Journal of Rural Medicine

Case report

Ceftriaxone pseudolithiasis detected by computed tomography and followed up until resolution

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Abstract

Introduction: Ceftriaxone is a third-generation cephalosporin antibiotic that has been widely used to treat various infectious diseases. We report a case of ceftriaxone pseudolithiasis that was detected by computed tomography (CT) and followed up until it was resolved.

Case: A 76-year-old woman with diabetes mellitus and renal impairment, but no history of gallstones, was diagnosed with septic shock due to renal and lung abscesses and treated with ceftriaxone. On day 22 after admission, abdominal CT revealed a gallstone, which increased in size up to day 50. Ceftriaxone was stopped on day 50, and the gallstone resolved completely after 10 weeks.

Conclusion: Ceftriaxone pseudolithiasis should be cautiously considered, specifically in a patient with renal impairment and a prolonged treatment period.

Key words: ceftriaxone, pseudolithiasis, gallstone

(J Rural Med 2020; 15(4): 230–233)

Introduction

Ceftriaxone, a third-generation cephalosporin antibiotic, is widely used for infectious diseases, such as community-acquired pneumonia, urinary tract infection, infectious endocarditis, cholecystitis, and meningitis, because it can penetrate tissues[1]. Previous studies showed that ceftriaxone can cause cholelithiasis[2]. This mainly occurs in children[3], but more adult cases have been reported recently[4]. The incidence of cholelithiasis varies from 2.6% to 25%[5–7]. It has been reported that, in most cases, the gallstone of ceftriaxone pseudolithiasis is resolved only by immediate cessation of ceftriaxone[1, 5, 7, 8]. However, to the best of our knowledge, studies assessing the images of the formation and dissolution of gallstones in chronological order have not been conducted yet. We report a case of an adult woman with reversible ceftriaxone-induced pseudolithiasis, which we could track by computed tomography (CT) imaging for the entire clinical course until the stone was completely resolved.

Received: April 27, 2020
Accepted: June 11, 2020
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Case Description

A 76-year-old woman presented to a local clinic 4 hours after the onset of fever with a 4-day history of lower back pain, anorexia, and nocturia. She was transferred to our hospital due to low blood pressure and elevated inflammatory markers, but her consciousness was not altered. She had a history of diabetes mellitus, hypertension, and dyslipidemia, but she had no history of kidney or liver impairment. She was taking amlodipine, metformin, sitagliptin, glimepiride, pravastatin, mirabegron, senna, and kallidinogenase. She had no family or personal history of gallstones. When examined in our hospital, she was afebrile, and her blood pressure, pulse, and respiratory rate were 109/66 mmHg, 104/min, and 23/min with an oxygen saturation of 99% on 3 L of oxygen via nasal cannula, respectively. We detected coarse crackles in both lungs and tenderness at the lumbar spine at the L4–L5 level. Other physical findings were unremarkable.

On admission, initial investigations showed normocytic anemia and increased white blood cells (hemoglobin, 11.5 g/L; mean cell volume, 86.3 fL; white cell count, 9.3 × 10^9/L). The patient's C-reactive protein level was 29.63 mg/

dL. Renal function tests (blood urea nitrogen, 63 mg/dL; creatinine, 1.26 mg/dL) showed deteriorated kidney function. Chest and abdominal CT revealed right renal abscesses and multiple lung abscesses. We diagnosed septic shock due to renal and lung abscesses. Treatment was initiated with piperacillin/tazobactam 4.5 g per day. Because *Klebsiella pneumoniae* was detected in the blood culture collected at admission, treatment was de-escalated to ceftriaxone 2 g per day (1 g/dose every 12 hours) on day 3 after admission. On day 11 after admission, abdominal echo showed no abnormalities. However, an abdominal CT revealed a small, high-density area on the neck of the gallbladder on day 22 after admission (Figure 1). On days 35 and 50, the high-density area was enlarged and was recognized as biliary sludge or a gallstone. The gallstone also impacted a common bile duct, but the patient did not complain of any abdominal symptoms, and there were no remarkable changes in laboratory findings (Figure 2).

