Case Report

A case of ceftriaxone-associated biliary pseudolithiasis in an elderly patient with renal dysfunction

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ABSTRACT

Prior literature suggests that ceftriaxone causes formation of gallbladder stones at a relatively high frequency, and when abdominal symptoms occur, prompt investigation of the gallbladder is required with institution of appropriate treatment. Aging, malnutrition, renal impairment, and sepsis are risk factors for pseudolithiasis, and prevention of these is important to suppress gallstone development.

Introduction

As the number of patients with infectious diseases in the elderly increases, the long-term half-life and its excellent tissue transferability increases the frequency of use of ceftriaxone. It is commonly prescribed against various serious infections such as meningitis and bacteremia as well as lower respiratory tract, complicated urinary tract, skin, bone, and joint infections. During intravenous ceftriaxone treatment, 85%–95% of the drug would remain in the blood for a long time by binding to serum albumin. Approximately 55% of the drug is excreted by the kidneys, whereas the other 45% is excreted through the gall-bladder [1].

The incidence of ceftriaxone-induced biliary pseudolithiasis in children is relatively high, and it has been reported to be 10.1%–46.5% in previous studies [2,3]. Because the unusual occurrence of abdominal symptoms in patients with biliary pseudolithiasis is reportedly 0%–19% [4,5], our case was observed to have symptoms. It is thought that many patients are overlooked in actual clinical practice.

Case report

An 89-year-old woman had been seen at another clinic. She had a nonproductive cough and felt to have pneumonia. Her cardiac and renal function were deteriorating with a NT-pro-BNP 8537 pg/mL and creatinine 6.46 mg/dL. She was felt to be malnourished (serum albumin 2.2 g/dL). Abdominal computed tomography (CT) at the time of admission did not show gallbladder stones (Fig. 1A). Because signs of pneumonia were recognized in the chest X-ray image, the patient was started on ceftriaxone, 1 g per day (every 24 h) (in consideration of her renal function), from the day of hospitalization.

On day 7 of admission, tenderness in the right hypochondral region and epigastralgia were observed, and abdominal CT very clearly showed gallbladder stones (Fig. 1B). Ceftriaxone-induced biliary pseudolithiasis was diagnosed and the antibacterial agent was changed to sulbactam/cefoperazone mixture 1 g per day (every 24 h) from day 7 to day 15 of admission. Then, we changed to tazobactam/piperacillin 4.5 g (every 12 h) because pneumonia did not improve completely.

Abdominal CT performed on day 15 of admission showed that the concentration of gallbladder stones had decreased and that biliary pseudolithiasis had improved (Fig. 1C).

Diet steadily improved, although by day 18, she remained on a suboptimal diet. Maintenance infusion (normal saline) was continued, but the renal function remained severely impaired as detected by both blood urea nitrogen and serum creatinine levels. The pneumonia gradually worsened along with the respiratory condition. She continued to deteriorate and died on day 27 of admission.

Discussion

Bile acids and ceftriaxone may use the same transport pathway, so biliary secretion of ceftriaxone could inhibit bile acids secretion. Whereas ceftriaxone is 85 to 95% bound to albumin in blood, 45% of unchanged is excreted in bile, therefore, ceftriaxone concentration in bile is 20-to 150-fold that in the serum [6,7]. When the concentration of ceftriaxone within the gallbladder exceeds a threshold, it is known to precipitate by binding to calcium ions secreted with the bile acids. Because ceftriaxone, like bilirubin, can precipitate with calcium, ceftriaxone-associated biliary sludge is thought to be composed mainly of calcium-ceftriaxone complexes. Afterward, the precipitated sludge forms stones and may finally develop into ceftriaxone-induced biliary pseudolithiasis. Therefore, ceftriaxone-induced biliary sludge is not derived from cholesterol monohydrate crystals or calcium bilirubinate.
The formation of this calcium-ceftriaxone complex is detected by ultrasound studies in the form of a gallstone or biliary sludge[8]. Pseudobiliary stones are considered structurally unstable; therefore, they can easily be excreted with bile[9].

