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Case Report

Ceftriaxone associated biliary pseudolithiasis in a child: a case report and review of the literature

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Abstract: Ceftriaxone is associated with the formation and development of urolithiasis and biliary pseudolithiasis which will dissolve spontaneously after antibiotic discontinuation in most situations. In this study, we present a case of a 9-year-old boy with fungal pneumonia and central nervous system infection who developed ceftriaxone-induced biliary pseudolithiasis. The patient received ceftriaxone (2 g, bid) for 50 days in order to bring infections under control. On the 5th day of antibiotic discontinuance, a CT scan revealed the presence of gallbladder. Later, the patient even developed with elevated liver enzymes and tenderness in hepatic area after 33 days following ceftriaxone withdrawal. But after discontinuation of drugs (vancomycin, fluconazole) possessing risks of hepatic injury and application of ursofalk aiming at promoting bile excretion, the patient's liver function index resumed normal finally. Also, the ceftriaxone-induced pseudolithiasis was resolved completely at about 4 months after ceftriaxone cessation. Since children are more susceptible to developing biliary pseudolithiasis than adults after long-term application of ceftriaxone, awareness of this phenomenon is crucial in preventing unnecessary treatment such as surgery especially when using ceftriaxone in pediatric settings.

Keywords: Ceftriaxone, pseudolithiasis, child, computed tomography, ultrasonographic examination, adverse drug reaction

Introduction

Ceftriaxone remains one of the most commonly used antimicrobials in the treatment of pediatric patients with severe infections, due to a combination of its favorable properties, such as low toxicity, pharmacokinetics, and broad spectrum of actions [1]. And it is worth noting that ceftriaxone is also widely used in children with bacterial meningitis for its effective concentration in cerebrospinal fluid, but what followed by may be some unusual side effects such as urolithiasis and biliary pseudolithiasis as is shown in our case, which resemble gallstones, formed temporarily and can resolve after ceftriaxone withdrawl [2] in most situations. However, some may develop symptoms of obstruction of the bile duct with or without signs of cholecystitis with long time of abnormality resolution, they may be at greater risk for developing large stones and renal damage aggravating the patients' existing diseases. Since risk factors of ceftriaxone-induced pseudolithiasis include both pediatric age and long-term treatment, we should pay more attention to its application especially in children in order to avoid unnecessary therapeutic procedures. In this report, we presented a 9-year-old boy with fungal pneumonia and central nervous system infection who developed biliary pseudolithiasis with elevated liver enzymes and even tenderness in hepatic area after receiving ceftriaxone therapy.

Case report

A 9-year-old boy was admitted to our institution complaining of a 3-months history of headache and fever associated with urinary and fecal incontinence on June 29th, 2013. He has been consecutively hospitalized for three times because of fungal pneumonia and central nervous system infections. The patient neither had a history of predisposing factors, a family his-

tory of gallstones, nor received drug therapy associated with gallbladder lithiasis, such as cyclosporine or furosemide.

During his previous two hospital stays, the cerebral spinal fluid (CSF) tests showed CSF pressure of higher than 330 mmH_2O, leukocyte count of 927 × 106/L, protein of 713 mg/L, chloridion of 108.6 mmol/L, glucose of 1.8 mmol/L, as well as with kind of cloudy appearance. Moreover, β-1,3-D-glucans (BDG) in the CSF was higher than 1000 pg/ml, confirming of the patient's brain infection of fungus. Subsequently, the brain magnetic resonance angiography (MRA) disclosed multiple lesions in the brain and meninges. The CSF culture demonstrated the growth of gram positive bacilli. Computed tomography (CT) images showed enlarged hilar and mediastinal lymph nodes as well as multiple lesions predominantly situated in bilateral lung. Otherwise, no abnormalities were observed in gallbladder (**Figure 1A**). In his follow-up treatment, ceftriaxone (2 g, bid) was administered intravenously for 50 days from May 3rd to June 21st in order to bring infections under control. On the 5th day of antibiotic discontinuance, a CT scan of the chest revealed a reduction in the volume of gallbladder and multiple circular high-density shadow in the capsule measuring approximately 17 × 6 mm (**Figure 1B**). Within his last hospitalization on June 29th, 2013, a combination medication regime of fluconazole (0.4 g, qd), vancomycin (0.5 g, q8h) and ambroxol hydrochloride (90 mg, qd) was administered intravenously to resist fungal and bacterial infections. On day 4 after admission, liver function tests revealed a total bilirubin of 5.2 umol/L (normal, 1.71-17.1 umol/L), AST 21 U/L (normal, 0-40 U/L), ALT 120 U/L (normal, 0-40 U/L), ALP 219 U/L (normal, 20-110 U/L) and GGT 1089 U/L (normal, 0-50 U/L), suggesting the symptoms of hepatic dysfunction in some degree. Evolutions of the liver function tests are shown in detail in **Table 1**. Then, the dosage of fluconazole was reduced to 0.2 g once a day in consideration of its potential hepatic injury. Since ceftriaxone-associated pseudolithiasis and gallbladder stones resembled in appearance, clinicians tended to take no interventions for the sake of further identification.