The patient was diagnosed with ceftriaxone pseudolithiasis, and her treatment regimen was changed from ceftriaxone to the internal use of cefalexin without using ursodeoxycholic acid or any drug. We performed an endoscopic sphincterotomy and placed a stent in the common bile duct because of the risk that the stone or debris would drop into the common bile duct and obstruct it completely. The abscesses were not resolved completely, but they decreased in size. We switched treatment to oral antibiotics, and the patient was discharged on day 71 after admission. We fol-

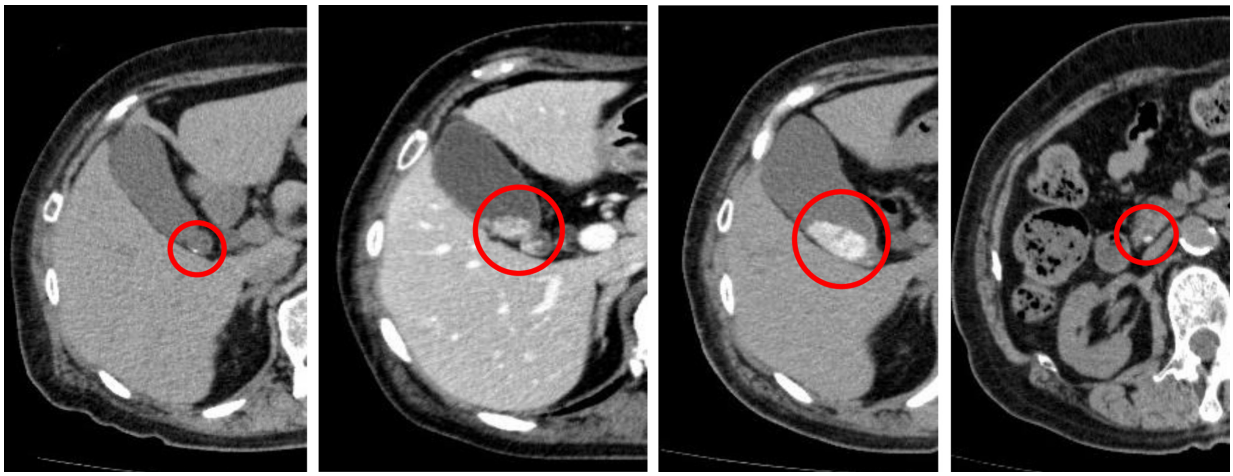

Figure 1 On day 22 after admission, an abdominal computed tomography revealed a small, high-density area on the neck of the gallbladder. On days 35 and 50, the high-density area was enlarged and was recognized as biliary sludge or a gallstone. The gallstone also impacted a common bile duct.

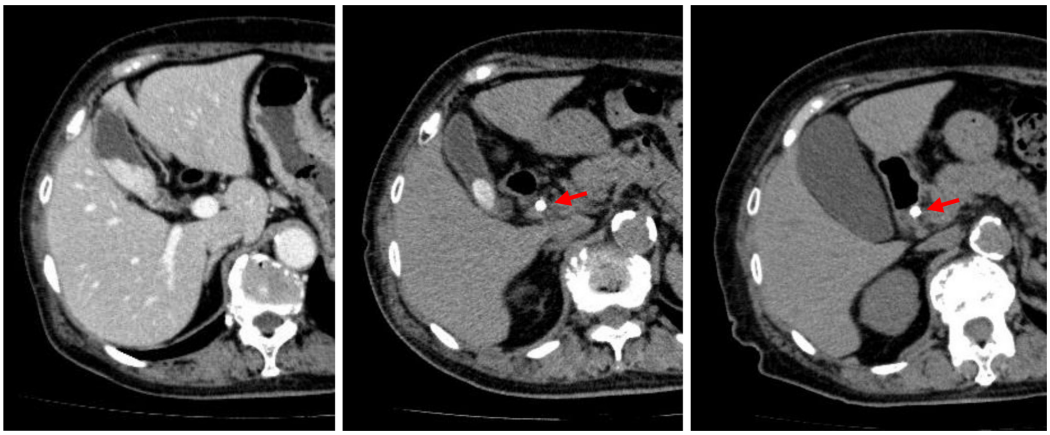

Figure 2 We diagnosed ceftriaxone pseudolithiasis and stopped ceftriaxone on day 50. The patient was discharged on day 71 after admission. We followed up the abscesses and the gallstone by abdominal computed tomography. The gallstone was still in the gallbladder body 5 weeks after cessation of ceftriaxone and completely resolved 10 weeks after cessation of ceftriaxone. A plastic stent was placed in the bile duct for choledocholithiasis (arrow).

lowed up the abscesses and the gallstone by abdominal CT. The gallstone was still in the gallbladder body 5 weeks after cessation of ceftriaxone and completely resolved 10 weeks after cessation of ceftriaxone.

