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Case Report

Acute Obstructive Pancreatitis Secondary to Ceftriaxone Induced Cholelithiasis

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Abstract

This, an Odyssey of a previously healthy, 6 years old girl who was admitted at Sidra Hospital in Doha-Qatar and was treated initially for acute mastoiditis complicated with an epidural abscess and sagittal sinus thrombossis, she was treated with a long course of Ceftriaxone and then presented abruptly with acute pancreatitis due to obstructing biliary stones. No other known risk factors were identified. Little is reported in the literature about developing this full-blown presentation in this age group and this is to serve as a word for the wise and concerned.

Background

Ceftriaxone is a broad-spectrum cephalosporin and is active against the majority of community associated enteric Gram-negative rods, beta-hemolytic Streptococci and Streptococcus pneumoniae and has an excellent CNS penetration, thus making it one of the commonest antibiotics used in the pediatric population [1]. It is eliminated predominantly in urine and bile and as reported in literature biliary pseudolithiasis is one of the commonest known ceftriaxone adverse reaction, most serious and a major cause of antibiotic discontinuation.

Although self-resolving cases of Ceftriaxone induced biliary sludges are well reported with incidences reaching 57% of treated cases [2], symptomatic and serious obstructive presentations are much less reported in Adults, and even lesser in the pediatric age group after the first month of life [3]. Considering this adverse side effect is of importance whenever Ceftriaxone is prescribed, especially in cases requiring higher and longer treatment course as this case report will delineate.

Case Presentation

This is the case of a previously healthy, fully immunized 6 years old girl who was admitted at Sidra Hospital in Doha-Qatar and was treated initially for acute mastoiditis complicated with an epidural abscess and sagittal sinus thrombosis, she was treated with a long course of Ceftriaxone and then presented abruptly with acute pancreatitis due to obstructing biliary stones.

Our patient's Condition started in the middle of November 2022 with mild fever, runny nose and bilateral ear pain. The illness was believed to be mostly viral given that most of her family were down with the same symptoms, she nevertheless received oral cefixime for 5 days before presenting with high grade fevers, left ear pain without discharge and redness and swelling behind that ear. There was no history of recurrent ear problems, blockages nor recurrent tonsillitis. Examination yielded a stable afebrile patient with local findings of left pushed pinna, swollen, hot and tender post auricular area with blunting of posterior auricular sulcus with a palpable left cervical lymph node. there were no overt signs of facial palsy and otoscopic examination showed a Red featureless tympanic membrane with bulging antero-inferior quadrant. Labs showed marked inflammatory markers (CRP 159).

The patient was admitted for observation and was covered with Ceftriaxone and Clindamycin as a case of acute left sided Mastoiditis. Further assessment by the pediatric ENT team documented the presence of left ear effusion, furthermore a CT

temporal bone scan found that the condition was complicated with abscess in soft tissues superficial to left Mastoid bone. Patient underwent Left mastoid abscess drainage, and left grommet tube placement. The morning after, the patient was further evaluated with an MRI+V temporal bones and yielded residual soft tissue and oto-mastoid inflammatory changes. Intracranially, it showed an epidural abscess (8 mm in thickness) with displacement and compression of a thrombosed the left sigmoid sinus. Patient hence underwent Left middle ear exploration and left epidural abscess drainage by the ENT and Neurosurgical teams.

Since the tissue and ear discharge cultures were showing no microorganismal growth; The Infectious diseases team recommended to continue double coverage with Ceftriaxone (100mg/kg daily dose) and Metronidazole for better CNS penetration and Hematology team commenced on Low Molecular Weight Heparin (Enoxaparin) at a dose of 1mg/kg. Patient was investigated by the immunology team and was cleared from suspicion of primary immunodeficiency (had Normal CBC. IgG&IgM, slightly high IgA. Normal antibacterial Abs, and normal Neutrophil fuction) Care was continued as such during the inpatient stay and was subsequently discharged after a 12-day hospital stay on subcutaneous anticoagulant (Enoxaparin), oral Metronidazole and Intravenous Ceftriaxone daily infusions via a peripherally inserted central catheter which was inserted during the inpatient stay.

Patient was followed in the Infectious Diseases and ENT clinics on each visit there was marked improvement on the posterior auricular swelling and inflammatory markers. Patient was furthermore evaluated with three MRI studies done every 3-4 weeks showing gradual but incomplete resolution of the otomastoiditis changes with poor/ incomplete subjacent dural venous sinus segmental recanalization which was explained by the family's poor adherence to the anticoagulant therapy. Which prompted to change to an oral anticoagulant (Rivaroxaban) and continued Ceftriaxone infusions. 10 weeks in Ceftriaxone infusions and at the beginning of February 2023, patient presented to our emergency room abruptly with severe on/off colicky abdominal pain, multiple episodes of vomiting and a low-grade fever. She described the pain as being all over the tummy and especially severe with meals. There were no loose motions, itching and no changes in urine color.