Onset of pseudobiliary stones varies from 2 to 22 days after starting treatment with ceftriaxone [2,4,10–12]. Kimura reported that stones appeared on day 30 after the end of 12 days of ceftriaxone administration [5]. Generally, spontaneous exclusion (or disappearance) of the stones occurs relatively quickly after stopping ceftriaxone administration, but the period varies from 2 days to 5 months after the

### Table 1
Reported cases of ceftriaxone-associated pseudolithiasis in adult.

| Year | Author    | Age | Sex | Infection Type | Dose          | Duration (days) | Complication   | Subsequent Management | Outcome | Time to Disappearance |
|------|-----------|-----|-----|----------------|---------------|-----------------|-----------------|----------------------|---------|-----------------------|
| 1    | Zinberg   | 73  | F   | Sepsis         | 2 g/day       | 19              | Cholecystitis   | CTRX stop           | Resolution | 28 days               |
| 2    | Kirejczyk | 19  | F   | Lyme disease   | 2 g q24hr     | 14              | Cholecystitis   | CTRX stop           | Resolution | 21 days               |
| 3    | Lorberboym| 54  | F   | Meningitis     | 2 g/day       | 42              | Cholecystitis   | CTRX stop           | Resolution | 14 days               |
| 4    | Fumellaro | 71  | F   | Radicular abscess | 2 g/day      | 10              | Cholecystitis/Cholecystectomy | Non-Resolution |                 |
| 5    | Bickford  | 53  | M   | Meningitis     | 2 g q12hr     | 7               | Obstructive jaundice | CTRX stop           | Resolution | 14 days               |
| 6    | Becker    | 55  | M   | Brain abscess  | 2 g q12hr     | ?               | Cholecystitis    | Cholecystectomy     | Resolution | ?                     |
| 7    | Rienstra  | 64  | M   | Aortitis       | 2 g q12hr     | 21              | Obstructive jaundice | Reduction of CTRX | Resolution | ?                     |
| 8    | Sasaki    | 35  | F   | Colon diverticulitis | 2 g q24hr | 12              | Pancreatitis    | CTRX stop           | Resolution | 2 months              |
| 9    | Sasaki    | 35  | F   | Colon diverticulitis | 2 g q24hr | 46              | Cholecystitis    | Cholecystectomy     | Non-Resolution | ?                     |
| 10   | Tsuzaki   | 24  | M   | Endocarditis   | 2 g q12hr     | 7               | Obstructive jaundice | CTRX stop           | Resolution | 12 days               |
| 11   | Rivera    | 49  | M   | Gastroenteritis | 1 g q24hr     | 4               | Obstructive jaundice | CTRX stop           | Resolution | 1 month               |
| 12   | Choi      | 21  | M   | Colon diverticulitis | 2 g q24hr | 5               | None            | CTRX stop           | Resolution | 1 month               |
| 13   | Choi      | 22  | M   | Meningitis     | 2 g q24hr     | 12              | None            | CTRX stop           | Resolution | 1 month               |
| 14   | Nakagawara| 65  | M   | Enteritis      | 2 g/day       | 7               | Cholecystitis    | Drainage            | Resolution | 14 days               |
| 15   | Hanata    | 49  | F   | Pneumonia      | 4 g/day       | 28              | Cholecystitis    | CTRX stop           | Resolution | 19 days               |
| 16   | Tomoda    | 47  | F   | Colon diverticulitis | 2 g q24hr | 8               | Cholecystitis    | CTRX stop           | Resolution | 6 days                |
| 17   | Imoto     | 66  | M   | Meningitis     | 4 g/day       | 22              | CBD stone       | Drainage            | Resolution | 21 days               |
| 18   | Imoto     | 67  | M   | Meningitis     | 4 g/day       | 23              | Cholecystitis    | CTRX stop           | Resolution | 42 days               |
| 19   | Tanahashi | 54  | F   | Colon diverticulitis | 2 g/day   | 7               | Cholecystitis/Cholangitis | Drainage            | Resolution | 33 days               |
| 20   | Tanaka    | 83  | F   | Renal abscess  | 2 g q12hr     | 36              | Cholecystitis    | Cholecystectomy     | Resolution | ?                     |
| 21   | Okazaki   | 19  | F   | Urinary tract infection | 2 g/day | 7               | Cholangitis     | CTRX stop           | Resolution | 12 months              |
| 22   | Shima     | 79  | F   | Bronchial pneumonia | 1 g q48hr | 13              | Cholecystitis    | CTRX stop           | Resolution | 48 days               |
| 23   | Niwa      | 23  | M   | Colon diverticulitis | 2 g/day   | 6               | Cholecystitis    | CTRX stop           | Resolution | 1 month               |
| 24   | Niwa      | 26  | F   | Subcutaneous abscess | 2 g/day  | 8               | Cholecystitis    | CTRX stop           | Resolution | 17 days               |
| 25   | Niwa      | 63  | M   | Hepatic abscess | 3–4 g/day     | 20              | Cholecystitis    | CTRX stop           | Resolution | 2 months               |
| 26   | Niwa      | 93  | M   | Pneumonia      | 2 g/day       | 7               | Cholecystitis    | CTRX stop           | Resolution | ?                     |
| 27   | Dohmen    | 76  | M   | Pneumonia      | 1 g q12hr     | 8               | Cholecystitis    | CTRX stop           | Resolution | 22 days               |