As it turned out, ultrasonographic examination later revealed the presence of gallbladder sediment with a hyperechoic image measuring about 5 × 6 mm in the gallbladder (**Figure 1C**). Besides, the hepatic laboratory data demonstrated significantly worsened liver functions in the transaminase values (AST 663 U/L, ALT 371 U/L), and other liver enzymes (ALP 273 U/L, GGT 697 U/L), corresponding to an aggressive condition characterized by swelling and tenderness in the liver. To solve this, vancomycin and fluconazole were discontinued promptly and ursofalk (0.25 g, bid) aiming at promoting bile excretion was administered for two weeks before he was discharged. Finally, the child was discharged in good general condition after treatment, with disappearance of gallbladder sediment which was confirmed by CT images performed 3 months later (**Figure 1D**).

Discussion

Ceftriaxone, a third-generation cephalosporin antibiotic, is usually applied in the treatment of severe bacterial infections especially in children. Nearly 60% of ceftriaxone is excreted unchanged in urine while the rest of it is excreted into the bile and intestinal tract. Specifically, ceftriaxone is a negatively charged anion possessing high calcium binding affinity with increasing ceftriaxone dose, thus forming an insoluble calcium-ceftriaxone salt precipitating out in the gallbladder bile especially when the solubility product of the salt in bile was increased [1]. In 1986, Schaad et al. [2] firstly reported this so-called reversible biliary pseudolithiasis in an 18-year-old male patient who experienced recurrence of bilateral fungal pneumonia and received ceftriaxone therapy (2 g, bid) for nearly 20 days. Since then, terms like "biliary pseudolithiasis" and "biliary sludge" have been employed to represent gallbladder abnormalities in patients treated with ceftriaxone to differentiate the reversible abnormalities found in patients receiving ceftriaxone therapy but bearing true operative stones.

Previous researches have exhibited a relatively high incidence of ceftriaxone-induced biliary pseudolithiasis. As early as 1988, Schaad et al. [3] reported 16 of 37 children treated with ceftriaxone developed biliary pseudolithiasis. Only 3 children were clinically symptomatic and one of them also had urolithiasis with renal colic and obstruction of the kidney. Pigrau et al. [4] reported the incidence of ceftriaxone-associat-

