

Complications of ceftriaxone-associated biliary pseudolithiasis and nephrolithiasis: a case report

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ABSTRACT

Introduction. Ceftriaxone is a wide-spectrum antibiotic frequently used in pediatrics. Biliary pseudolithiasis is a well-known side-effect occurring in 15-57% of cases. However, nephrolithiasis is extremely infrequent, with very few related publications.

Case report. We present the case of a 9-year-old patient with ceftriaxone-treated complicated acute appendicitis who developed biliary pseudolithiasis and nephrolithiasis. During hospitalization, the patient presented with pseudolithiasis complications such as mild pancreatitis and bilateral ureterohydronephrosis with acute renal failure.

Remarks. Suspecting ceftriaxone-associated biliary pseudolithiasis and/or nephrolithiasis is key to achieve an early diagnosis and prevent complications such as those reported in this patient. Early discontinuation is essential as an initial treatment measure.

KEY WORDS: Ceftriaxone; Nephrolithiasis; Children; Gallstones.

COMPLICACIONES POR PSEUDOLITIASIS VESICULAR Y NEFROLITIASIS ASOCIADA A CEFTRIAXONA. REPORTE DE CASO

RESUMEN

Introducción. La ceftriaxona es un antibiótico de amplio espectro frecuentemente utilizado en pediatría. La pseudolitiasis vesicular es un efecto adverso bien conocido, que se presenta en un 15 a 57% de los casos. En cambio la litiasis renal es extremadamente infrecuente con muy pocas publicaciones al respecto.

Caso clínico. Se presenta el caso de un paciente de 9 años que, durante tratamiento con ceftriaxona por una apendicitis aguda complicada, desarrolla pseudolitiasis vesicular y urinaria. Durante la misma internación el paciente presenta una pancreatitis leve y una ureterohidronefrosis bilateral, con insuficiencia renal aguda, como complicaciones de las pseudolitiasis.

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Comentarios. La sospecha de la formación de litiasis renal y/o vesicular asociada al uso de ceftriaxona es fundamental para un diagnóstico temprano y prevención de complicaciones como las reportadas en este paciente, siendo fundamental la suspensión precoz del fármaco como inicio del tratamiento.

PALABRAS CLAVE: Ceftriaxona; Nefrolitiasis; Niños; Colelitiasis.

INTRODUCTION

Ceftriaxone is a wide-spectrum, third-generation cephalosporin antibiotic frequently used in pediatrics. Biliary pseudolithiasis is a well-known side-effect widely described in the literature and occurring in 15-57% of cases⁽¹⁾. However, nephrolithiasis is extremely infrequent, with very few related publications.

We present the case of a patient developing biliary pseudolithiasis and nephrolithiasis during ceftriaxone antibiotic treatment as a result of an appendicular plastron. During hospitalization, he had significant complications associated with such lithiasis, developing mild pancreatitis and obstructive acute renal failure.

CLINICAL CASE

This is the case of a 9-year-old previously healthy boy with 11-day unspecific abdominal pain. He started to have 39°C fever and vomit 72 hours prior to consultation. Physical examination revealed a painful tumor with right-flank defense. An abdominal ultrasound examination was carried out. It demonstrated a heterogeneous mass in the right flank and iliac fossa, where thin loops were identified, with intra-abdominal free liquid and without peristalsis. No biliary lithiasis or nephrolithiasis was found.

Following abscessed appendicular plastron diagnosis, antibiotic therapy was initiated, and exploratory laparoscopy was carried out. Surgery demonstrated an appendic-



Figure 1. Abdominal x-ray demonstrating lithiasis (arrows) in both kidneys.



Figure 2. Left kidney. Nephrolithiasis (arrows).



Figure 3. Gallbladder with biliary lithiasis (arrow).

ular plastron involving the last small bowel, cecal, and omental loops, as well as perforated gangrenous appendicitis. Appendectomy was performed, with partial omental resection and free abdominal liquid aspiration. He was admitted at the Intermediate Care Unit for postoperative control.

Pathological anatomy confirmed the presence of acute perforated gangrenous appendicitis and marked periappendicitis.

Patient evolution was torpid, with multiple residual collections occurring 48 hours following the procedure. This led to 8 *open vacuum* scheduled re-interventions for 17 days until parietal closure was achieved.

He received multiple antibiotic plans: first ampicillin-sulbactam (2 days), followed by metronidazol (21 days), ceftriaxone (21 days), and meropenem (19 days). Ceftriaxone was administered at 100 mg/kg/day doses, in 3 doses with a 30-minute infusion rate, diluted in saline solution. Peritoneal fluid cultures were positive for *Klebsiella pneumoniae* –which produces wide-spectrum β -lactamases and is meropenem-sensitive– from the second surgery. Prior to abdominal wall closure, 3 peritoneal fluid cultures without bacterial growth were obtained.

The patient received total parenteral nutrition (TPN) for 7 days, and cycling parenteral nutrition for 9 days, with a total 16 days.

On ceftriaxone day 19 (hospitalization day 22, with the enteral route reinstated), the patient had macroscopic hematuria, dysuria, urinary microlithiasis excretion, and

colic pain in both lumbar fossae, so an abdominal x-ray was performed, which demonstrated the presence of nephrolithiasis (Fig. 1).

