Asymptomatic ceftriaxone-associated pseudolithiasis

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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.

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

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

(Continues)
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.

### 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. 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.

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%, and symptoms occur in a minority of patients (0%-19%). 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. 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 report\(^ {25}\) 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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CONFLICT OF INTEREST

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

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