

Rapid Onset of Ceftriaxone-Induced Cholelithiasis in an Adult Patient

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Abstract

Ceftriaxone is a third-generation cephalosporin with broad-spectrum antibacterial activity. Here, we report a case of ceftriaxone-induced cholelithiasis in an adult patient after a short period of administering ceftriaxone. A 57-year-old female was admitted to our hospital for meningitis and treated empirically with ceftriaxone 2 g every 12 hours. Other medications given included vancomycin, ampicillin and acyclovir. Based on culture results and a sensitivity report, ceftriaxone was continued while other medications were discontinued on day three after admission. Her liver function test (LFT) demonstrated an elevation in hepatic transaminases, and alanine and aspartate transaminases peaked on the fifth day (339 and 153 IU/L, respectively). Computed tomography (CT) and ultrasound (US) confirmed the presence of uncomplicated cholelithiasis. Ceftriaxone was discontinued and switched to cefotaxime 2 g every four hours. Hepatic transaminases started declining after ceftriaxone discontinuation and dropped to normal levels on day nine. After the administration of cefotaxime on the 25th day, repeated US imaging revealed the persistence of biliary sludge. The patient was discharged in a good and stable clinical condition with follow-up planned at the outpatient clinic. When the concentration of ceftriaxone in the gallbladder exceeds the solubility of its calcium salt, precipitation occurs, forming a biliary sludge. Using the Naranjo Probability scale, the score was found to be 4, indicating a possible relationship between ceftriaxone and cholelithiasis. Multiple case reports of ceftriaxone-induced cholelithiasis have been documented previously, most of which focused on children or on the prolonged use of ceftriaxone. However, our case report highlights the development of cholelithiasis in adults after administering ceftriaxone for a short time.

Keywords: Ceftriaxone, cholelithiasis, liver enzymes

INTRODUCTION

Ceftriaxone is a third-generation cephalosporin antibiotic; it has a broad spectrum of antibacterial activity, including both Gram-positive and Gram-negative bacteria.^[1] It is indicated for the treatment of various infections, including bacterial meningitis, where ceftriaxone is considered one of the drugs of choice when treating empirically.^[2,3] Biliary and hepatic adverse effects associated with ceftriaxone have been reported. These adverse effects include gallbladder pseudolithiasis, elevated hepatic function enzymes, and hepatic toxicity.^[4] Biliary pseudolithiasis is an uncommon but known adverse effect secondary to treatment with ceftriaxone, which has been cited in the literature with incidences of up to 40%.^[5,6]

It is important to note that the literature interchanges the terms ceftriaxone-associated cholelithiasis and ceftriaxone-associated biliary pseudolithiasis.

Here, we report a case of ceftriaxone-induced biliary cholelithiasis, with an elevation in hepatic enzymes, in an adult patient after five days of therapy with ceftriaxone.

CASE REPORT

A 57-year-old female admitted to hospital with a history of fever and headache for 5 days. She presented with a progressively worsening headache, photophobia, and vomiting. The patient was alert but slightly disoriented. Physical examination revealed neck rigidity and tenderness

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in the left leg. The past medical history was significant for hypertension and anxiety. Current medications included: hydrochlorothiazide 12.5 mg PO daily, atenolol 100 mg PO daily, and oxazepam 15 mg PO at bedtime as needed.

A work-up and empiric treatments for suspected meningitis were initiated and included acyclovir 800 mg intravenous (IV) every 8 h, ceftriaxone 2 g IV every 12 h, ampicillin 2 g IV every 4 h, vancomycin 1600 mg IV every 8 h. The following medications were also given: hydrochlorothiazide 25 mg PO Daily, dexamethasone 12 mg IV every 6 h, ibuprofen 400 mg PO every 4-6 h prn, metoclopramide 10 mg IV every 6 h prn, and morphine 3 mg SC every 4 h prn.

During the patient’s stay in hospital, their laboratories were monitored closely. On hospital day 2, liver function tests (LFTs), including alanine transferase (ALT), aspartate transferase (AST), and total bilirubin were normal. From hospital day 2 to day 4, LFTs demonstrated a progressive elevation in hepatic transaminases. Table 1 shows the ALT and AST trends over the patient’s stay in hospital.

Hospital day 3, the cerebrospinal fluid (CSF) microscopy showed protein of 2 mmol/L, leukocytes of 3112.8×10^6 cells/L, and glucose of more than 3 mmol/L, indicating a bacterial infection. Based on these CSF results, acyclovir was discontinued.

On hospital day 4, culture and sensitivity of the CSF identified *Streptococcus viridians*, which showed susceptibility to ceftriaxone. Due to the results of the culture and sensitivity, ceftriaxone was continued while ampicillin and vancomycin were discontinued.

On day 5, ALT and AST peaked at 339 and 153 IU/L, respectively. In addition, ultrasonography showed the patient’s gallbladder was contracted and there was evidence of uncomplicated cholelithiasis. Subsequently, an abdominal ultrasound was performed and confirmed the presence of uncomplicated cholelithiasis [Figure 1]. The patient did not report any symptoms associated with cholelithiasis. The decision was made to discontinue ceftriaxone and switch to cefotaxime 2 g every 4 h, due to the known but uncommon risk of cholelithiasis with ceftriaxone.



