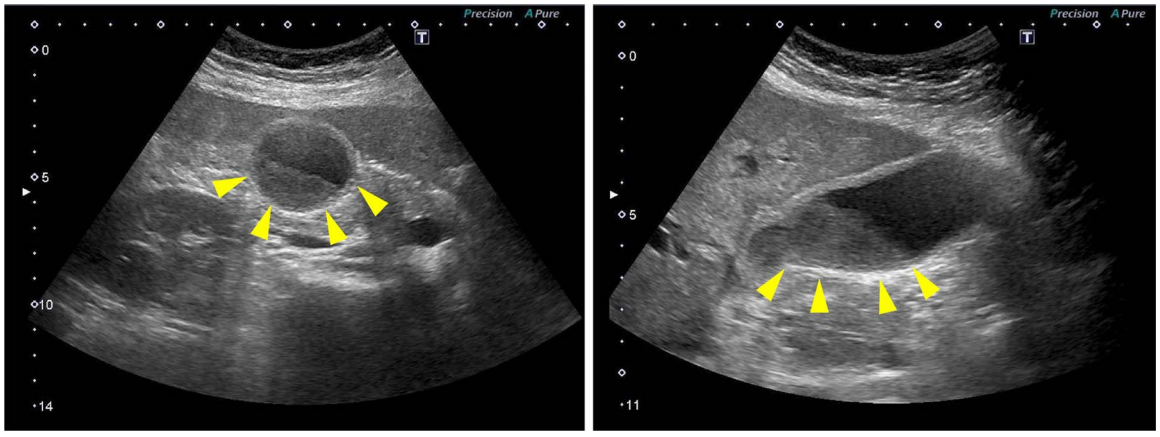

Fig. 1. Abdominal ultrasound on admission revealed a distended gallbladder, thickening of the gallbladder wall, and biliary sludge (arrowheads).

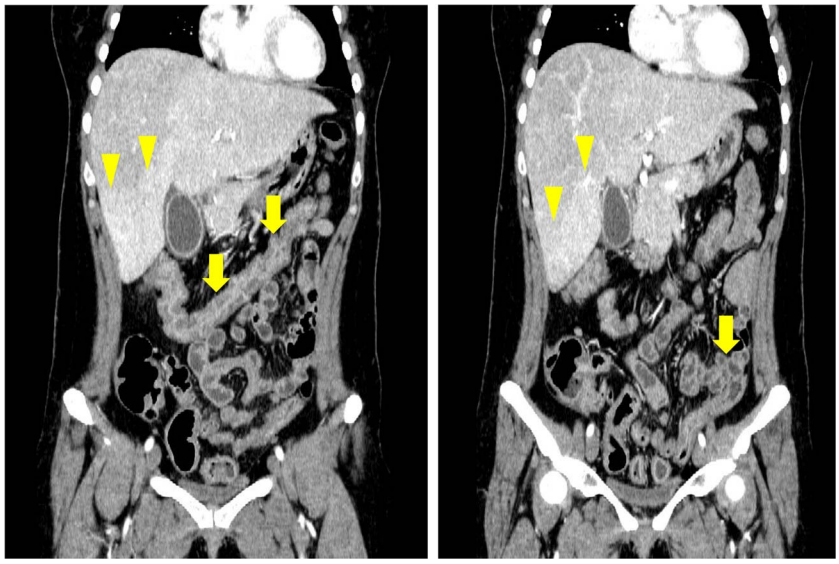

Fig. 2. Abdominal contrast CT on admission demonstrated edematous change of the gallbladder, early patchy enhancement of the liver (arrowheads), and edematous change of the intestinal tract (arrows).

Fig. 3. Drained purulent bile by percutaneous trans-hepatic gallbladder aspiration puncture.

p47^{phox}, *NCF2* encoding p67^{phox}, and *NCF4* encoding p40^{phox} [2]. Although originally believed as X-linked in male infants only, late onset X-linked CGD has been described in adult women, with some cases caused by a *de novo* mutation [3,4]. Based on the results of familial genetic analysis, our patient's CGD was caused by a *de novo* mutation in the *CYBB* gene in the paternal-origin X-chromosome and skewed inactivation of the normal maternal X-chromosome [1]. DNA analysis of the *CYBB* gene revealed heterozygosity for the nonsense mutation 618 G→A in exon 6 to produce ^{206}Trp(TGG)→stop(TGA) [1].

