

CASE REPORT

Asymptomatic ceftriaxone-associated pseudolithiasis

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Abstract

An 88-year-old woman with a history of meningioma and dementia was admitted with high fever, loss of appetite, and nausea in July. Urinary tract infection was suspected. Computed tomography (CT) showed no significant findings. Urinary findings improved with administration of ceftriaxone. However, high fever appeared on hospital day 28, and CT identified a gallbladder stone without any abdominal symptoms. We considered the possibility of ceftriaxone-associated pseudolithiasis and changed pharmacotherapy to cefmetazole. CT on day 34 showed a reduction in the size of the gallbladder stone. Ceftriaxone-associated pseudolithiasis might arise in the absence of abdominal symptoms, and clinicians should take the patient background and season into account when using this agent.

KEYWORDS

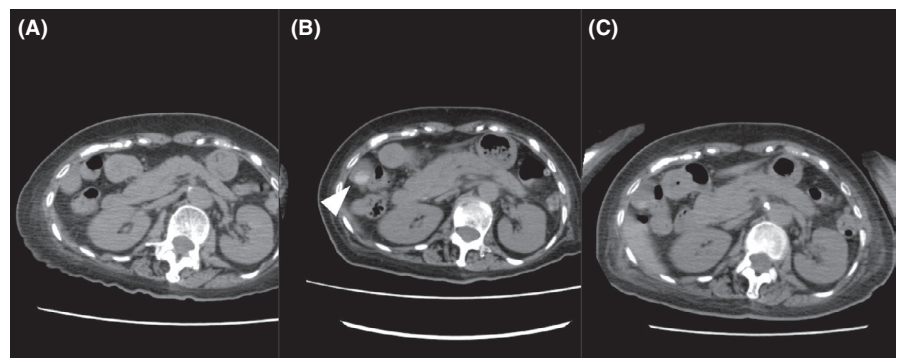
asymptomatic, ceftriaxone, high temperature, pseudolithiasis

1 | INTRODUCTION

Ceftriaxone is a third-generation cephalosporin that is widely used for various infectious diseases, such as respiratory tract and gastrointestinal tract infections and meningitis. Schaad et al first reported ceftriaxone-associated pseudolithiasis in 1986,¹ and both adult and pediatric

cases have been reported recently. Obesity, fatty diet, aging, pregnancy, oral contraceptive, gallbladder dysfunction due to fasting, high dose of ceftriaxone, low albumin, and kidney disease have been reported as factors contributing to gallbladder stone formation.² Pseudolithiasis after ceftriaxone initiation is thought to be one of the side effects, but few reports have described asymptomatic presentations.

FIGURE 1 A, Abdominal CT on admission shows no gallbladder stone. B, Abdominal CT on hospital day 28 (during ceftriaxone treatment) clearly shows a gallbladder stone (arrowhead). C, CT on hospital day 34 (after discontinuation of ceftriaxone) shows a reduction in size of the gallbladder stone



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TABLE 1 Reported cases of ceftriaxone-associated pseudolithiasis in Japan