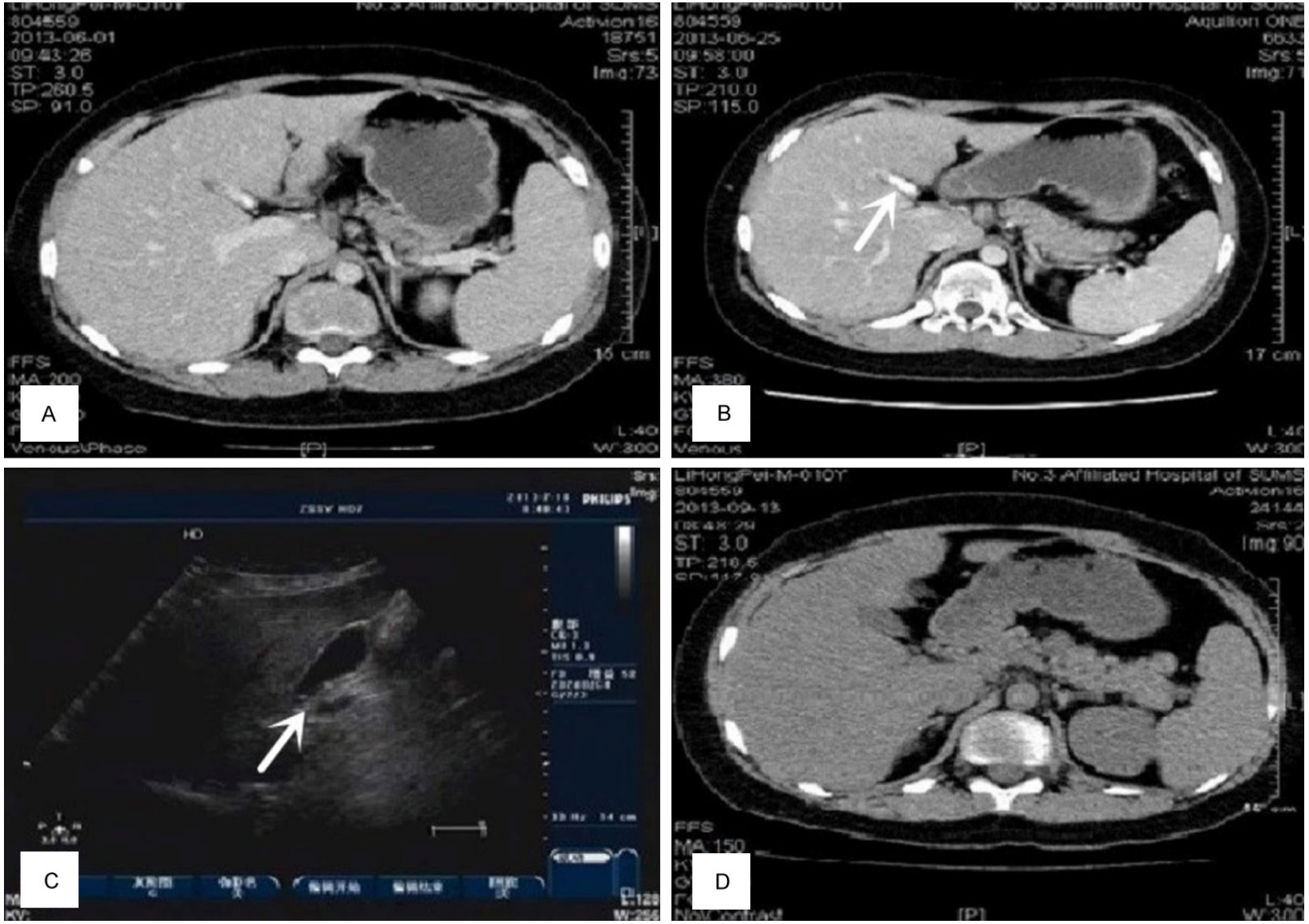

Figure 1. A. Computed tomography (CT) image showing no abnormalities were observed in gallbladder; B. CT image showing reduction in the volume of gallbladder and multiple circular high-density shadow in the capsule measuring approximately 17 × 6 mm; C. Ultrasonographic examination revealing the presence of gallbladder sediment with a hyperechoic image measuring about 5 × 6 mm in the gallbladder; D. CT image showing no abnormalities were observed in gallbladder.

Table 1. Evolution of liver function tests

	6/25	7/2	7/10	7/24	7/26	7/28	8/1	8/5
AST	19	21	18	663	51	21	16	24
ALT	16	120	22	371	213	98	34	27
TBILI	1.6	5.2	4.9	10	4.9	6.8	4.1	3.2
DBILI	3.2	2.4	1.7	5.3	1.6	2.0	1.5	1.0

ALT indicates alanine aminotransferase (U/L); AST, aspartate aminotransferase (U/L); TBILI, total bilirubin (mg/dl); DBILI, direct bilirubin (mg/dl); ALP, alkaline phosphatase (U/L); Albumin (g/L); GGT glutamine transpeptidase (U/L).

ed stone or sludge in the gallbladder was 14% in adults (10 of 71) with a maximum dose of 2 g/day. Heim-Duthoy et al. [5] discovered that gallbladder abnormalities were presented in 21.4% (6 of 28) of adult patients who underwent ceftriaxone therapy. And four of the above six patients didn't show any symptom. Ozturk et al. [6] prospectively evaluated the incidence of biliary pseudolithiasis in children treated with ceftriaxone in 2005. In their study of 33 children treated with ceftriaxone at a dosage of 100 mg/kg/day, 19 of them developed biliary pseudolithiasis and sludge but all were asymptomatic. Mohkam et al. [7] implemented a prospective study involving 284 children who received 75 mg/kg of intravenous ceftriaxone for about 9-10 days. They found that 4 children (3 boys and 1 girl) developed nephrolithiasis but none of them had metabolic problems.