CGD patients are particularly vulnerable to catalase-positive microorganisms, including *Staphylococcus aureus, Nocardia spp, Escherichia coli, Serratia marcescens, Burkholderia cepacea, Salmonella spp, and Aspergillus spp* [7], with an existing case report of relapsing infection caused by *Salmonella spp* [6]. *Salmonella spp* is categorized as typhoidal or non-typhoidal and over 2500 serotypes have been identified and distinguished [8]. The *S.* Enteritidis in this case was non-typhoidal *Salmonella* species. Virtually all (95%) causes of salmonella infection are foodborne [9], such as in contaminated raw eggs in Japan. Other less common modes of transmission are pets (e.g., reptiles and birds), direct personal contact, nosocomial transmission, and waterborne transmission. Here, the husband had symptoms of enterocolitis 6 days prior to her *S.* Enteritidis infection, so transmission from the husband was suspected. The bacterium invades intestinal epithelial cells, causes inflammation, and increases intestinal fluid. Patients typically present with an acute onset of fever, diarrhea, vomiting, and epigastric pain after an incubation period of 6–72 h after exposure [9]. Bacteria initially translocate from the gut through the lymphatic system to survive and multiply at an intracellular location in gut lymphoid follicles, mesenteric lymph nodes, and reticuloendothelial tissue in the liver and spleen [10].

Salmonella is known to colonize bile ducts and the gallbladder in some cases, even after apparent recovery [11]. This may be due to the bacteria entering the biliary tract via a descending route after systemic infection (portal vein blood stream), through an ascending route directly from the small intestine via the duodenal papillae, or by direct transfer into the gallbladder from the liver [11]. *Salmonella* can self-adapt to survive in the gallbladder by the production of biofilm and acquisition of antimicrobial resistance [11].

In this case, *S.* Enteritidis detection in bile, blood, and stool cultures suggested that orally ingested bacteria had caused the bacteremia and chronic carriage in the gallbladder. Approximately 5% of patients with non-typhoidal *Salmonella* enteritis develop bacteremia, which is more likely to occur in immunologically compromised patients [9]. However, cholecystitis caused by non-typhoidal *Salmonella* is relatively rare and the subject of only 6 case reports to date (Table 2) [12–15]. To our knowledge, this is first case of *S.* Enteriditis cholecystitis complicating adult-onset X-linked CGD.

Salmonella infection is easily treated with such antibacterials as fluoroquinolones and third-generation cephalosporins. Carrier state in gall bladder may cause recurrence bacteremia and enteritis following antimicrobial treatments. Symptoms of acute cholecystitis can be subtle in patients with CGD

We encountered the rare case of a 40-year-old woman with CGD caused by a *de novo* mutation who contracted relapsing *S.* Enteritidis infection. In immunocompromised patients with recurrent *Salmonella* enteritis, clinicians should bear in mind the importance of the gallbladder as a bacterial reservoir.

Table 2
Cases of cholecystitis caused by non-typhoidal *salmonella*.

Age	Sex	Underlying disease	Symptom(s)	Serotype	Gastroentero -colitis	Antibiotic(s)	PTGBD	Cholecystectomy	Reference
36	F	(−)	Abdominal pain	*S. virchow*	(−)	CP	(−)	(+)	[12]
55	F	(−)	Vomiting, diarrhea, abdominal pain, icteric	*S. virchow*	(+)	CPFX	(−)	(+)	[13]
35	F	Peptic ulceration	Abdominal pain, diarrhea	*S. enteritidis*	(+)	CPFX	(−)	(+)	[13]
74	F	(−)	Diarrhea, abdominal pain	*S. enteritidis*	(+)	CPFX	(−)	(+)	[13]
27	M	(−)	Abdominal pain, nausea, fever	*S. enteritidis*	(+)	CPFX, MNZ	(−)	(−)	[14]
11	M	(−)	Abdominal pain, fever	*S. enteritidis*	(+)	SBT/CPZ, AMK	(+)	(−)	[15]
40	F	CGD	Diarrhea, fever, abdominal pain	*S. enteritidis*	(+)	LVFX, CTRX	(+)	(+)	Present case

AMK, amikacin; CGD, chronic granulomatous disease; CP, chloramphenicol; CPFX, ciprofloxacin; CTRX, ceftriaxone; F, female; LVFX, levofloxacin; M, male; MNZ, metronidazole; PTGBD, percutaneous transhepatic gallbladder drainage; SBT/CPZ, sulbactam/cefoperazone.

Author statement

All authors meet the ICMJE authorship criteria.

Conflicts of interest

The authors declare that they have no conflict of interest.

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