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ORIGINAL ARTICLE

Computed tomography findings of ceftriaxone-associated biliary pseudocholelithiasis in adults

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Abstract

Purpose This study aimed to characterize the computed tomography (CT) findings of pseudolithiasis and investigate the outcomes and natural history in adult patients receiving CTRX therapy.

Methods A total of 17 patients were diagnosed with CTRX-associated biliary pseudolithiasis on CT between April 2013 and March 2017. The medical records, characteristics, complications, treatment options, and outcomes of these patients were examined. Serial CT images and the form, density, and location of pseudolithiasis were reviewed by two radiologists.

Results Of the 17 patients with CTRX-associated pseudolithiasis, seven were men and ten were women. The median patient age was 78 years (range 31–88 years). The median interval from CTRX administration to the diagnosis of pseudolithiasis was 10 days (range 4–32 days). The CT findings of pseudolithiasis included a sludge pattern (11 patients [64.7%]), stone pattern (two patients [11.8%]), and stone plus sludge pattern (four patients [23.5%]). Seven patients (41.2%) showed gall bladder enlargement along with a common bile duct (CBD) stone. Two patients with CBD stones underwent endoscopic CBD stone removal. The median time to pseudolithiasis resolution after CTRX cessation was 69 days.

Conclusion The high-density sludge pattern is the most common typical CT finding of CTRX-associated pseudolithiasis in adults.

Keywords Ceftriaxone · CTRX · Biliary pseudolithiasis · Computed tomography · Adult

Introduction

Ceftriaxone (CTRX), a third-generation cephalosporin antibiotic used for treating bacterial meningitis and acute pyelonephritis, can cause transient cholelithiasis (also referred to as pseudolithiasis) in some children [1]. CTRX-associated pseudolithiasis and biliary sludge have been mainly reported in children; these conditions are occasionally symptomatic and resolve spontaneously after cessation of CTRX therapy [2–8]. The incidence of CTRX-associated biliary pseudolithiasis has been reported to be relatively high (approximately 10.1–46.5%) in children [9, 10]. However, globally, some studies have reported the occurrence of CTRX-associated biliary pseudolithiasis in adults [11–14].

The incidence of pseudolithiasis has been suggested to be high in elderly individuals who show low activity and a high risk of dehydration. Therefore, patients receiving CTRX therapy should be carefully monitored for the early detection of conditions such as cholecystitis and pancreatitis [11]. Computed tomography (CT) findings of CTRX-associated biliary pseudolithiasis have not yet been established [15]. As CT is performed widely in patients receiving CTRX therapy, the identification of the typical CT findings of CTRX-associated pseudolithiasis will help in its early detection and diagnosis. The early detection of pseudolithiasis and adoption of appropriate management (cessation or alteration of antibiotic therapy) might help prevent the progression of pseudolithiasis to severe conditions such as cholecystitis.

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The present study aimed to characterize the CT findings of pseudolithiasis and investigate the outcomes and natural history in adult patients receiving CTRX therapy.

Materials and methods

Patients

Our institutional review board approved this retrospective study and waived the requirement for obtaining informed consent from each patient. We retrospectively reviewed the information system of our hospital and radiological information system and identified 1737 patients treated with CTRX between April 2013 and March 2017. Of these 1737 patients, 284 did not undergo abdominal CT and 50 without gallbladder due to history of biliary system surgery were excluded from the study. The remaining 1403 patients with gallbladder received CTRX therapy and underwent abdominal CT. The flow chart of patients' selection is shown in Fig. 1.

The inclusion criteria were as follows: (1) age over 20 years; (2) patients with gallbladder, (3) gallbladder stone/sludge that appeared after CTRX administration, its disappearance was confirmed; and (4) imaging (CT or ultrasonography) within 2 months before the start of CTRX therapy, i.e., the presence of cholelithiasis was negated before CTRX therapy, and (5) CT imaging after CTRX therapy.

The exclusion criteria were as follows: (1) history of biliary system surgeries such as pyloric ring-preserved pancreaticoduodenectomy, pancreaticoduodenectomy, hepatectomy, cholecystectomy, and choledochojejunostomy; (2) contrast enhance media in biliary system; (3) history and existence of gallbladder stone before CTRX therapy; and (4) although it was gallbladder stone/sludge that appeared after CTRX administration, its disappearance was not confirmed.

