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Ceftriaxone-Associated Gallbladder Pseudolithiasis in a Pediatric Patient, Case Report and Review of the Literature

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Abstract: Ceftriaxone plays a vital role in modern medicine due to its broad-spectrum coverage of common microbes. A relatively frequent, yet underplayed side effect is pseudolithiasis, especially in the pediatric setting. While most cases resolve spontaneously, there have been reports of patients requiring surgical treatment after developing further complications. We report a case of an abrupt onset (<3 days) pseudolithiasis occurring after just four moderate doses of Ceftriaxone. A previously healthy 2 years and 9-month-old girl was admitted as a case of exudative tonsillitis with secondary gastroenteritis. On day three of Ceftriaxone treatment, sudden onset severe abdominal pain ensued which warranted an abdominal ultrasound showing multiple gallbladder stones. Consequently, Ceftriaxone was changed to Cefotaxime and the pain subsided following a further two inpatient days and outpatient follow-up appointments were scheduled. Ceftriaxone has a high elimination in the bile, which gives predominance for potential biliary complications. It is well documented that high and prolonged doses increase the likelihood of these complications. In our case the accelerated progression of the pseudolithiasis could be due to the dehydration caused by the background gastroenteritis. Reduced oral intake and dehydration causes biliary stasis which accelerates the formation of biliary sludge and gallbladder precipitates due to biliary stasis. In the future, physicians could reconsider the use of ceftriaxone in patients with similar presentations.

Keywords: Ceftriaxone, Pseudolithiasis, Gallstones, Cholelithiasis, Children, Cholecystectomy

1. Introduction

Gallstones take a heavy toll on medical services annually, affecting around a quarter of the men and women aged over 50 [1]. Recent studies have reported an increase in the incidence of pediatric gallstones and attribute this to a rise in childhood obesity [2]. Several conditions including hemolytic disorders, prolonged total parenteral nutrition, and cystic fibrosis have been identified as major causes of gallstones in children [3].

Third-generation cephalosporins such as cefotaxime and ceftriaxone have widely replaced chloramphenicol in the past two decades due to their superior toxicity profiles, broad-spectrum coverage, and their effectiveness against encapsulated bacteria. Although Ceftriaxone is 50% more expensive than Cefotaxime, its IM route of administration, long half-life and single dose regimen has made it a great drug of choice for common and serious infections of the young [4]. The recommended daily dosage in infants and young children is 20 to 80 mg/kg[5].

Most commonly, side effects include diarrhea, exanthema, pruritus, and reactions at the injection site. Ceftriaxone may also cause slight derangement of liver and renal function, but symptomatic nephrotoxicity and hepatotoxicity have not been reported [5]. Moreover, due to the high bile ceftriaxone concentration, high and prolonged doses can predispose patients to biliary sludge or cholelithiasis. Looking more specifically; in the pediatric population, four different prospective studies looking into pseudolithiasis with ceftriaxone administration using ultrasonography modalities found the average combined incidence was approximately 35% [6-8]. Although usually a

self-limiting side-effect, it is by no means a rare one.

Across the literature, there have been several similar cases of gallstones attributed to the use of ceftriaxone, typically after a prolonged course of ceftriaxone [7-9 days]. While relatively few studies investigated the risk factors and doses which favor their formation, high doses and prolonged treatment courses have been identified as significant factors to consider [7, 9]. On the contrary, in our case the patient developed gallstones after a short course of only 3 days consisting of 4 moderate doses of ceftriaxone.

It is well documented that a significant number of patients tend to develop reversible asymptomatic gallstones secondary to ceftriaxone use, however, most cases are asymptomatic and are only identified using ultrasound findings [15]. Our patient's acute development of severe biliary colic after only a few doses of ceftriaxone is unusual and warrants further investigation into other causes and risk factors for this accelerated presentation.