Year	Author	Age	Gender	Infection type	Underlying disease	Dose (g)	Duration	Abdominal symptom	Course	Time to disappearance	Outcome
2009	Sasaki ¹⁰	35	F	Colon diverticulitis	none	2	13 d	epigastralgia	EST/ERBD	2 mo	EST/ERBD
2009	Tsuzaki ¹¹	24	M	Endocarditis	none	2, 4	46 d	hypochoondralgia	Cholecystectomy	82 d	Cholecystectomy
2012	Nakagawara ¹²	65	M	Enteritis	Diabetes, hypertension	2	7 d	none	EST	15 d	EST
2013	Tomoda ¹³	47	F	Colon diverticulitis	none	2	8 d	none	CTR stop	6 d	Disappearance
2013	Imoto ¹⁴	66	M	Meningitis	Diabetes, renal failure	4	22 d	none	ERBD	21 d	ERBD
2013	Imoto ¹⁴	67	M	Meningitis	Hypertension, dyslipidemia	4	23 d	none	CTR stop	42 d	disappearance
2015	Tanaka ¹⁵	83	F	Renal Abscess	Hypertension	2	36 d	epigastralgia	Cholecystectomy	Unknown	Cholecystectomy
2015	Shima ¹⁶	79	F	Bronchial Pneumonia	Renal failure	1	13 d	stomachache	CTR stop	48 d	disappearance
2016	Dohmen ¹⁷	76	M	Pneumonia	Hypertension, dyslipidemia, diabetes	2	8 d	Abdominal pain	Change to another antibiotic	22 d	Disappearance
2016	Niwa ¹⁸	23	F	Colon diverticulitis	none	2	6 d	epigastralgia	Change to another antibiotic	1 mo	Disappearance
2016	Niwa ¹⁸	76	F	Subcutaneous abscess	none	2	8 d	hypochoondralgia	Change to another antibiotic	1 mo	Disappearance
2016	Niwa ¹⁸	63	M	Hepatic abscess	Diabetes, lung cancer, colon cancer	3, 4	20 d	none	Change to another antibiotic	2 mo	Disappearance
2016	Niwa ¹⁸	93	M	Pneumonia	Brain infarction (hemiplegia)	2	7 d	hypochoondralgia	Change to another antibiotic	Unknown	Disappearance
2017	Tsukagoshi ¹⁹	70	M	Brain abscess	ANCA-associated vasculitis	4	14 d	none	CTR stop	14 d	Disappearance
2017	Tsukagoshi ¹⁹	39	M	Meningitis	none	4	7 wk	none	CTR stop	2 wk	Reduction
2017	Tsukagoshi ¹⁹	35	M	Brain abscess	Myasthenia gravis	4	2 wk	none	CTR stop	5 wk	Resolved
2017	Doi ²⁰	91	F	Pulmonary edema, Pneumonia	Renal failure, hypertension, glomerulonephritis	2	10 d	Abdominal pain	ERBD	4 wk	ERBD
2017	Doi ²⁰	82	F	Acute enteritis	Dermatomyositis, interstitial pneumonitis, diabetes, chronic heart failure	2	5 d	Abdominal pain	EST ERBD,	Unknown	Died

(Continues)

TABLE 1 (Continued)

Year	Author	Age	Gender	Infection type	Underlying disease	Dose (g)	Duration	Abdominal symptom	Course	Time to disappearance	Outcome
2017	Abe ²¹	89	F	Pneumonia	End-stage renal disease	1	7 d	epigastralgia	Change to another antibiotic	Unknown	Died
2018	Nakagawa ²²	74	M	Bronchial pneumonia	Lung cancer	2	5 d	epigastralgia	ERCP	Unknown	ERCP
2018	Murata ²³	85	M	Acute enteritis	Lung cancer	-	8 d	hypochondralgia	Cholecystectomy	22 d	Cholecystectomy
2018	Ishikawa ²⁴	78	F	Ischemia colitis	Hypertension, chronic kidney disease, diabetes	-	8 d	none	CTRX stop	41 d	Disappearance
2018	Ishikawa ²⁴	84	M	Pneumonia	none	1	17 d	none	CTRX stop	Unknown	Unknown
2018	Our case	88	F	Urinary infection	Dementia, brain tumor (hemiplegia), bedridden state	2	14 d	none	Change to another antibiotic	34 d	Reduction

Abbreviations: CTRX, ceftriaxone; ERBD, endoscopic retrograde biliary drainage; ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy.

2 | CASE

An 88-year-old woman with a history of meningioma and dementia was admitted with high fever, appetite loss, nausea, and weight loss in July. Urinalysis showed increased white blood cells and presence of nitrite, and urinary tract infection was suspected. Computed tomography (CT) showed no significant findings (Figure 1A). Ceftriaxone was administered at 2 g/d, and urinary findings improved after 14 days. However, inappetence continued. We discussed with the patient and her family the possibility of providing nutrition by percutaneous endoscopic gastrostomy (PEG), and consent was provided. On hospital day 20, PEG was successfully implemented. We initiated tube feeding by PEG, and her condition remained stable. However, high fever developed on hospital day 28. Urinary tests showed normal results, but C-reactive protein was increased (5.8 mg/dL) in blood tests. CT identified a gallbladder stone (Figure 1B), but the patient reported no abdominal symptoms. We considered viral or bacterial infection as a potential cause of high fever. In terms of the gallbladder stone on CT, we considered the possibility of ceftriaxone-associated pseudolithiasis and changed pharmacotherapy to cefmetazole for the bacterial infection. Her general condition improved, and CT on hospital day 34 showed a reduction in the size of the gallbladder stone (Figure 1C). She was discharged on hospital day 47.