A total of 23 patients were suspected with CTRX-associated pseudolithiasis on CT. However, six patients were excluded because these did not meet the fourth exclusion criterion. Thus, 17 patients diagnosed with CTRX-associated pseudolithiasis on CT were finally enrolled in this study.

CT technique

Abdominal CT was performed using Aquilion ONE (Toshiba, Tokyo, Japan) and Aquilion CX (Toshiba). Oral contrast medium was not used routinely. Images of the entire abdomen were obtained at 5-mm thickness. Abdominal CT images and soft-tissue window images were reconstructed by obtaining three cross-sectional images (namely, axial, coronal, and sagittal images; width 350 HU; level 30 HU).

Image interpretation

Two radiologists (R.Y. and T.K.), who had 14 and 18 years of experience, respectively, assessing abdominal CT images, reviewed the study CT images independently using a DICOM viewer (SDS DICOM Viewer; Techmatrix Ltd., Tokyo, Japan). These radiologists were blinded to the clinical information of the patients but were aware that each patient had cholelithiasis. The two radiologists evaluated the following points:

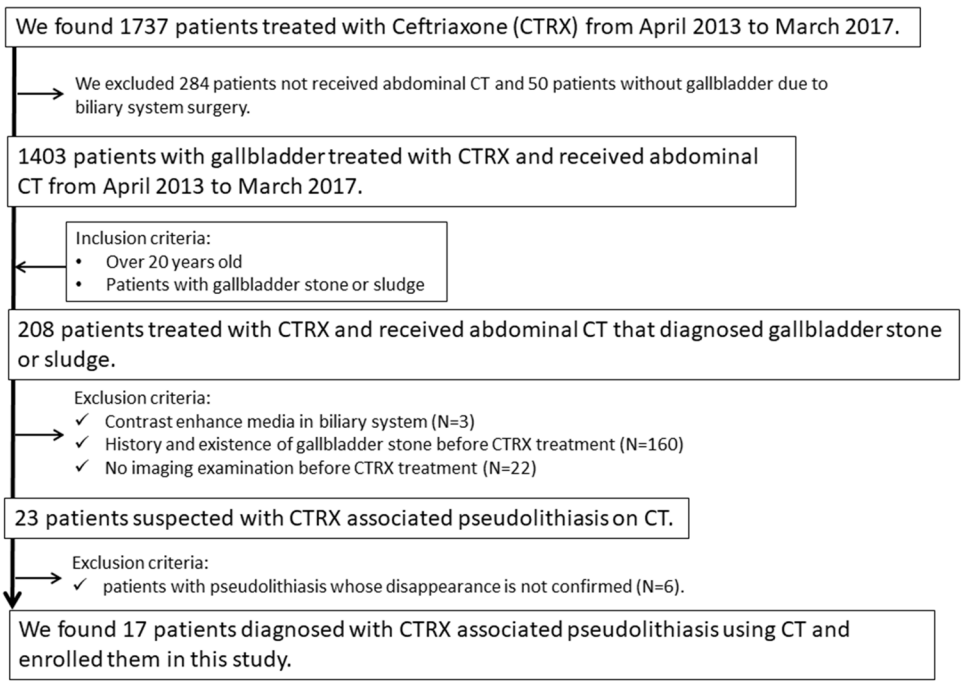

Fig. 1 Flow chart of patients' selection

1. Clinical findings of pseudolithiasis

   The date of CT examination after the first diagnosis of pseudolithiasis, the interval from CTRX administration to pseudolithiasis diagnosis (days), the interval from pseudolithiasis diagnosis to cholelithiasis resolution (days), and the interval from CTRX therapy cessation to cholelithiasis resolution (days).
2. CT findings of the pseudolithiasis

   The density, location (gallbladder and common bile duct [CBD]), pattern (stone, sludge, and stone plus sludge) (Fig. 2), and natural course of CT findings.

   The diagnostic criteria of positive gallbladder stones and sludge on the basis of CT were identifiable intracholecystic focus whose density differed enough from generally gallbladder contents to be easily detected [16]. Calcification is a sufficient condition for stones, but not a requirement [16]. In particular, we defined that the stone showed clear circular or oval shape, and the sludge showed high concentration without circular shape.

   The disappearance criteria of stone or sludge on the basis of CT was the concentration in the gallbladder was almost same as generally bile.

   Disagreements between the two radiologists were resolved through consensus. The density of pseudolithiasis was determined by averaging the measurements made by the two radiologists.

