Ceftriaxone-associated pancreatitis captured on serial computed tomography scans

Nozomu Nakagawa MD a, Nobuaki Ochi MD, PhD a, Hiromichi Yamane MD, PhD a, Yoshihiro Honda MD, PhD a, Yasunari Nagasaki MD a, Noriyo Urata MD b, Hidekazu Nakanishi MD, PhD a, Hirofumi Kawamoto MD, PhD b, Nagio Takigawa MD, PhD a, *

a Department of General Internal Medicine 4, Kawasaki Medical School, 2-6-1, Nakasange, Kita-ku, Okayama 700-8505, Japan
b Department of General Internal Medicine 2, Kawasaki Medical School, Okayama, Japan

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ABSTRACT
A 74-year-old man was treated with ceftriaxone for 5 days and subsequently experienced epigastric pain. Computed tomography (CT) was performed 7 and 3 days before epigastralgia. Although the first CT image revealed no radiographic signs in his biliary system, the second CT image revealed dense radiopaque material in the gallbladder lumen. The third CT image, taken at symptom onset, showed high density in the common bile duct and enlargement of the pancreatic head. This is a very rare case of pseudolithiasis involving the common bile duct, as captured on a series of CT images.

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Introduction
Ceftriaxone, a semisynthetic third-generation cephalosporin, is associated with biliary sludge formation [1]. It forms a precipitate after excretion and concentration in bile in the gallbladder, the major constituent of which is a ceftriaxone-calcium salt [2]. Ceftriaxone use is considered to be a risk factor for cholelithiasis in children [3]; however, symptomatic cholelithiasis in adults has seldom been reported [4]. Here, we describe computed tomography (CT) images obtained 7 and 3 days before, and at the onset of, ceftriaxone-associated pseudolithiasis with acute pancreatitis.

Competing Interests: The authors have declared that no competing interests exist.
Our institution of the review committee/ethics committee exempts its review in case of a case report. Informed consent was obtained from his daughter because the patient was deceased.

* Corresponding author.
E-mail address: ntakigaw@gmail.com (N. Takigawa).
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A 74-year-old man with advanced squamous cell lung cancer underwent endobronchial stent placement for tracheobronchial stenosis because of tumor enlargement. Laser ablation was performed because tumor progression into the bronchial stent led to further tracheobronchial stenosis. The patient received ceftriaxone (2 g/day, 5 days) for bronchial pneumonia after laser ablation. On the day when ceftriaxone was stopped, he was transferred to our hospital and he developed severe epigastric pain. More specifically, he had upper abdominal pain 5 days after ceftriaxone initiation. Laboratory data were listed in Table 1. The patient developed mild leukocytosis and liver, pancreatic, and renal dysfunction. Abdominal CT showed high density in the gallbladder and the lower common bile duct, and the pancreatic head was enlarged with peripancreatic inflammation.

We retrospectively evaluated previous chest CT images obtained to evaluate lung cancer and pneumonia 7 and 3 days before the onset of epigastralgia, at which time the patient’s upper abdominal region was scanned accidentally. The first CT image before ceftriaxone initiation revealed no radiographic findings in the biliary system (Figs. 2A and B). The second CT image, taken 3 days after initiation of ceftriaxone, revealed dense radiopaque material in the gallbladder lumen (Figs. 2C and D). The patient developed pancreatitis 5 days after initiation of ceftriaxone.

**Table 1 – Laboratory data on admission to our hospital.**

| Parameter | Value (normal range) |
|-----------|----------------------|
| WBC (/µL) | 10,850 (3,500-9,500) |
| RBC (10^6/µL) | 439 (410-540) |
| HB (g/dL) | 11.2 (13.0-16.5) |
| Hct (%) | 35.9 (39.0-48.0) |
| PLT (10^9/µL) | 33.8 (15.0-35.0) |
| TP (g/dL) | 6.5 (6.5-8.0) |
| ALB (g/dL) | 3.5 (3.8-4.9) |
| T-Bil (mg/dL) | 0.9 (0.3-1.2) |
| AST (U/L) | 241 (7-42) |
| ALT (U/L) | 83 (10-35) |
| ALP (U/L) | 1333 (110-360) |
| γGTP (U/L) | 437 (5-60) |
| LDH (U/L) | 494 (120-240) |
| AMY (U/L) | 1818 (42-118) |
| BUN (mg/dL) | 17 (8-22) |
| CRE (mg/dL) | 1.25 (0.6-1.1) |
| Na (mEq/L) | 141 (137-146) |
| K (mEq/L) | 3.5 (3.6-5.0) |
| Cl (mEq/L) | 97 (101-110) |
| Ca (mg/dL) | 8.9 (8.4-10.2) |
| CRP (mg/dL) | 7.25 (<0.3) |
| D-dimer (µg/mL) | 8.60 (<1.0) |