3 | DISCUSSION

This case suggests an important clinical issue. Ceftriaxone is a broad-spectrum, third-generation cephalosporin used to treat various infectious diseases. Ceftriaxone is 85%-95% bound to albumin in blood, with 60% excreted unchanged in urine and 40% in bile. As a result, ceftriaxone concentration in bile is 20 to 150 times that in serum.³ High-concentration ceftriaxone inhibits bile acid excretion, and calcium ions in bile are increased. Ceftriaxone shows high affinity to calcium ions and produces a biliary sludge comprising the calcium salt of ceftriaxone.³

The first issue to consider in association with this case is that asymptomatic gallbladder stones can form when using ceftriaxone. The incidence of pseudolithiasis has been reported as between 10.1% and 57.5%⁴⁻⁷, and symptoms occur in a minority of patients (0%-19%).^{4,8,9} Our patient also had no abdominal symptoms, with the gallbladder stone only found incidentally on CT. Thus, even though ceftriaxone-associated pseudolithiasis can occur, many patients may show no symptoms, so clinician should pay careful attention to this possibility when using ceftriaxone.

Second, patients who have a complicated background may be at greater risk of ceftriaxone-associated pseudolithiasis. Case reports from Japan of ceftriaxone-associated pseudolithiasis in adults are shown in Table 1.¹⁰⁻²⁴ These patients have shown various underlying conditions, and most patients have been elderly. The clinical course after the diagnosis of ceftriaxone-associated pseudolithiasis is usually good following conservative therapy. However, very elderly patients often have several underlying diseases and tend to be

dehydrated, increasing the susceptibility to ceftriaxone-associated pseudolithiasis, so careful treatment is needed. Japan has an aging society, and increasing use of ceftriaxone with the growing burden of infectious disease is expected. Patients with dementia, relative inactivity, dysfunction of the gastrointestinal tract, and a long-term bedridden state might be at greater risk of asymptomatic gallbladder stone formation when using ceftriaxone.

Third, the summer season might be a risk factor for ceftriaxone-associated pseudolithiasis. A past report²⁵ showed that high environmental temperatures may represent an important risk factor for pseudolithiasis in children. In Japan, high temperature is common throughout summer and may induce a loss of body fluids, promoting sludge formation. Closer attention to meteorological conditions may thus be warranted.

In conclusion, ceftriaxone-associated pseudolithiasis might arise in the absence of abdominal symptoms, and clinicians should take into account the patient background and season when determining the dose and duration of use for this agent.

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None.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article

