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【 CASE REPORT 】

Ceftriaxone-associated Pseudolithiasis in the Gallbladder and Bile Duct of an Elderly Patient

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Abstract:
A 78-year-old man had been undergoing treatment with Cefamezin for pyogenic spondylitis. Because of complication of a urinary tract infection, the medication was switched to ceftriaxone (CTRX) 2 g/day. On day 18 after starting CTRX, the patient began experiencing abdominal pain. Computed tomography (CT) and endoscopic ultrasound led to the identification of calculi in the gallbladder and extrahepatic bile duct with a peculiar formation. We suspected CTRX-associated pseudo-cholecystolithiasis and pseudo-choledocholithiasis, although CT performed at admission had shown no such findings. Therefore, CTRX was discontinued. By day 17 after CTRX cessation, both the pseudo-cholecystolithiasis and pseudo-choledocholithiasis had disappeared.

Key words: ceftriaxone, pseudo-cholecystolithiasis, pseudo-choledocholithiasis, endoscopic ultrasound

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Introduction

Ceftriaxone (CTRX), a broad-spectrum cephem antibiotic with a long half-life, is a frequently used antibiotic in clinical settings. However, a 1986 report noted that CTRX administration causes the temporary appearance of gallstone-like sediment in the gallbladder (1). Although the ultrasound image of this gallstone-like substance resembles that of gallstones, spontaneous disappearance occurs in many cases shortly after CTRX discontinuation. This condition is known as biliary pseudolithiasis (2).

Subsequent research led to the identification of the main pseudolithiasis component as being the calcium salt of CTRX (3). Most reports of pseudolithiasis involve high doses of the drug being administered to children, and pseudolithiasis is rare in adults. Furthermore, the process of pseudo-choledocholithiasis formation remains unclear, as its appearance in the extrahepatic bile duct is rare.

We herein report an elderly patient in whom both pseudo-cholecystolithiasis and pseudo-choledocholithiasis with a peculiar formation occurred as a result of CTRX administration.

Case Report

A 78-year-old man with a history of type 2 diabetes was examined at our hospital for lumbar pain, and computed tomography (CT) and magnetic resonance imaging led to a diagnosis of pyogenic spondylitis. On the day the patient was admitted to the orthopedic surgery department, he was placed on a course of Cefazolin 3 g/day. His medication was switched to CTRX 2 g/day on day 24 of his hospital stay because of complication with a urinary tract infection. The patient was subsequently maintained on CTRX, but he complained of abdominal pain on day 18 of CTRX administration (day 42 of hospital stay; total administered amount of CTRX: 36 g).

CT was performed again, showing areas of high absorption in the gallbladder and extrahepatic bile duct (Fig. 1). Endoscopic ultrasound (EUS) used to confirm the presence of lesions related to abdominal pain revealed a single calculus associated with an acoustic shadow (AS) in the gallbladder, a single calculus associated with AS of approximately 10 mm, and a hyperechoic structure adhering to the long axis of the bile duct wall. No abnormalities were found in

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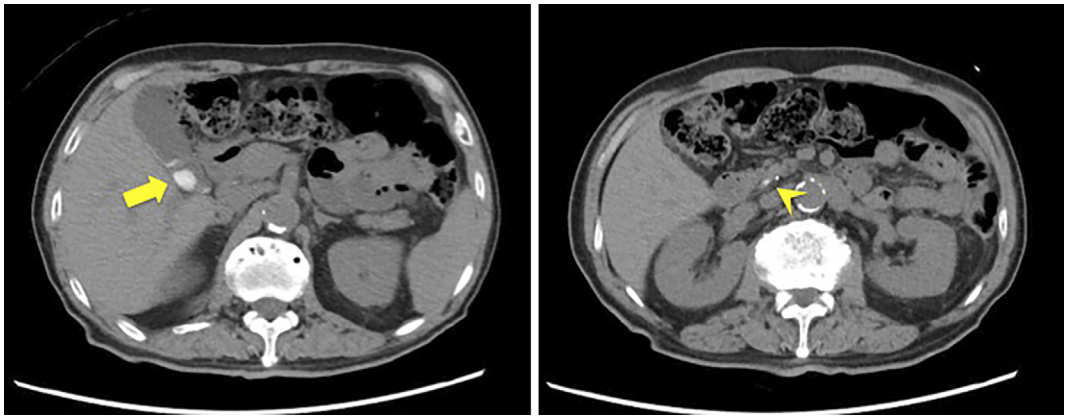