Details of CTRX therapy, treatment options, and clinical outcomes during follow-up.

We retrospectively reviewed the hospital information system and investigated the CTRX therapy received by the study patients by evaluating the following points:

1. Details of CTRX therapy

   Target diseases such as pneumonia, pyelonephritis, and peritonitis; dose per day (g); duration of administration (days); total dose (g); and presence of symptoms and liver dysfunction associated with pseudolithiasis at diagnosis.
2. Treatment options and clinical outcomes

After the diagnosis of CTRX-associated pseudolithiasis, we investigated the treatment options in each patient by analyzing the medical records. The options were conservative treatments, including CTRX therapy cessation and antibiotic drug change, and interventions, including endoscopic retrograde cholangiopancreatography with endoscopic bile duct stone removal and cholecystectomy.

Results

Patients

The clinical characteristics of the study patients are summarized in Table 1. Among the 17 patients, three underwent hemodialysis and three used diuretics.

Table 1 Patient characteristics

Patient characteristics	Number of cases
Total cases	17
Male:female	7:10
Age, median ± SD, range (years)	78 ± 13.3 (31–88)
eGFR, median ± SD, range (mL/min)	43.6 ± 9.7 (8.2–128.0)
Comorbidity	
Hemodialysis	3 (17.6)
Use of diuretics	3 (17.6)
Presence of fasting	4 (23.5)
Diabetes mellitus	7 (41.2)
Malignancy	7 (41.2)
Liver dysfunction at diagnosis	3 (17.6)

The figures in parentheses indicate percentage unless otherwise indicated

SD standard deviation, *eGFR* estimated glomerular filtration rate

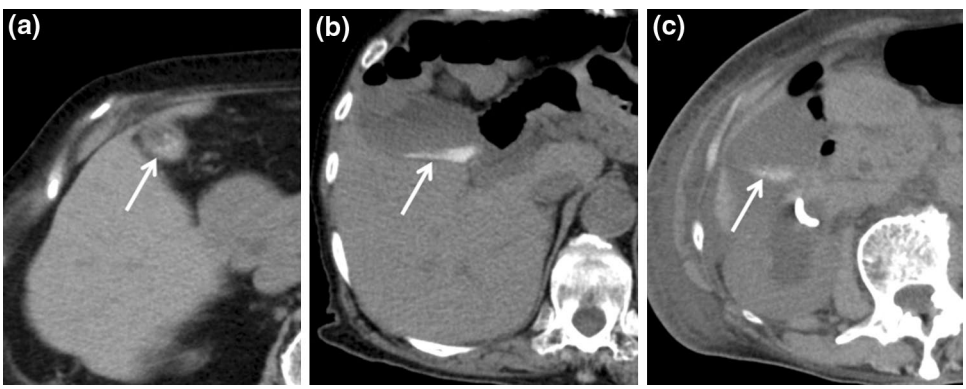

Fig. 2 Computed tomography findings of CTRX-associated pseudolithiasis. **a** Stone pattern, **b** sludge pattern, **c** stone plus sludge pattern

Clinical findings

The median radiological follow-up duration was 69 days (range 9–798 days). During the follow-up period, CT was performed 2–16 times in the patients (median seven times per patient). Moreover, CT was performed for the follow-up of other diseases (not pseudolithiasis) in all patients, except five with biliary tract symptoms.

CT findings of pseudolithiasis

Table 2 shows the CT findings in the patients with CTRX-associated pseudolithiasis. The median pseudolithiasis density on CT was high at 83 HU (range 58–202 HU). The sludge pattern was the most common typical CT finding of CTRX-associated pseudolithiasis (11 patients [64.7%]). Seven patients (41.2%) showed gall bladder enlargement and seven (41.2%) showed gall bladder enlargement with a CBD stone. No significant correlations were observed among the total dose/dose per day of CTRX, estimated glomerular filtration rate, and pseudolithiasis density.