Examination showed a mildly dehydrated, afebrile, stable patient with the local examination yielding no jaundice but a diffused abdominal pain with maximum intensity on the epigastrm and no visceral organomegaly. labs showed elevation in Alkaline phosphatase, 5 folds elevation in liver enzymes, elevated INR (1.8) along with marked elevation in Lipase (>600 iu/L) and Amylase (1300 u/L). She had normal Triglyceride levels, negative virology panels, serum Calcium levels and immunoglobin levels.

US abdomen showed Distended and hyperaemic gallbladder contains sludge and few stones in association with dilated intra and extrahepatic biliary duct with at least two CBD stones (4 mm) seen at its mid and distal segments suggesting acute calculus cholecystitis with possible cholangitis. Also showed edematous bulky pancreas likely to represent pancreatitis secondary to obstructive biliary cholelithiasis. No peripancreatic fluid collection.

Findings were further confirmed with an MRCP+MR Pancreas and the patient was diagnosed as having acute obstructive pancreatitis and cholangitis secondary to Ceftriaxone induced cholelithiasis (Figure 1-4) & (Charts 1,2)

Figure 1: Predominant mastoid air cells on left side are opacified. A peripherally enhancing localized collection of size 3.0 X 2.8 X 1.4 cm (Cc X AP X TR) is noticed in the soft-tissues superficial to the mastoid bone retro-auricular area.

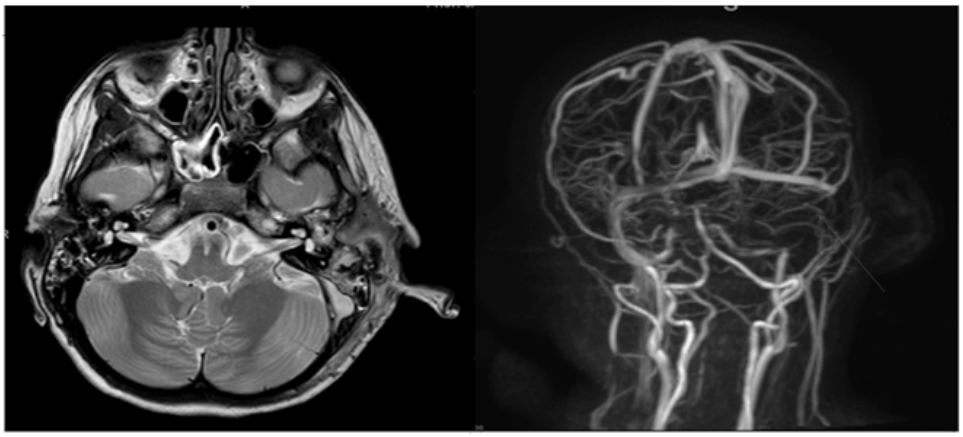

Figure 2: Residual of soft tissue and oto-mastoid inflammatory changes.Intracranially, an epidural abscess (8 mm in thickness) in seen displacing and compressing the left sigmoid sinus which may also be thrombosed.

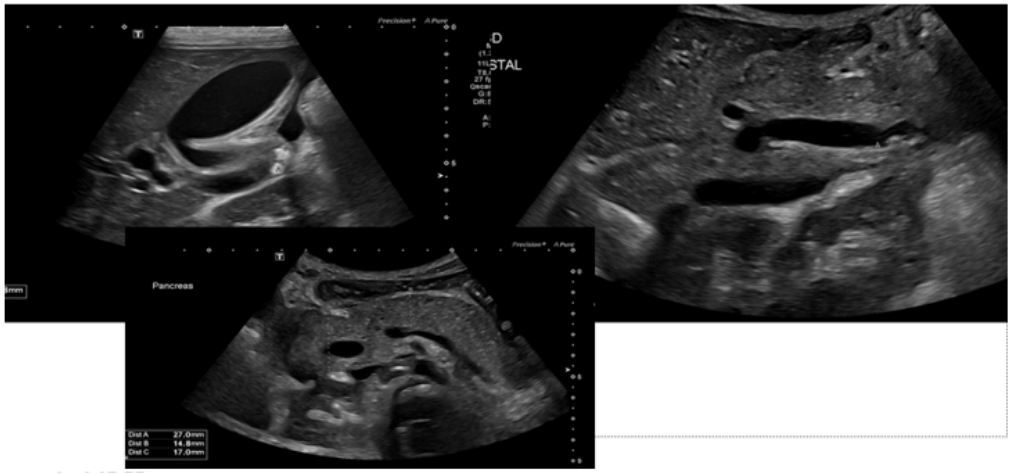

Figure 3: Distended and hyperemic gallbladder contains sludge and stones with at least two CBD stones (4 mm) seen at its mid and distal segments along with an Edematous bulky pancreas. No peripancreatic fluid collection.