Risk factors of ceftriaxone-induced nephrolithiasis and biliary pseudolithiasis include hypercalcemia, renal failure, prolonged fasting, application of total parenteral nutrition, consumption of high-doses of ceftriaxone (≥2 g/day) [8, 9]. Biner et al. [10] prospectively conducted 156 children treated with different ceftriaxone doses (50, 75, and 100 mg/kg/day) and found that age and high ceftriaxone dosage were two independent risk factors for ceftriaxone-induced biliary pseudolithiasis. Fretzayas et al. [11] reported UGT1A1 gene polymorphisms may be a risk factor in ceftriaxone-induced pseudolithiasis. In our present study, the 9-year-old boy had received long-term ceftriaxone treatment. In consideration of the coexistence of hepatic dysfunction, the gallbladder abnormalities may be at higher risk of ceftriaxone-induced pseudolithiasis. Additionally, the other two antibiotic agents used (fluconazole, vancomycin) in the subsequent therapies might had affected the excretion of calcium and ceftriaxone sediment in the bile, conferring a higher risk for the development of biliary pseudolithiasis.

Based on the 12 case reports of ceftriaxone-induced pseudolithiasis or urolithiasis after a Medline search of all English-language articles from January 1988 to January 2017, the clinical characteristics of ceftriaxone-induced pseudolithiasis or urolithiasis were preliminarily analyzed. As indicated in **Table 2** [12-22], patients developed ceftriaxone-induced pseudolithiasis or urolithiasis aged from 28-day to 79-years-old and most of them were male. Moreover, a daily dose of ceftriaxone ranged from 100 mg/kg/day to 4 g/day with a duration varying from 3 to 14 days. Moreover, biliary pseudolithiasis or urolithiasis could develop after receiving ceftriaxone 3-22 days and resolve 2-63 days after cession of the drugs in these cases. In three cases, some patients were asymptomatic, probably due to the highly reversible nature of ceftriaxone-associated pseudolithiasis [17-21], whereas some develop symptoms of lumbar or abdominal pain [12, 13, 18, 20], with hepatic injury [15, 16, 22] or renal injury [14, 18, 20], or even with signs of hematuria [14].

In our case, gallbladder abnormalities observed in the 9-year-old male patient developed on the 5th day after ceftriaxone withdrawal, and then disappeared 4 months later after ceftriaxone treatment. During this period, the patient started with elevated liver enzymes, followed by abdominal discomfort and even tenderness in hepatic areas. It's noteworthy that the renal and/or liver functions of this patient are the predisposing and contributing factors to ceftriaxone-associated "stone" formation for the reason that biliary excretion may increase in patients with impaired renal or liver functions. And drug-induced renal or liver injury in turn affects the excretion of biliary pseudolithiasis, forming a vicious circle in our reported case. So, special attention should be paid to when the combined medications that could potentially cause liver or renal damage are adopted.

In conclusion, side effects induced by ceftriaxone treatment could be attributed to hepatic injury, gastrointestinal neurosis, elevated transaminase levels, hematological abnormalities and anaphylactic reactions such as fever, rash, eosinophilia, anaphylactic shock [23]. It is vital that these complications should be understood

Table 2. Summary of clinical manifestations of 12 reported cases of ceftriaxone-induced biliary pseudolithiasis, urolithiasis