Figure 1. CT (coronal) at the appearance of abdominal pain, on day 18 after the start of CTRX. High-absorption structures were observed in the gallbladder (arrow) and in the common bile duct (arrowhead).

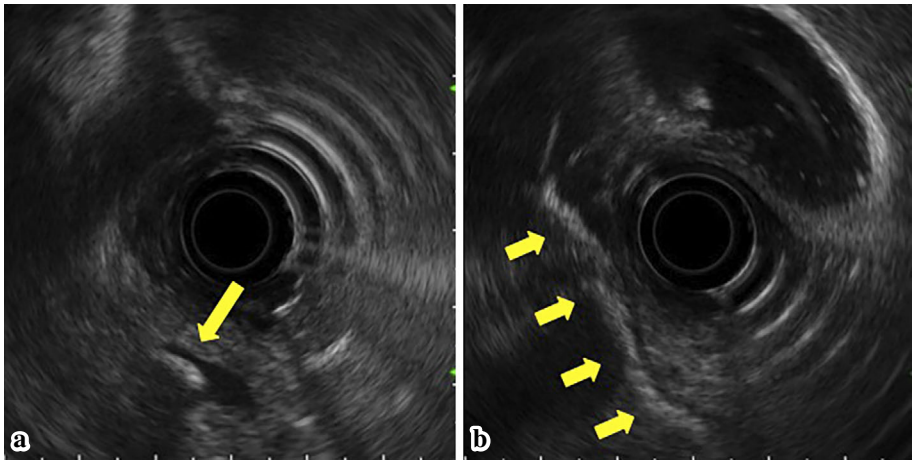

Figure 2. EUS at the appearance of abdominal pain, on day 18 after the start of CTRX. a: One calculus associated with an acoustic shadow (AS) measuring approximately 10 mm in the distal bile duct. b: Hyperechoic structure observed adhering to the long axis of the bile duct wall

Table. Blood Sampling Data at the Time of Accidental Onset.

WBC	7,400 /μL		AST	25 IU/L
RBC	356 /μL	↓	ALT	30 IU/L
Hb	11.1 g/dL	↓	ALP	292 IU/L
Plt	38.6 /μL		Γ-GTP	82 IU/L
Alb	2.6 g/dL	↓	T-bil.	0.3 mg/dL
Na	141 mEq/L		CRP	0.76 mg/dL
K	4.1 mEq/L		BUN	15.7 mg/dL
Cl	107 mEq/L		Cre	0.63 mg/dL

WBC: White Blood Cell, RBC: Red Blood Cell, Hb: Hemoglobin, Plt: Platelet, Alb: Albumin, T-bil.: Total billirubins, CRP: C-reactive protein, BUN: Blood urea nitrogen, Cre: Creatinine

the bile duct, including the ampulla, other than the calculi (Fig. 2). These calculi and hyperechoic structures had not been apparent on CT performed at hospital admission. Based on these findings, we suspected CTRX-associated pseudo-cholecystolithiasis and pseudo-choledocholithiasis.

A blood sample showed no abnormality in the hepatobiliary enzymes; neither cholecystitis nor cholangitis had occurred (Table). At this point, biliary colic was suspected. Because the abdominal pain was mild, CTRX administration was discontinued, and the antibiotic was switched to levofloxacin 500 mg/day. During this period, the patient was managed initially with fasting and was followed up for two days. After the abdominal pain had ceased, he resumed taking meals. No recurrence of abdominal pain occurred after resuming meals. CT and EUS performed on day 17/21 following CTRX discontinuation showed that both pseudo-cholecystolithiasis and pseudo-choledocholithiasis had disappeared (Fig. 3). The patient had no recurrence of abdominal pain.