Discussion

Gallstone induced by treatment with ceftriaxone was first reported by Schaad in 1986[1] and was named "ceftriaxone pseudolithiasis" because the gallstone formed but dissolved spontaneously after stopping ceftriaxone treatment. The incidence rate of ceftriaxone pseudolithiasis in children is up to 46.5%[9], but its incidence rate in adults has not been well studied. A study in Iran reported that 8.8% of adult patients developed gallstones after ceftriaxone treatment[7], and a study in Japan reported that only 2.6% of adult patients had biliary complications after ceftriaxone treatment[6]. However, these rates may be underestimated because the patients in both studies were asymptomatic, and we do not routinely monitor for cholelithiasis because it is reversible in most cases. Although there are few reports of cholelithiasis requiring surgical or endoscopic intervention, it may be advisable to pay attention to the adverse effect of ceftriaxone.

Ceftriaxone's concentration is 20 times higher in the bile than in the plasma and is dose dependent[10, 11]. Supersaturation of ceftriaxone induces the passive entry of calcium ions (Ca^{2+}) into the bile[11]. The gallstone formation mechanism has been explained by the supersaturated ceftriaxone salt in bile binding with Ca^{2+} to form calcium-ceftriaxone salt. According to previous studies in children, fasting, bed rest, high-dose treatment, long treatment duration, and rapid bolus injection are considered risk factors of pseudolithiasis[4, 6, 7, 12]. It may be reasonable that high-dose treatment, long treatment duration, and rapid injection can cause ceftriaxone supersaturation in the bile. Since ceftriaxone's pharmacokinetics should be similar in adults and children, these risk factors should be common to adults and children. The possible reason why ceftriaxone pseudolithiasis has been reported more frequently in children compared to adults is as follows: the dose in children with severe infections is usually higher than that in adults when the dosage unit is converted into milligrams per kilogram of body weight. Fasting and bed rest inhibit gallbladder contraction, which delays bile clearance and calcium-ceftriaxone salt precipitation, leading to pseudolithiasis. Theoretically, this should be true for adults as well. A study has indicated that ceftriaxone itself may inhibit gallbladder contraction[13]. In adults, a few studies have indicated that high-dose treatment (60 g), long treatment duration (19 days), female sex, renal dysfunction (estimated glomerular filtration rate [eGFR] < 60 mL/min), and possibly older age may be associated with ceftriaxone pseudolithiasis[5–7]. However, studies assessing the number of ceftriaxone dose or single dose have not been conducted yet. According to the manufacturer's label and previous studies, there is no need for dosage adjustment in patients with renal impairment. This may make ceftriaxone more likely to be administered as a first-choice antibiotic agent. However, careful attention should be paid when determining the indication for ceftriaxone treatment because renal impairment may be related to ceftriaxone-induced pseudolithiasis in adults. We may also need to pay extra attention to patients who are undergoing hemodialysis because ceftriaxone is not eliminated by hemodialysis, and the regular dose is far higher than the concentration needed to treat infectious diseases. The average steady-state concentration of ceftriaxone in patients with renal failure is similar to that in healthy subjects, although the plasma clearance of ceftriaxone is longer in patients with renal failure than that in patients without renal failure[14]. If the concentration is far above the treatment requirement, we may need to consider dose adjustment, specifically in patients undergoing hemodialysis, to avoid ceftriaxone supersaturation in the bile.

In the present case, the possible risk factors for ceftriaxone pseudolithiasis included eGFR at 32 mL/min during admission, female sex, having fasted for 2 days, and having been bedridden for 5 days. The eGFR was less than 60 mL/min until day 7 after admission. Based on previous studies, formation of biliary sludge or a gallstone should have been expected in advance. Although the patient was asymptomatic and appeared to not require further treatment, we mistakenly only focused on kidney abscesses and noticed the gallstone 30 days later, when the high-density area was shown in the gallbladder. The dissolution of stone required a period of 70 days in this case. There were almost no reports and various reports about the dissolution. It was important to perform periodical image inspections such as abdominal CT or ultrasound for evaluation.

Because ceftriaxone has a long half-life and a broad spectrum of coverage against Gram-positive and Gram-negative bacteria, it is convenient not only for inpatients but also for outpatients and those receiving at-home care. We should consider the use of ceftriaxone carefully, specifically when the patient is bedridden or has renal impairment or the expected treatment period is long. If we decide to use ceftriaxone, pseudolithiasis should be cautiously considered, and some types of screening, such as abdominal ultrasound, may be indicated.

Conflict of interest: In connection with this presentation, there is no conflict of interest to be disclosed with any companies.

Case description: We have given a sufficient explanation of the patient's presentation for this journal publish and have given their consent and permission.

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