A new abdominal and urinary tract ultrasound examination was performed. Main findings included gallbladder with multiple lithiasis inside and posterior shadow cone, without main biliary duct dilatation; bilateral ureteropyelocalyceal dilatation (10 mm right renal pelvic anteroposterior diameter, and 19 mm left renal pelvic anteroposterior diameter); and multiple lithiasis of up to 10 mm in the right and left kidney. Both ureters were dilated, with multiple lithiasis of 5-11 mm in the left ureter (Figs. 2 and 3).

In light of these findings, and given the suspected relationship between lithiasis and ceftriaxone, the latter was discontinued.

In this episode, creatinine levels were 3.45 mg/dl, and nitrogen levels were 0.91 mg/dl, with negative urine cultures and a normal complete blood count.

In light of the nephrolithiasis ultrasound finding, with urinary system repercussion and obstructive acute renal failure, decision was made to place double J catheters bilaterally (Fig. 4). The patient had a good clinical evolu-



Figure 4. Abdominal and pelvic x-ray following double J catheter placement.

tion, with normal nitrogen and creatinine levels 48 hours following surgery.

48 hours following the hematuria episode, the patient had repeated biliary vomit and epigastric abdominal pain, so an analytical examination was performed. Main findings included 1,436 U/L amylase levels, 1,046 U/L lipase levels, and a new abdominal ultrasound test demonstrating no changes vs. the previous one. Mild acute pancreatitis was diagnosed, without multiorgan dysfunction or infection, so oral feeding was discontinued for 72 hours and ursodeoxicolic acid treatment was initiated. Oral feeding was progressively reinstated with decreased 137 U/L amylase levels on control day 5, and 50 U/L lipase levels on control day 10.

The patient was discharged after 52 days in hospital. Ursodeoxicolic acid treatment was prescribed.

Following discharge, 24-hour calcium, phosphorus, uric acid, potassium, and sodium urine levels were analyzed, as well as calcium, phosphorus, uric acid, parathormone, and vitamin D blood levels, with normal results.

Outpatient controls were carried out with various ultrasound examinations, which demonstrated the biliary lithiasis had disappeared 1 month and 25 days following discharge (75 days since ceftriaxone discontinuation). At that very moment, ursodeoxicolic acid treatment was discontinued. Right nephrolithiasis disappeared on the same day, while left micronephrolithiasis persisted for 1 extra month.

Double J catheters were removed 3 months after placement, with a nice subsequent evolution.

REMARKS

Ceftriaxone is a third-generation semi-synthetic cephalosporin with bactericide action. It is frequently used in pediatrics owing to its wide-spectrum action, long half-life, and good penetration in the anatomical sites hosting the most frequent infections^(2,3).

Pharmacologically speaking, it is cleared through primary renal elimination. However, 40-65% is eliminated through the bile, without modifications, with a high concentration at the gallbladder lumen and levels up to 150 times higher than blood concentration levels. It behaves as an anion, and it combines and precipitates with insoluble calcium salts, for which it has great affinity⁽³⁾. In addition, ceftriaxone reduces gallbladder motility, thus favoring precipitation with calcium salts⁽⁴⁾.

Ceftriaxone-associated biliary lithiasis is relatively frequent in children as it occurs in 15-57% of patients treated with ceftriaxone⁽¹⁾. Most cases are asymptomatic and self-resolved⁽⁵⁻¹²⁾. Lithiasis have been described to disappear from the 2nd day following treatment initiation to the 63rd day following treatment discontinuation^(6,13).

Ceftriaxone-associated nephrolithiasis has a lower incidence. Mokham et al. reported 1.4%⁽¹⁾, whereas Avci et al. reported 7.8%⁽¹⁴⁾. There are few cases reported in the literature, since most patients are asymptomatic⁽¹³⁻¹⁸⁾. Nephrolithiasis has been proposed to be made up of/caused by ceftriaxone itself given its low urine solubility, or possibly of/by its metabolic effects favoring lithiasis formation⁽¹⁸⁾.

Ceftriaxone treatments lasting more than 5 days⁽⁸⁾, high doses (≥ 100 mg/kg/day), and prolonged fast⁽⁹⁾, as well as any condition causing slow gallbladder emptying (total parenteral nutrition or major abdominal surgery), contribute to the precipitation process^(3,19).

Ceftriaxone infusion time also seems to be associated with pseudocholelithiasis and biliary sludge – when it is short (3-5 minutes), they occur in 55% of patients, and when ceftriaxone is infused every 30 minutes or more, they occur in 29% of patients⁽⁷⁾.

In this patient, ceftriaxone administration was considered as the main cause of biliary lithiasis and nephrolithiasis, which were prolonged at high doses and disappeared following ceftriaxone discontinuation. Other predisposing factors such as prolonged fast, parenteral nutrition, and major abdominal surgery were also associated with it.

It should be highlighted that severe complications of both lithiasis led to a series of invasive procedures and a longer hospital stay.

CONCLUSION

Suspecting ceftriaxone-associated biliary lithiasis and nephrolithiasis is key to achieve an early diagnosis and prevent complications such as those reported in this patient. Early discontinuation is essential.

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