Discussion

The broad-spectrum, third-generation cephem antibiotic CTRX has a long half-life and good tissue transferability. Consequently, it is used in various fields. Between 85% and 95% of CTRX in the bloodstream binds to albumin. The un-

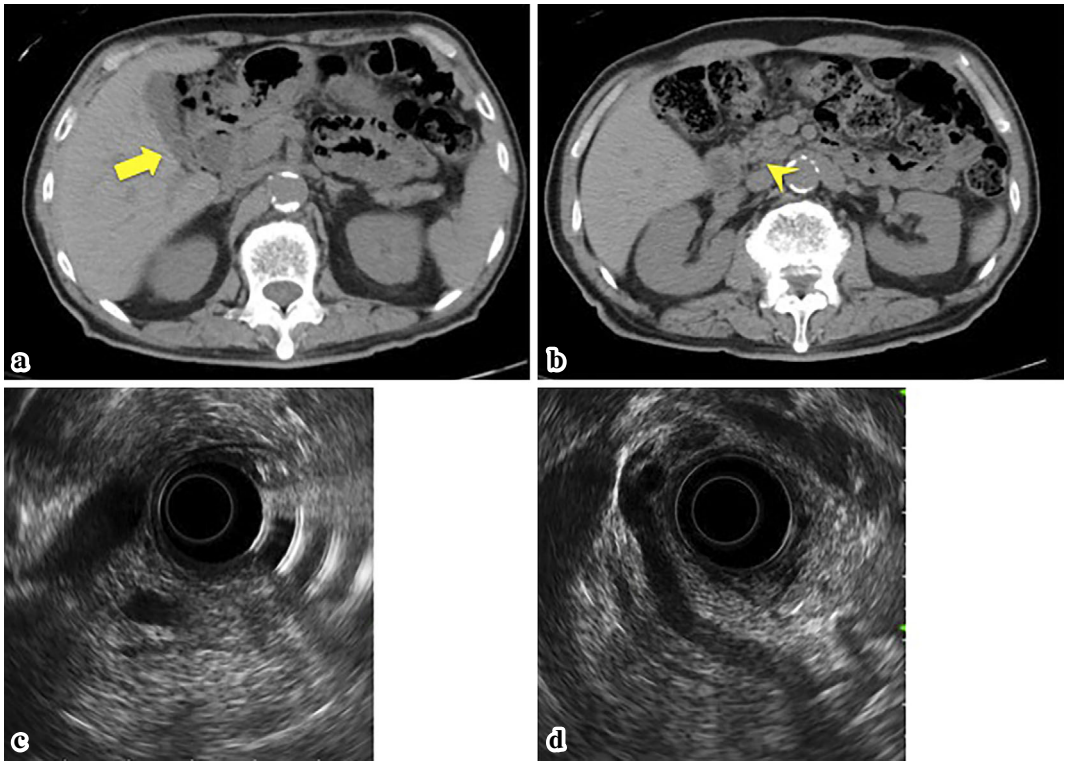

Figure 3. **a, b: CT on day 17 after the discontinuation of CTRX. The high-absorption structures in the gallbladder (arrow) and the common bile duct (arrowhead) had disappeared. c, d: EUS on day 21 after the discontinuation of CTRX. No calculus was observed in the gallbladder. The hyperechoic structure in the common bile duct had disappeared.**