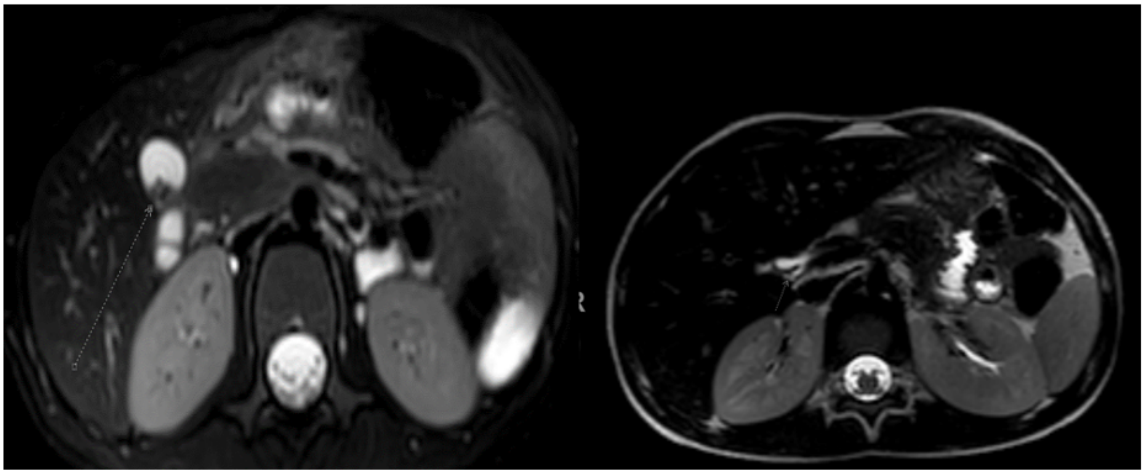

Figure 4: Slight prominent common hepatic duct with two small stones. Distal CBD stone noted with no significant dilatation or wall thickening. Multiple gallbladder filling suggestive of debris/stones.

