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Abdominal Pain in the Setting of Atypical Hemolytic Uremic Syndrome Caused by *Streptococcus pneumoniae* Pneumonia

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Case Presentation

A previously healthy 3-year-old fully immunized male presented with upper respiratory tract symptoms, fever, cough, increased work of breathing, and fatigue. The symptoms began 6 days prior to presentation and progressively worsened. Initial evaluation at the outside hospital included chest and abdominal X-ray, a complete blood count, a comprehensive metabolic panel, and blood and urine cultures. Chest X-ray showed right lower lobe pneumonia with small parapneumonic pleural effusion (Figure 1), while abdominal X-ray showed similar lower right airspace disease and hepatomegaly. Complete blood count was remarkable for leukopenia with left shift, anemia, and mild thrombocytopenia (white blood cell = 1.6×10^3 units/μL with 38% bands, hemoglobin = 10.2 mg/dL, and platelets = 196×10^3 units/μL). Comprehensive metabolic panel showed mild transaminitis (aspartate transaminase = 107 U/L, alanine transaminase = 152 U/L) and elevated blood urea nitrogen (53 mg/dL; Table 1).

He was started on ceftriaxone (CTX) and vancomycin and transferred to the pediatric intensive care unit for close monitoring, where he was intubated due to respiratory status and escalated to cefepime and vancomycin. Laboratory evaluation revealed worsening microangiopathic hemolytic anemia (nadir of 4.0 g/dL), worsening thrombocytopenia (nadir 3000/μL), and acute kidney injury with creatinine trending up (peak = 2.1 mg/dL) concerning for hemolytic uremic syndrome (HUS). Other significant laboratory findings included elevated lactate dehydrogenase (peak = 17 935 units/L), decreased haptoglobin (<8.0 mg/dL), and presence of schistocytes on peripheral smear. Subsequently, the initial blood culture grew penicillin susceptible *Streptococcus pneumoniae*. Repeat blood cultures were negative. He was transitioned to CTX monotherapy on day 9 at 100 mg/kg/d for a total of 21 days of treatment with cephalosporins. Patient was NPO (nil per os) for the first 8 days of his hospital stay and on parenteral nutrition for 4 days. Clinical course was complicated by hypertension, worsening kidney function requiring continuous renal replacement therapy for 4 days, and development of corticated pleural effusion requiring video-assisted thoracoscopic surgery procedure. The patient was stabilized on

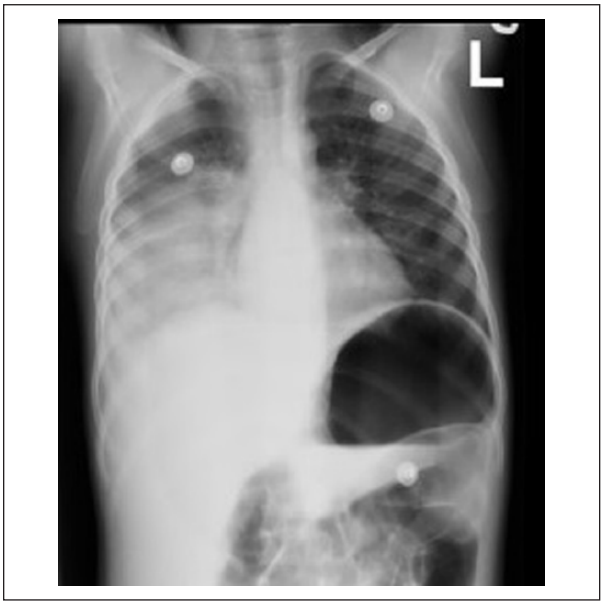

Figure 1. Chest X-ray at time of presentation. Note significant right parapneumonic effusion.

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Table 1. Laboratory Values Throughout Hospitalization.

	Day of Illness						
Laboratory Parameters	Day 1	Day 2	Day 3	Days 10-13	Day 25	Day 29	Day 32
WBC ($\times 10^3/\mu L$)	1.6	5.2	7.1	13.6	7.9	14.6	8.6
Hb (g/dL)	10.2	4.0	9.3	8.9	11.1	11.2	11.0
LDH (units/L)	2741		17 935	2175			
Platelet count ($\times 10^3/\mu L$)	196	3	25	650	602	586	518
Cr (mg/dL)	0.8	1.0	2.1	1.0	0.3	0.3	0.3
BUN (mg/dL)	53	64	119	47	5	3	5
AST (units/L)	162	435	681		1312	1064	80
ALT (units/L)	107	42	107		951	709	321
Amylase (units/L)					70	58	58
Lipase (units/L)					351	110	37
Total bilirubin (direct bilirubin; mg/dL)	1.9 (0.7)	9.4 (6.2)	3.4		1.0	2.2	0.6
GGT (units/L)					348	449	321

Abbreviations: WBC, white blood cell count; Hb, hemoglobin; LDH, lactate dehydrogenase; Cr, creatinine; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ-glutamyltransferase.

room air by day 15 and chest tubes were removed by day 21. Bacterial cultures from pleural effusion were negative, as well as *S pneumoniae* polymerase chain reaction.