Abbreviations: WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; Hct, hematocrit; PLT, platelet cell; TP, total protein; ALB, albumin; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; AMY, amylase; BUN, blood urea nitrogen; CRE, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; CRP, C-reactive protein.

**Discussion**

Transient formation of precipitates in the gallbladder associated with ceftriaxone use was first reported in 1986 [5]. Although it is difficult to differentiate the ceftriaxone-associated sludge from the usual gallbladder sludge on ultrasonographic or CT images, the pseudolithiasis can rapidly disappear after discontinuation of ceftriaxone [4]. It is important to suspect the pseudolithiasis when a patient treated with ceftriaxone complains about abdominal pain. Although the sludge could be resolved after interruption of ceftriaxone in most cases, cholecystectomy [3,6] and endoscopic retrograde biliary drainage as the present case might be necessary.

Ceftriaxone-associated cholelithiasis is frequently observed in children [3,7]. An association between ceftriaxone treatment and the development of cholelithiasis on ultrasound examination in adults has also been reported [8]. A double-blind, controlled study evaluated the serial gallbladder sonograms of 44 adult patients who received ceftriaxone at 2 g or a placebo daily for 14 days. Ultrasound examinations of the gallbladder were performed on days 1 and 14 [8]. Six (32, 37, 39, 54, 56, and 64 years old) of 28 ceftriaxone-treated patients (21.4%) and 1 (42 years old) of 8 patients (12.5%) who received the placebo demonstrated abnormal gallbladder sonograms on day 14. In addition, a 71-year-old woman experienced acute cholecystitis and pancreatitis after 10 days of treatment with ceftriaxone (2 g/day) [6]. However, ceftriaxone-associated pseudolithiasis with pancreatitis captured on a series of CT images has not been previously reported except 1 Japanese case report [9] to the best of our knowledge. In the case reported herein, biliary sludge leaked from the gallbladder into the CBD, causing pancreatitis by flowing into the pancreatic duct in a retrograde manner.
In this case, there were no specific CT signs in the biliary tract system 7 days before the epigastric pain developed. A high-density lesion was seen in the gallbladder on the CT image 3 days before the onset of epigastralgia, and a high-density area was seen in the CBD after symptom onset. After endoscopic retrograde cholangiopancreatography, biliary drainage was performed successfully. If ceftriaxone had been stopped when the high-density area in the gallbladder (Fig. 2C) was noticed, pancreatitis might not have developed. Why did this patient have ceftriaxone-associated pseudolithiasis? Because ceftriaxone harbors high calcium-binding affinity and the solubility of calcium-ceftriaxone is low, the bound substance tends to be retained in bile [1]. Thus, the biliary sludge, whose major constituent was a ceftriaxone-calcium salt, was developed [2]. Children are at risk of pseudolithiasis after even short periods of fasting and bed rest [7]. Because he underwent endobronchial stent placement and laser ablation for progressive lung cancer, the patient’s oral intake had been decreased and he was on bed rest. Although poor oral intake and bed rest are insufficient evidence in the elderly, they might be related with the development of pseudolithiasis. In addition, mild hypoalbuminemia (3.5 g/dL) and renal damage (serum creatinine level, 1.25 mg/dL) might contribute to the occurrence of pseudolithiasis because ~90% of ceftriaxone binds to serum albumin and ~55% of the drug is excreted by the kidneys [10].

The serial CT images obtained from this patient demonstrated that biliary sludge formation secondary to ceftriaxone use can develop rapidly, 3 days after initiation of ceftriaxone, and physicians should be aware of the associated risk of pancreatitis.

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