Figure 1: Abdominal ultrasound showing uncomplicated cholelithiasis

From Day 6 to Day 10, hepatic transaminases started to decline after the ceftriaxone was discontinued, and subsequently dropped to normal levels by day 10.

On Day 25, repeated ultrasound revealed persistence of biliary sludge [Figure 2]. The patient was discharged in a stable clinical condition with follow-up planned on an outpatient basis.

Using the Naranjo Probability scales, the score was found to be 4, indicating a possible relationship between ceftriaxone and cholelithiasis.

DISCUSSION

Approximately 60% of ceftriaxone is eliminated unchanged in the urine, while the remaining is excreted through the biliary route.^[7] When the concentration of ceftriaxone in the gallbladder exceeds the solubility of its calcium salt, precipitation occurs, forming a biliary sludge.^[8] It was reported that the incidence of cholelithiasis ranges from 25% to 46%.^[9]

Most of the literature showed that cholelithiasis developed more often with prolonged use of ceftriaxone.^[10,11] Our case showed the development of cholelithiasis after only 5 days of therapy with ceftriaxone. Similarly, Biner *et al.* found that cholelithiasis developed in 27 of 156 children (17%) within 3–7 days.^[12] Abe and Choi *et al.* reported the development of cholelithiasis in adult patients after 5 and 7 days, respectively.^[13,14] Alehossein *et al.* reported a case series of 14 children in which the onset of the development of cholelithiasis ranged from 2 to 25 days.^[15]

Most of the case reports of ceftriaxone-induced cholelithiasis documented in the literature are among the pediatric

Table 1: Hepatic Transaminases course during hospital stay

Hepatic Transaminases	Day										
	1	2	3	4	5	6	7	8	9	10	15
AST	-	53	79	116	153	69	37	20	15	15	20
ALT	-	67	139	227	339	274	217	149	99	73	39

ALT: Alanine transferase, AST: Aspartate transferase



Figure 2: Abdominal ultrasound showing persistence of biliary sludge

population.^[15-19] Despite this, as seen in our case, the risk of developing cholelithiasis is still a concern in the patient population. The risk of ceftriaxone-induced cholelithiasis among adults has been reported in the literature. A Medline literature review by Du *et al.* from 1988 to 2017 found 12 case reports of ceftriaxone-induced cholelithiasis; of those, 6 out of 12 (50%) were adults.^[20] Another recent literature review done by Shuichi *et al.* reported 27 cases of ceftriaxone-induced cholelithiasis among adults from 1991 to 2016.^[14]

Although acyclovir is also associated with elevated liver enzymes, in our case, transaminase levels continued to increase after discontinuing acyclovir. The transaminase levels only started to decline after the ceftriaxone was discontinued. This timeline of events helps to exclude the possibility of acyclovir causing the hepatic injury.

On day 25, and just before the patient was set to be discharged, the biliary sludge was still present, which is a common finding in such cases. The literature showed that the time for cholelithiasis to dissolve and disappear ranges anywhere from 15 days to 5 months.^[14] In some cases, the sludge can persist longer and requires surgical intervention.^[9] Therefore, our patient was referred to an outpatient clinic for follow-up after discharge from the hospital. One of the major concerns regarding ceftriaxone-induced cholelithiasis is that it may progress to cholecystitis.^[21] In our case, this, fortunately, did not happen.

Baseline imaging studies to rule out cholelithiasis were not done to rule out the presence of cholelithiasis before initiating ceftriaxone. The literature has shown that the formation of biliary sludge can develop in a short time after starting ceftriaxone.^[15]

Risk factors associated with ceftriaxone-induced cholelithiasis include high dose or prolonged use of ceftriaxone, dehydration, renal impairment, the elderly population, and those with sepsis.^[6,13] Our patient did not have any of the above-mentioned risk factors, except high-dose ceftriaxone. The absence of such risk factors does not, however, preclude the formation of cholelithiasis.

This confirms the importance of monitoring liver enzymes during moderate-to-high dose ceftriaxone therapy. A study done by Rivkin showed the elevation of hepatic enzymes without the development of cholelithiasis in those treated with ceftriaxone. In that study, the liver enzymes started to decrease after the ceftriaxone was discontinued.^[22] Therefore, with all patients receiving moderate-to-high dose ceftriaxone, monitoring liver enzymes for the risk of both cholelithiasis and liver toxicity is important during the duration of therapy.

As an alternative option for patients at high risk of developing ceftriaxone-induced cholelithiasis, cefotaxime has a lower incidence of inducing nephrolithiasis as shown by a prospective study by Ustyol *et al.* This study demonstrated a smaller number of nephrolithiasis induced by cefotaxime compared to ceftriaxone.^[23] Our case report supports this recommendation

to use cefotaxime in patients at higher risk of developing cholelithiasis, as her hepatic enzymes declined after switching from ceftriaxone to cefotaxime.

Importance to practitioners

It is essential to monitor liver enzymes for signs of cholelithiasis and hepatic injury in patients receiving high doses of ceftriaxone, regardless of age.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for his images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Research quality and ethics statement

The authors followed applicable EQUATOR Network (<http://www.equator-network.org/>) guidelines, notably the CARE guideline, during the conduct of this report.

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Conflicts of interest

There are no conflicts of interest.

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