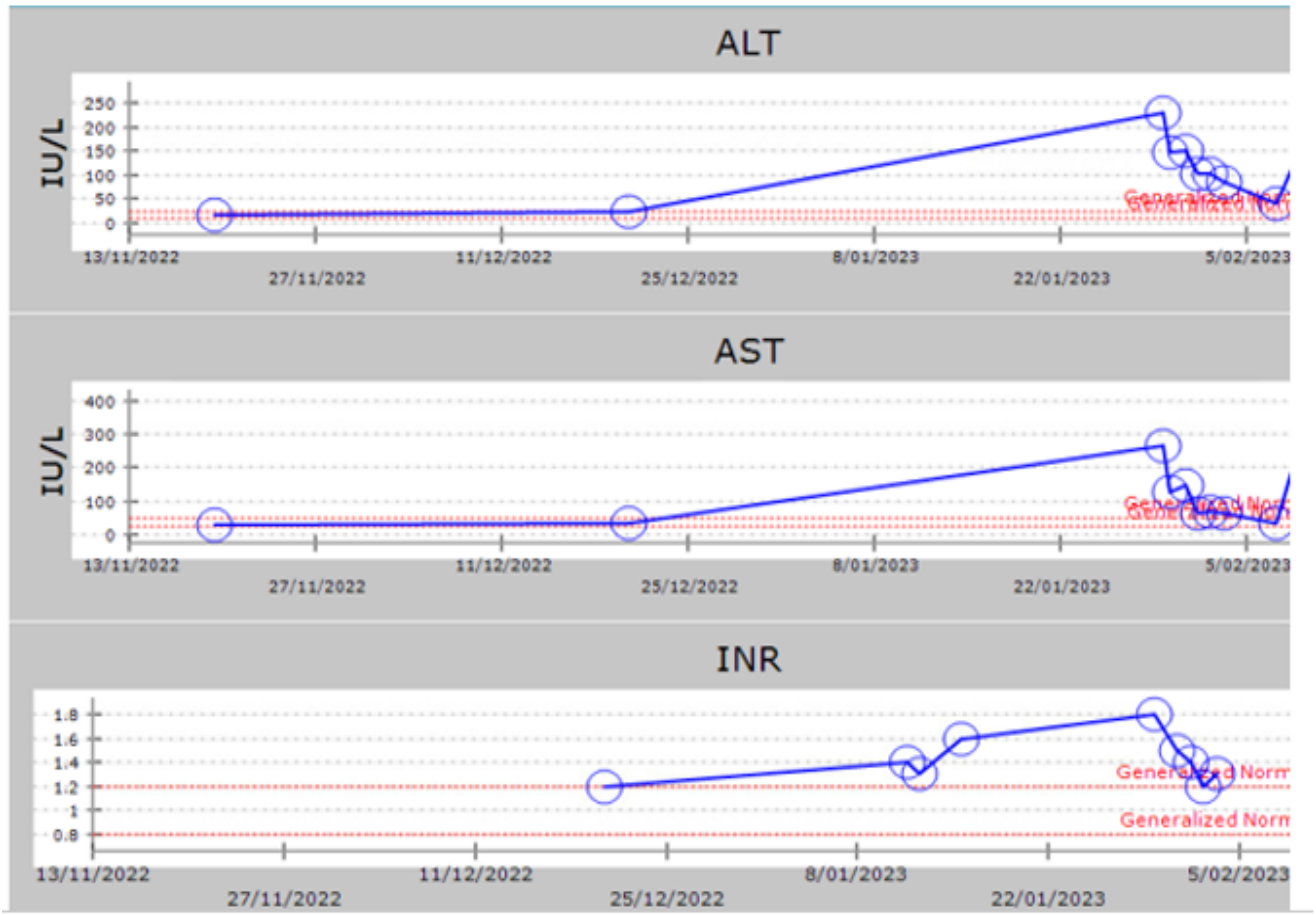

Chart 1: Trend of Liver enzymes and INR during admission.

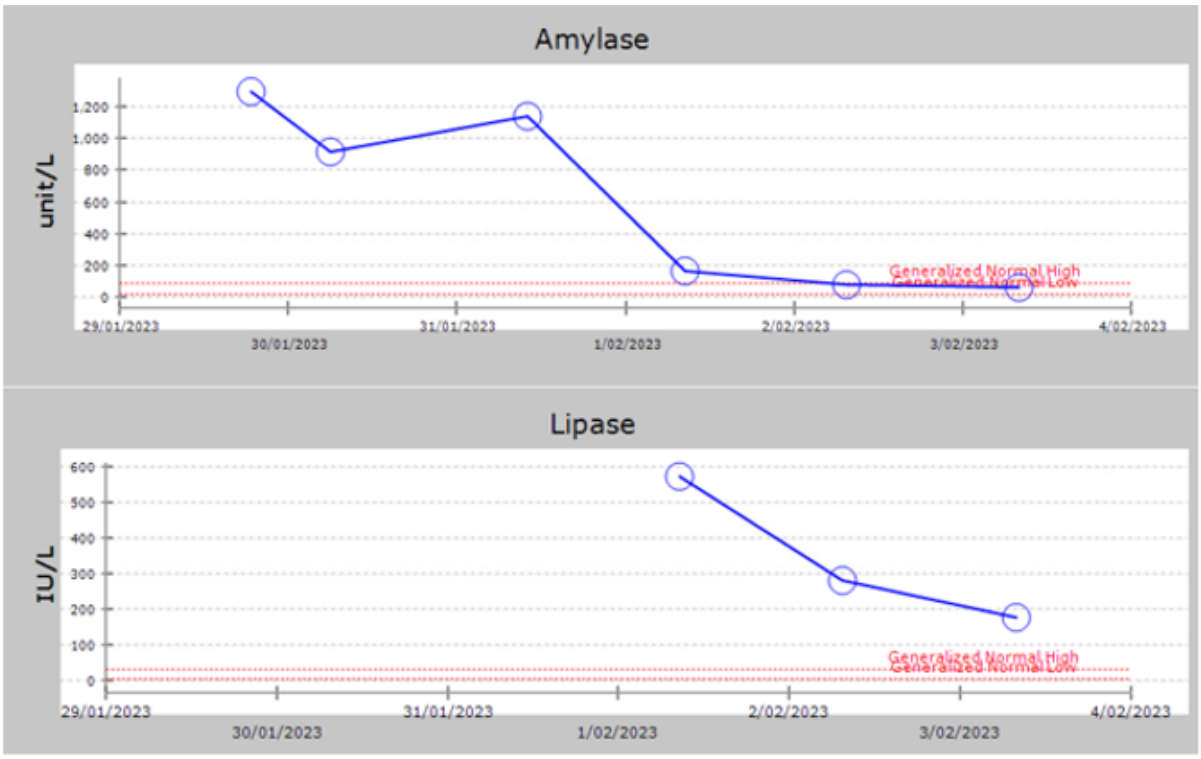

Chart 2: Trend of Pancreatic enzymes during admission.