altered portions are excreted in the urine (approximately 60%) and the bile (approximately 40%). As a result, the CTRX concentrations in the bile can be 20 to 150 times higher than those in the serum (4, 5). High concentrations of CTRX in the bile interfere with bile acid excretion, which in turn raises the ionized calcium levels in the bile because the sodium salts in CTRX have a high degree of affinity for calcium ions, biliary sludge, and sand forming in the gallbladder from the resulting CTRX/calcium composite (3). A report of an *in vitro* study indicated that doses of ≥2 g/day cause precipitation of CTRX and calcium in the bile (5). In addition, CTRX reduces the ability of the gallbladder to contract, probably as part of the mechanism through which crystals become more likely to be precipitated (6). However, in their prospective study of 20 adults administered CTRX, Pigrau et al. reported that 5 patients developed pseudolithiasis at 4-17 days after administration (7). All of these patients were asymptomatic. The pseudolithiasis disappeared 7-26 days after CTRX discontinuation. Similarly, in their prospective study of adult subjects, Heim-Duthoy et al. reported that 6 of 28 patients administered CTRX (21.4%) developed pseudolithiasis. The onset frequency was equal to that for children (8).

Only 0-19% of patients with pseudolithiasis are presumed to be symptomatic. For that reason, many pseudolithiasis patients might not be detected in clinical settings (9, 10). An investigation into the causes of the onset has indicated an increased frequency of onset attributable to the CTRX dose, duration of administration, degree of bed rest, abstention from food, dehydration, and hypoalbuminemia (9-11). It is usually difficult to differentiate gallstones from pseudolithiases using imaging studies; the key factor used for differentiation is the history of CTRX administration (12). Furthermore, pseudolithiasis disappears spontaneously and quite rapidly upon discontinuation of CTRX administration. The time until disappearance has been reported to be 14-60 days after discontinuation (9, 10). The therapeutic strategy for most patients is observation, as few symptoms are present in most cases. Furthermore, the condition disappears spontaneously in many cases. Some patients, however, present with symptoms such as strangulation of the common bile duct and pancreatitis, which require emergency care and must be managed aggressively.

The only action taken in the present case was observation of the patient's progress. Both CT and EUS performed after CTRX discontinuation on days 17 and 21, respectively, indicated that the pseudolithiasis had disappeared from both the gallbladder and common bile duct. Consequently, the courses of both pseudo-cholecystolithiasis and pseudo-choledocholithiasis were as expected.

CTRX administration does not necessarily induce pseudolithiasis formation. Although various factors can contribute to the disease onset, the fact that the present patient was elderly and had experienced long-term bed rest, which contributed to the slowing of his gallbladder contractions, suggested that he was at a high risk of pseudolithiasis morbid-

ity (13). Long-term bed rest because of pyogenic spondylitis likely contributed to the pseudolithiasis formation. Furthermore, this patient was administered CTRX with a high dose (total 36 g) and long duration (18 days). These treatments were inferred to also be involved in the pseudolithiasis formation. Hypoalbuminemia (2.6 g/dL) might have been involved as well. Consequently, based on the results obtained in our case, we recommend that, whenever avoidable, CTRX not be used in cases with multiple risk factors for pseudolithiasis.

The patient in this case was also found to have pseudolithiasis in the extrahepatic bile duct. Yoshida et al. (14) reported that 7 patients (41.2%) showed gallbladder enlargement along with a common bile duct stone and reported the high-density sludge pattern as the most common CT finding of CTRX-associated pseudolithiasis in adults. In our patient, EUS showed a hyperechoic structure adhering to the long axis of the bile duct wall. No previous report had described a study in which image findings indicated that the pseudolithiasis had adhered contiguously with the wall of the bile duct, as in the present case. The sludge accumulated in the bile duct because of the long-term administration of CTRX. Choledocholithiases then formed, clinging to the wall of the bile duct because of his long-term bed rest. Furthermore, although no finding was made of either cholangiectasis, abdominal symptoms or papillary dysfunction, cholestasis of some type is believed to have occurred in conjunction with the decreased gallbladder contractility.

The fact that pseudo-cholecystolithiasis and pseudocholedocholithiasis caused by CTRX have been observed in adults as well as children is important. Periodic imaging studies should be conducted during and after CTRX administration. In addition, CTRX should be discontinued immediately in cases where pseudolithiasis is suspected.

The authors state that they have no Conflict of Interest (COI).

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