2. Case Illustration

A 2 year and 9-month-old girl was admitted to the hospital complaining of high fever and a runny nose. The fever was measured to be 40 degrees tympanically, associated with rigors and decreased activity. She previously sought medical care the day before at another facility where she received one dose of ceftriaxone and was discharged on antipyretics. She then presented to the emergency room due to lack of improvement and development of poor oral intake with recurrent vomiting and 7 episodes of watery diarrhea. On examination, the patient was febrile and moderately dehydrated, throat examination revealed enlarged tonsils with exudate and there were no other abnormal findings during the systemic physical exam. Lab results showed a WBC count of 15460/mm^3 with 72% Neutrophils, a CRP level of 54.6 and a negative result for the Rapid Strep Test via throat swab. The patient was given 1.7mg of Ondansetron in addition to one dose of ceftriaxone (1 gram) and admitted to the inpatient ward as a case of exudative tonsillitis with secondary gastroenteritis and mild dehydration. She was prescribed 850 mg of Ceftriaxone twice daily (95mg/kg per day) along with regular IV fluids and paracetamol.

The patient's overall health started to improve initially but the following night she developed sudden severe abdominal pain. It was clearly significant causing the child to cry excessively which prompted immediate medical attention. Abdominal examination revealed tenderness localized to the right side with no rigidity or signs of peritonitis. An abdominal ultrasound was conducted immediately which showed multiple gallbladder stones with the largest being 0.7cm. (See Figure 1). The gallbladder was normally distended with normal wall thickness and no signs of inflammation or pericholecystic fluid.

Laboratory data was insignificant with a normal white blood cell count of 5400/mm^3, hemoglobin level of 10.3 g/dL, total bilirubin of 7 μmol/L, Alkaline phosphatase level of 205 IU/L and normal Transaminase levels (AST 35 IU/L, ALT 24 IU/L). The patient's pain subsided with paracetamol and she was placed under close observation for possible recurrence of her symptoms. Ceftriaxone induced biliary cholelithiasis was suspected and her antibiotic agent was changed to cefotaxime 850mg every 8 hours (143mg/kg per day).

The patient remained admitted for a further 2 days and did not have any recurrence of abdominal pain. She began tolerating food orally and her exudative tonsillitis had completely resolved. She was discharged and scheduled an outpatient clinic follow up one month later. The parents were advised to return earlier if she developed abdominal pain or any other symptoms associated with gallstones for further evaluation and management.

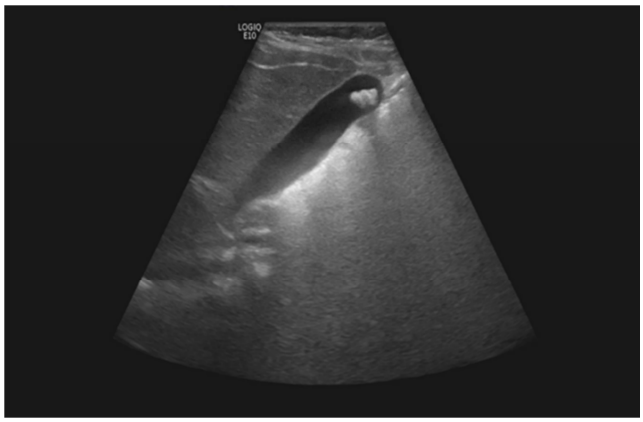

Figure 1. *Ultrasound image of the gallbladder showing multiple gallbladder stones with normal wall thickness and no signs of cholecystitis.*

3. Discussion

This patient's young age, absence of risk factors for gallstone formation and the timing of her presentation strongly suggests these stones were secondary to ceftriaxone administration. Ceftriaxone induced gallstones are an uncommon but well documented complication of treatment especially in pediatric patients, which has resulted in a number of unnecessary cholecystectomies in the past [6, 10, 11].