*Abbreviations: CBD: common bile duct, CTRX: ceftriaxone.*
discontinuation of ceftriaxone administration [3–5,8,10,12,13]. In an in vitro study, at doses of ceftriaxone greater than or equal to 2 g, precipitation of ceftriaxone could occur, and the development of ceftriaxone-induced biliary sludge could be because of poor solubility that occurs in patients receiving a high-dose treatment (greater than or equal to 2 g) [6].

Cases of ceftriaxone-associated biliary pseudolithiasis in adults worldwide are reported in Table 1. Since it is anticipated that the incidence of pseudolithiasis increases in more elderly with low activity and high risks of dehydration, careful observation for early detection such as cholecystitis and pancreatitis is necessary in patients receiving ceftriaxone. Table 1 shows that many complications such as cholecystitis and pancreatitis occurred, and ceftriaxone-associated biliary pseudolithiasis disappeared within approximately two months after stopping its administration. Because discontinuation of ceftriaxone almost eliminates gallstones, considering biliary pseudolithiasis may lead to the avoidance of excessive additional examinations and invasive treatments such as cholecystectomy. Prevention of biliary pseudolithiasis requires shortening the duration of administration and invasive treatments such as cholecystectomy. Prevention of biliary pseudolithiasis requires shortening the duration of administration of ceftriaxone, sufficient maintenance infusion for prevention of dehydration, and avoiding excessive rest. It is believed that ceftriaxone causes the formation of gallbladder stones at a relatively high frequency, and when abdominal symptoms occur, it is necessary to promptly scrutinize the gallbladder and start appropriate treatment. It is reasonable to follow the progress by ultrasound or CT for two months after the administration of ceftriaxone.

Ceftriaxone is a parenteral cephalosporin with a broad-spectrum activity against gram-positive and gram-negative bacteria [1]. The drug has enhanced stability against various β-lactamase-producing bacteria [4], and a reportedly prolonged elimination half-life of 6 to 9 h. On the other hand, because the mean half-life during dialysis is 16 h, it has been reported that ceftriaxone is hardly removed during dialysis [14]. When ceftriaxone is administered to patients with renal insufficiency or on dialysis, it is necessary to adjust the dosage of ceftriaxone, keeping in mind that high concentrations of ceftriaxone in blood and bile may cause biliary pseudolithiasis. It is necessary to start treatment early and it is necessary to adjust medical treatment for the pseudolithiasis cases with renal failure. Even when ceftriaxone administration was discontinued in our case, the gallbladder stone did not completely disappear because of renal function deterioration. When ceftriaxone is administered to patients with renal insufficiency or dialysis, it is necessary to adjust the dose while keeping in mind that rising blood and bile concentrations may cause pseudolithiasis.

After initiation of ceftriaxone treatment, biliary pseudolithiasis was noted at a significantly greater frequency in the fasting and bed rest groups. Rapid decrease in oral intake, leading to long-term fasting and weight loss, is a typical risk factor for biliary pseudolithiasis [11]. Since malnutrition, renal impairment, and sepsis due to pneumonia are risk factors for pseudolithiasis, prevention of these is important to suppress gallstone development. During ceftriaxone treatment, attention should be paid to the required oral intake and level of bed rest following the start of therapy, depending on the disease pathology.

Conflict of interest

The author declares that he has no conflicts of interest (COI).

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