Case	Age	Gender	Admitting diagnosis	Ceftriaxone dose	Imaging performance	Clinical manifestations	Laboratory examination	Management	Outcome
1 [12]	19	Female	Chronic Lyme disease	2 g/day for 14 days	Multiple gallstones	Severe pain in the right upper quadrant, 39.4°C, vomiting	No	Without special therapy	Gallstones were disappeared 3 weeks later
2 [13]	7	Male	Acute bacterial meningitis	3 g/day for 4 days	Biliary sludge, a slightly dilated collecting system with a right calyceal stone	Colicky abdominal pain	No	Ceftriaxone was replaced by benzylpenicillin	Urinary tract and gallbladder ultrasonography were normal 10 days after admission
3 [14]	14	Male	Severe sinusitis complicated by epidural abscess	4 g/day for 8 days	High density material in gallbladder, kidneys, ureters	Colicky abdominal pain, back pain and emesis	Hematuria, serum creatinine 4.8 mg/dl	Ceftriaxone was replaced by meropenem therapy and bilateral ureteral stents were placed to pass urolithiasis.	Complete resolution of biliary pseudolithiasis and bilateral urolithiasis as well as normal serum creatinine value were observed 3 weeks after stent placement.
4 [15]	5	Male	Pneumonia	2 g/day for 7 days	A hyperechoic band within the gallbladder, bile duct dilatation	Abdominal pain	Elevated AST, ALT, T-Bil level	Ceftriaxone therapy was ceased, patient was treated conservatively	No abnormality could be detected on a follow-up sonogram on the 13th day
5 [16]	49	Male	Peritoneal dialysis	1 g/day for 4 days	Gallbladder filled with echogenic biliary sludge	Jaundice	A prominent elevation of bilirubin, normal liver enzymes	Ceftriaxone was stopped	Gallstones were disappeared after 12 days of ceftriaxone withdrawal
6 [17]	21	Male	Diverticulitis	2 g/day for 5 days	Huge gallbladder stone without inflammation	No symptoms	No	Ceftriaxone was stopped	Gallstones were disappeared one month later.
7 [17]	22	Male	Pneumonia	2 g/day for 12 days	Gallbladder stone	No symptoms	No	Observation	Gallstones were disappeared on the follow-up CT.
8 [18]	5	Male	Hypercalciuria and community acquired pneumonia	1 g/day for 6 days	Grade II hydronephrosis of the right kidney; calculi of the kidney	Intensive right sided lumbar pain	Moderate hypercalciuria (5.4 mg/kg/day), hydronephrosis revealed by ultrasound scans and numerous red blood cells of the urinary sediment revealed by microscopic examination.	Forced hydration were adopted within the next two hospital days	Spontaneous passage of three calculi as calcium ceftriaxonate were excreted under forced hydration and prompt resolution of the right hydronephrosis was observed.

9 [19]	28-day-old infant	Boy	Spontaneous severe epidural hematoma	100 mg/kg/day for 3 days	Mass-like sludge in the gallbladder	No symptoms	A slightly elevated level of total bilirubin	The ursodeoxycholic acid was administered at a dose of 15 mg/kg twice a day and fat-soluble vitamins for two weeks	Ultrasound examination showed complete normalization of image.
10 [20]	25	Male	Scalp and skin lacerations	4 g/day for 3 days	Bilateral mild hydronephrosis and proximal ureter ectasia	Colicky abdominal pain, anuria and bilateral renal colic.	Elevated serum creatinine and blood urea	Moxifloxacin (400 mg/d), intravenous dextrose solution, and phloroglucinol were commenced. Also, haemodialysis once dalily for three sessions and bilateral double-J ureteral stents were given.	The patient was discharged with normal serum creatinine about 1 month after discontinuation of ceftriaxone.
11 [21]	14	Male	Lyme arthritis	4 g/day for 14 days	Multiple biliary concrements and sludge in gallbladder	Severe nocturnal abdominal pain, emesis	Elevated bilirubin and liver enzymes	Conservative treatment	Abnormal findings were disappeared 4 months later
12 [22]	79	Female	End-stage renal disease receiving maintenance hemodialysis with bronchial pneumonia	7 g/13 days (1 g of ceftriaxone on alternating days)	One gallstone (16 × 9 mm) in the gallbladder	Stomachache around the right hypochondrium with a firm, round mass and a slight fever of 37.2°C	The WBC count was 10,560/μl, the CRP level was 8.8 mg/dl, and hepatic and biliary enzymes were within normal limits	Ceftriaxone was stopped.	Gallstone completely disappeared 48 days following ceftriaoxone cessation

in case of over medicalization such as surgery. So, clinicians should be aware of the side effects of ceftriaxone and periodical imagining examinations are still necessary when patients present signs of biliary pseudolithiasis, which is indistinguishable from the typical symptoms of cholecystolithiasis.

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Disclosure of conflict of interest

None.

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