While 60% of ceftriaxone is eliminated in the kidney, up to 40% is eliminated in the bile [4]. Once it's concentration in the gallbladder exceeds a certain limit it begins to bind to available calcium ions to form precipitates. Park et al. [12] looked into the composition of these precipitates using thin-layer chromatography, high-performance liquid chromatography (HPLC), and electron microprobe analysis. The study concluded that the major constituent of these gallbladder stones was identified as a ceftriaxone-calcium salt. Further studies done on animals suggest that ceftriaxone can inhibit gallbladder contractility which may further contribute to the formation of these precipitates [13].

It is important to note that in most cases these changes are completely reversible, with ultrasound abnormalities completely resolving within 2-63 days after cessation of treatment [14]. While a significant number of patients tend to develop these ultrasound findings, most are asymptomatic and resolve spontaneously without developing symptoms of

biliary colic [15]. However, there have been many cases reported of more severe presentations such as acute cholecystitis and gallstone pancreatitis secondary to prolonged ceftriaxone treatment [16-19].

Although the association between ceftriaxone and gallstones is well documented, few studies investigated the different risk factors and doses which favor their development. It is generally viewed that high doses (over 2g daily) and a prolonged treatment course increase the probability of gallstone formation [7, 9]. This complication is also more common in children as studies suggest that the incidence is higher in children less than 10 years old [20]. Other risk factors such as short infusion time, dehydration, poor oral intake and associated kidney disorders have also been reported.

In our case the patient was given a total of 4 moderate doses of ceftriaxone over a period of three days to treat her acute tonsillitis. She was first given one gram of ceftriaxone in another health facility, an additional dose of 1 gram of ceftriaxone was administered in our ER the day after, followed by two 850 mg doses (95mg/kg per day) during admission before she developed severe abdominal pain. This was unusual as most cases reported in the literature occurred after a prolonged course of ten days or longer [7, 9, 10].

One factor that can explain this patients' accelerated presentation was the development of acute gastroenteritis during a similar time period to her acute tonsillitis. The patient was dehydrated on presentation to the ER and had not been tolerating anything orally for one day. She was placed on IV fluids throughout her admission to help alleviate her recurrent diarrhea and vomiting. Dehydration and restriction of oral intake are well documented risk factors for ceftriaxone induced gallstones due to biliary stasis, which favors the formation of biliary sludge.

Management strategies for children with ceftriaxone induced gallstones are not well defined in the literature. In many cases thorough assessment is carried out to rule out other risk factors that could lead to this adverse event. The need for ceftriaxone should also be evaluated and other antibiotics with similar properties should be considered. Since it is well documented that this condition is reversible it does not require any specific treatment but rather observation for recurrence of symptoms. This is warranted as in many cases these stones completely resolve and do not require unnecessary surgical procedures.

4. Conclusion

Symptomatic gallstones can be an extremely alarming finding for both parents and physicians often prompting invasive diagnostics and surgical procedures. While using Ceftriaxone, it is essential physicians are aware of this uncommon yet significant complication. This case serves as a reminder to suspect gallstones as a cause of right upper quadrant pain that should warrant a gallbladder focused abdominal ultrasound as part of the initial approach. Due to the reversible nature of these stones, close observation along with outpatient follow up is advised.

This case also shines a light on another significant risk factor for developing these stones. Extremely poor oral intake and dehydration secondary to gastroenteritis potentially accelerates the formation of these precipitates after ceftriaxone use. This important association may cause physicians to reconsider prescribing ceftriaxone and instead prescribe other effective antibiotics in similar cases where there is a clear clinical picture of dehydration.

In the future, further studies need to be carried out looking at the direct correlations between decreased oral intake and the acceleration of gallstone precipitation secondary to ceftriaxone use. While decreased oral intake is a well-documented factor that accelerates gallstone formation, a clear association with ceftriaxone-induced pseudolithiasis should be established. Studies looking into the dosage and treatment regimens that favor gallstone formation are also recommended, which will aid pediatricians in preventing similar complications. And lastly, increased awareness about this underplayed side effect should be instilled across the medical field to provide a more systematic and cost-effective approach to dealing with similar cases.

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