Treatment Course

During the course of hospitalization, the patient received supportive care with intravenous fluids and potent analegesia. He was kept on gut rest with nil per mouth protocol and his liver functions al pancreatitis enzymes were trended every other day and showed marked decline and correction of associated coagulopathy with 1 dose of Vitamin K. Though our patient was afebrile and clinically pain free Antibiotics were shifted to Meropenem and was covered for 7 days until cultures were out and non-yielding of a pathogen.

After reaching clinical recovery (both symptom-free and with low amylase/Lipase), patient underwent Lap cholecystectomy with intra operative cholangiography. Pathology result showed Gallbladder with patchy mild mural fibrosis. The mucosa showed focal erosion and patchy chronic inflammation. There is no evidence of dysplasia or malignancy after discussions with radiologist, neurosurgeons and infectious disease teams, patient was discharged on oral Amoxiclav with a appointment for subsequent Imaging and follow-up booked at discharge the patient was symptom free and enjoying her regular home cooked meals.

Discussion

Although First Attack acute pancreatitis (AP) can have many causes (systemic illness and metabolic causes, infections, toxins and alcohol, trauma or without a known cause), Drug induced etiologies and stones are still two major culprits for both pediatric and adult populations [4].

Ceftriaxone has been reported to cause AP in both stone forming and primary induction capacities as described in Ruggiero et al. 2010 [5]. Where symptoms of acute pancreatitis appeared on the 3rd day of infusion in a 2 years old treated empirically with ceftriaxone no other risk factor was identified an no stones were reported on imaging, and patient symptoms resolved after discontinuation of the antibiotic. The mechanism of which has not yet been described.

As for Ceftriaxone's stone forming capacity in both gallbladder and kidneys; multiple postulated reasons were discussed, of which it's high concentration in bile and affinity to precipitate with Calcium, lipids and bilirubin [6]. This Capacity is augmented by other cited risk factors that might affect bile execration and increase ceftriaxone concentration like longer

duration of treatment, higher and frequent daily dosages, rapid infusion times, presence of biliary or renal abnormalities, prolonged fasting among other [2,7,8].

Although most cases of Ceftriaxone "stones" are asymptomatic, some cases can present with biliary colic with an incidence reaching 19% of such cases [9], few of which are reported in literature. Lemberg et al, 2005 [10], is one of the few reports that depict a symptomatic case following treatment of "Meningitis". Ceftriaxone was given for 2 weeks as most guidelines recommended and without subsequent abscess which warranted a prolonged course in our case. The patient presented with sporadic colic's without fulminant obstructive complications and self-recovered within a month of stopping Ceftriaxone without a need for surgical intervention.

During this review we encountered only two reported pediatric cases to have this serious and full-blown picture of symptomatic obstructive "gallstone" pancreatitis following ceftriaxone administration with great variation in course and outcome. Sienna et al. 2020 [11] described one of these rare symptomatic cases where acute obstructive pancreatitis occurred in a 9 years old patient who was treated for acute appendicitis with a 7 days course of Ceftriaxone, symptoms appeared as soon as the 5th day of infusion and the condition was self-resolved with the interruption of the infusions. Interestingly there was an associated nephrolithiasis and acute renal injury as well which highlighter the seriousness even more.

The second reported case of Maranan et al. 1998 [12] is very similar to ours in that it depicted 13 years old who received 5 weeks of ceftriaxone for sinusitis complicated by a subdural abscess. patient developed acute pancreatitis due to stones and underwent subsequent cholecystectomy. This patient had exposure to nephrotoxic which contributed no doubt to the presentation.

Learning Points

It's observed that younger patients and children, who are receiving a ceftriaxone regiment that's high in dose or long in duration and those with slowed gallbladder emptying might be at higher risk of developing theses stones. Although "pseudolithiasis" or sludging as described in the literature, is self-resolving after stopping the antibiotic, serious complications that warrant surgical interventions at a significant burden on the family, can arise. This warrants careful evaluation of the need for such long and high courses are needed, and constant vigilance on follow-ups.

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