Table 2 CT findings of CTRX-associated pseudolithiasis

Interval from diagnosis to disappearance, median, range (days)	69 (9–798)
Density, median ± SD, range (HU)	83 ± 43.3 (58–202)
CT findings ($n = 17$)	
Stone pattern	2 (11.8)
Stone plus sludge pattern	4 (23.5)
Sludge pattern	11 (64.7)
Enlargement of the gallbladder	7 (41.2)
Cholelithiasis along with a CBD stone	7 (41.2)

The total number of cases is 17. The figures in parentheses indicate percentage unless otherwise indicated

CT computed tomography, *CTRX* ceftriaxone, *HU* hounsfield unit, *SD* standard deviation, *CBD* common bile duct

Details of CTRX therapy

Table 3 shows the details of CTRX therapy. The target diseases were pneumonia (8/17, [47.1%]), pyelonephritis (7/17, [41.2%]), peritonitis (1/17, [5.9%]), and appendicitis (1/17, [5.9%]). Most patients (15/17 [88.2%]) received CTRX therapy at a dose of more than 2 g/day. The median interval from CTRX administration to cholelithiasis diagnosis was 10 ± 6.4 days (range 4–32 days).

Five patients showed biliary pseudolithiasis symptoms such as right epigastric pain and elevated liver enzyme or bilirubin levels at diagnosis.

Treatment options and clinical outcomes

Table 4 shows the treatment options and clinical summary. Events related to pseudolithiasis occurred in five patients (29.0%).

The conservative treatment options were as follows: bowel rest/fasting, five patients (29.0%); CTRX therapy cessation, nine patients (52.9%); and antibiotic drug change, nine patients (52.9%). Among the 17 patients, two underwent endoscopic CBD stone removal. No patient underwent surgery. A representative case is presented in Fig. 3.

Discussion

With regard to CT findings, CTRX-associated biliary pseudolithiasis mainly showed a biliary sludge pattern. Additionally, CTRX administration at doses of ≥ 2 g/day resulted in the development of CTRX-associated biliary pseudolithiasis within 2 weeks, and the condition resolved in about 2 months.

CT is a useful initial imaging modality in patients with suspected abdominal diseases [16], and gallstones have been identified in about 80% of individuals using CT [16].

Table 3 Details of CTRX therapy

Target disease	Pneumonia	8 (47.1)
	Pyelonephritis	7 (41.2)
	Peritonitis	1 (5.9)
	Appendicitis	1(5.9)
Details of CTRX dose	Dose/day, median ± SD, range (g)	2 ± 1.1 (1–4)
	Duration of administration (median ± SD, range days)	9 ± 3.7 (4–16)
	Total dose, median ± SD, range (g)	22 ± 14.4 (8–56)
Status at diagnosis of CTRX-associated pseudolithiasis	Interval from administration of CTRX to diagnosis of pseudolithiasis, median ± SD, range (days)	10 ± 6.4 (4–32)
	Presence of symptoms owing to pseudolithiasis	5 (29.0)
	Liver dysfunction at diagnosis	3 (17.6)

The figures in parentheses indicate percentage unless otherwise indicated

CTRX ceftriaxone, *SD* standard deviation

Table 4 Clinical summary

Outcomes, *n* (%)	No event	12 (71.0)
	Event related to pseudolithiasis	5 (29.0)
Conservative treatment, *n* (%)	Bowel rest/fasting	5 (29.0)
	CTRX cessation	9 (52.9)
	Antibiotic drug change	9 (52.9)
Intervention, *n* (%)	Endoscopic bile duct stone removal	2 (11.8)
	Surgery	0

The total number of cases is 17. The figures in parentheses indicate percentage unless otherwise indicated
CTRX ceftriaxone

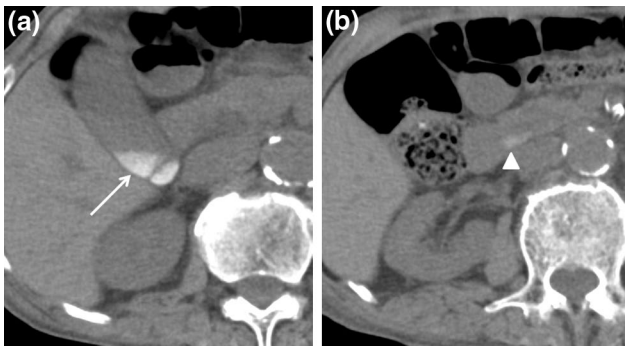

Fig. 3 A representative symptomatic case. An 80-year-old man presented with a complaint of right epigastric discomfort. Plain abdominal computed tomography shows gallbladder enlargement, a high-density biliary sludge pattern, and fluid–fluid level formation in the gallbladder (Fig. 2a, arrow) and common bile duct (Fig. 2b, arrowhead)