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REFERENCES

- Schaad UB, Tschäppeler H, Lentze MJ. Transient formation of precipitations in the gallbladder associated with ceftriaxone therapy. *Pediatr Infect Dis*. 1986;5:708–10.
- Murata S, Aomatsu T, Yoden A, Tamai H. Fasting and bed rest, even for a relatively short period, are risk factors for ceftriaxone-associated pseudolithiasis. *Pediatr Int*. 2015;57:942–6.
- Park HZ, Lee SP, Schy AL. Ceftriaxone-associated gallbladder sludge. Identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. *Gastroenterology*. 1991;100:1665–70.
- Papadopoulou F, Efremidis S, Karyda S, et al. Incidence of ceftriaxone-associated gallbladder pseudolithiasis. *Acta Paediatr*. 1999;88:1352–5.
- Palanduz A, Yalçın I, Tonguç E, et al. Sonographic assessment of ceftriaxone-associated biliary pseudolithiasis in children. *J Clin Ultrasound*. 2000;28:166–8.
- Bor O, Dinleyici EC, Kebapci M, Aydogdu SD. Ceftriaxone-associated biliary sludge and pseudocholelithiasis during childhood: a prospective study. *Pediatr Int*. 2004;46:322–4.
- Ozturk A, Kaya M, Zeyrek D, Ozturk E, Kat N, Ziylan SZ. Ultrasonographic findings in ceftriaxone-associated biliary sludge and pseudolithiasis in children. *Acta Radiol*. 2005;46:112–6.
- Heim-Duthoy KL, Caperton EM, Pollock R, Matzke GR, Enthoven D, Peterson PK. Apparent biliary pseudolithiasis during ceftriaxone therapy. *Antimicrob Agents Chemother*. 1990;34:1146–9.
- Schaad UB, Suter S, Gianella-Borradori A, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *N Engl J Med*. 1990;322:141–7.
- Sasaki Y, Aoki S, Aoki K, et al. Acute pancreatitis associated with the administration of Ceftriaxone in an adult patient. *Nippon Shokakibyo Gakkai Zasshi*. 2009;106:569–75.
- Tsuzaki K, Sada R, Azuma T, Ishimaru H, Hatta K, Kohri Y. A case of ceftriaxone-induced cholecystolithiasis in a 24-year old male requiring laparoscopic cholecystectomy. *Tenri Med Bull*. 2009;12:75–81.
- Nakagawara H, Ogawa M, Nakagawara A, et al. A case of ceftriaxone-induced obstructive jaundice. *J Nihon Univ Med Ass*. 2012;71:436–40.
- Tomoda T, Ueki T, Saito S, et al. A case of ceftriaxone-associated pseudolithiasis in an adult patient that disappeared after the discontinuation of ceftriaxone. *Nippon Shokakibyo Gakkai Zasshi*. 2013;110:1481–6.
- Imoto A, Masuda D, Ogura T, Takii M, Umegaki E, Higuchi K. Two cases of ceftriaxone (CTRX)-induced cholecystolithiasis during therapy for bacterial meningitis in elderly adults. *JJBA*. 2013;27:835–41.
- Tanaka M, Yabuki T, Chishima S, et al. A case of ceftriaxone-associated gallbladder stone and cholangitis after the long-term discontinuation of ceftriaxone. *Prog Dig Endosc*. 2015;87:136–7.
- Shima A, Suehiro T, Takii M, Soeda H, Hirakawa M. Reversible Ceftriaxone-Induced Pseudolithiasis in an Adult Patient with Maintenance Hemodialysis. *Case Rep Nephrol Dial*. 2015;5:187–91.
- Dohmen K, Yamamoto A, Tanaka H, Haruno M, Shimoda S. An elderly case of ceftriaxone-associated pseudolithiasis that developed during therapy for acute pneumonia. *Kanzo*. 2016;57:106–12.
- Niwa M, Tochii K. Four cases of ceftriaxone-associated biliary pseudolithiasis. *Nippon Shokakibyo Gakkai Zasshi*. 2016;113:281–8.
- Tsukagoshi S, Ishizawa K, Hirayanagi K, et al. Progressive Pseudolithiasis Associated with the Intravenous Administration of Ceftriaxone in Patients with Central Nervous System Infections. *Intern Med*. 2017;56:3189–92.
- Doi Y, Takii Y, Ito H, et al. Usefulness of Endoscopic Managements in Patients with Ceftriaxone-Induced Pseudolithiasis Causing Biliary Obstruction. *Case Rep Med*. 2017;2017:3835825.
- Abe S. A case of ceftriaxone-associated biliary pseudolithiasis in an elderly patient with renal dysfunction. *IDCases*. 2017;9:62–4.
- Nakagawa N, Ochi N, Yamane H, et al. Ceftriaxone-associated pancreatitis captured on serial computed tomography scans. *Radiol Case Rep*. 2017;13:43–6.
- Murata T, Nishio K, Kitamura Y, Goto T, Sasaki K, Yano M. Laparoscopic cholecystectomy for biliary pseudolithiasis caused by ceftriaxone in an adult. *Nippon Shokakibyo Gakkai Zasshi*. 2018;79:1077–82.
- Ishikawa S, Komatsu Y. Two cases of ceftriaxone-associated biliary pseudolithiasis in adults. *Jpn J Chemother*. 2018;66:762–5.
- Araz N, Okan V, Demirci M, Araz M. Pseudolithiasis due to ceftriaxone treatment for meningitis in children: report of 8 cases. *Tohoku J Exp Med*. 2007;211:285–90.

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