The mechanism underlying the pathogenesis of pseudolithiasis is as follows. Bile acids and CTRX have been suggested to use the same transport pathway; therefore, biliary secretion of CTRX may inhibit bile acid secretion. Approximately 85–95% of CTRX is bound to albumin in the blood and 45% unchanged CTRX is excreted in bile. Thus, the CTRX concentration in bile is 20- to 150-fold higher than that in the serum [11, 17, 18]. When the CTRX concentration in the gallbladder exceeds its threshold level, CTRX precipitates by binding to calcium ions secreted along with bile acids. As CTRX can precipitate with calcium, CTRX-associated biliary sludge is suggested to be mainly composed of calcium–CTRX complexes [1, 9, 19–23].

The density of CTRX-associated biliary pseudocholelithiasis was high on CT, and this finding is consistent with the findings in previous studies [11, 12, 15, 24]. Sonographic abnormalities showed echogenic material without and with acoustic shadowing in gallbladder [9]. Moreover, CTRX-associated biliary pseudolithiasis has been reported to resolve within approximately 2 months after CTRX therapy cessation [9, 11]. In our study, CTRX-associated pseudolithiasis resolved within approximately 2 months after CTRX therapy cessation in eight of 17 patients (47%). Patients with a long interval between pseudolithiasis diagnosis and resolution were asymptomatic and therefore did not undergo follow-up examination. The date of pseudolithiasis resolution was confirmed by analyzing CT images obtained for other diseases.

An in vitro studies showed that CTRX administration at doses of ≥ 2 g/day resulted in the precipitation of CTRX and formation of CTRX-induced biliary sludge [11, 17]. Poor solubility of CTRX has been reported in patients with renal dysfunction who receive high-dose CTRX (≥ 2 g/day) [11, 17, 24]. Most patients included in the present study received high-dose CTRX. Thus, the results of the present study are broadly consistent with those of previous studies [17].

CTRX has a long elimination half-life of 6–9 h. As the mean half-life during dialysis is 16 h, CTRX is negligibly removed during dialysis [25]. When CTRX is administered in patients with renal dysfunction or those undergoing hemodialysis, it might be necessary to adjust the CTRX dose because high CTRX concentrations in the blood and bile might cause biliary pseudolithiasis. The incidence of biliary pseudolithiasis has been found to be high in patients under fasting and bed rest who receive CTRX therapy [11, 23]. A rapid decrease in oral intake, which leads to long-term fasting and weight loss, is a typical risk factor of biliary pseudolithiasis [26]. Biliary pseudolithiasis can be prevented by decreasing the duration of CTRX therapy and by preventing dehydration, long-term fasting, and excessive rest.

According to previous studies [11, 12, 15, 24], CTRX-associated biliary pseudolithiasis is related to many complications such as cholecystitis and pancreatitis. Therefore, when abdominal symptoms are observed, it is necessary to promptly examine the gallbladder and initiate the appropriate treatment. CTRX therapy cessation almost completely eliminates gallstones, and consideration of biliary pseudolithiasis might help avoid excessive examinations and invasive treatments such as cholecystectomy. Progress can be assessed by performing ultrasonography or CT at 2 months after CTRX administration [11]. The gallbladder showing sludge with high concentration on CT should be investigated for a history of recent CTRX therapy.

The present study had several limitations. First, this was a retrospective study with a relatively small number of patients. Second, this study used different imaging conditions, including the timing of CT examination. In many patients, pseudolithiasis resolution was confirmed coincidentally through imaging performed for other diseases. Moreover, in some patients, pseudolithiasis might have resolved at an early stage. Third, CT is associated with radiation exposure. Therefore, follow-up tools, such as ultrasonography, might be good options for confirming pseudolithiasis resolution in asymptomatic patients. A standardized imaging follow-up protocol is needed for patients receiving CTRX therapy to allow data comparisons in future studies. Fourth, the present study did not compare the outcomes of conservative treatments with those of interventions. Fifth, the follow-up duration was insufficient in patients who were recently diagnosed with pseudolithiasis. Therefore, we plan to perform a prospective study with a large sample size, a standardized imaging follow-up protocol, and different treatment algorithms in the future.

In conclusion, the results of the present study indicate that a high-density sludge pattern is the most common typical CT finding of CTRX-associated pseudolithiasis in adults.

Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to declare.

Ethical approval This study was approved by the institutional review board of our institution.

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