On day 25 of hospitalization, he developed acute abdominal pain and emesis. Laboratory values were obtained, which showed elevated liver enzymes as well as elevated lipase and amylase (Table 1). Abdominal ultrasound obtained that day showed significant choledocholithiasis with stones obstructing common bile duct at the pancreatic head.

Final Diagnosis

Choledocholithiasis in the setting of CTX use in *Streptococcus pneumoniae* hemolytic uremic syndrome (SP-HUS).

Hospital Course

On day 26, a magnetic resonance cholangiopancreatography showed "innumerable hypointense stones, dilation of the intra and hepatic ductal system, and 2.3 cm of stones in tandem within the common bile duct" (Figure 2). He failed conservative management, and laparoscopic cholecystectomy with intraoperative cholangiogram was done on day 29 with resolution of symptoms and laboratory parameters (Table 1). Final pathology of gallbladder showed associated acute cholecystitis with mural eosinophil and neutrophil infiltrates, microscopical sandy-like stone structure present, grossly, no definitive stone identified. Follow-up at 2 months with ultrasound showed complete resolution of hepatomegaly and the common hepatic and common bile duct without remaining stones.

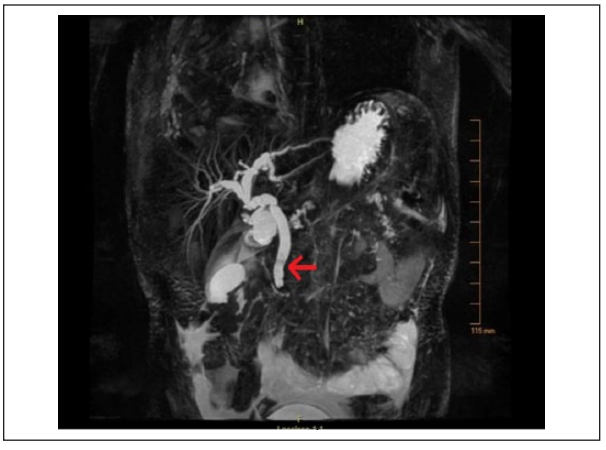

Figure 2. Magnetic resonance cholangiopancreatography on day 26 showing significant biliary tree dilation, in tandem gallstones at the level of the pancreatic head, obstructing the common bile duct.

Discussion

We described the clinical evolution of a previously healthy 3-year-old male who developed choledocholithiasis secondary to CTX in the setting of SP-HUS.

The purpose of this case study is to highlight the important, but often forgotten, association between prolonged CTX use and choledocholithiasis in children. This is especially important when dealing with an underlying condition such as HUS, which independently predisposes patients to development of choledocholithiasis.

HUS is defined as the triad of acute hemolytic anemia, thrombocytopenia, and acute kidney injury. The most common etiology is diarrhea-positive HUS, associated

with Shiga-toxin producing *Escherichia coli* with preceding diarrheal illness. However increasing number of cases have been found to be associated with *S pneumoniae*,[1] ranging from 5% to 10% of all HUS and 40% of atypical HUS cases.[2] Patients with *S pneumoniae*–associated HUS typically present at a younger age than typical diarrhea-positive HUS and may have more severe renal findings often requiring dialysis and a longer hospitalization.[3,4] The frequency of SP-HUS in younger age groups is likely related to the increased carriage rates of pneumococcus during the first 2 years of life.[5]

Pneumococcal neuraminidase A is a major determinant of *S pneumoniae* pathogenesis, and it is thought to play a role[1] in HUS by exposing the Thomsen-Friedenreich antigen on various cell types, including erythrocytes, platelets, glomeruli (to give the characteristic triad of disease),[6] and hepatocytes.[2] Endotoxin, cytokines, and leukotrienes released during the disease lead to increased vascular permeability with plasma extravasation leading to decreased bile flow and thus cholestasis.[6] These can result in intrahepatic vasculitis and microangiopathic thrombosis, leading to hypoxia, liver damage, and ultimately cholestasis.[7]

CTX is commonly used to treat complicated pneumococcal pneumonia.[2] Although CTX offers the benefit of once daily dosing over ampicillin in treating susceptible pneumococcal infections, its prolonged use can lead to gallbladder stones.[8] The concentration of CTX in the gallbladder can be 50 to 120 times greater than systemic, leading to increased likelihood of precipitating with calcium.[9] CTX has also been shown to decrease gallbladder contractility, further predisposing to stone formation.[10] Couple this with decreased contractility in the setting of severe illness, general anesthesia, fasting, and use of total parenteral nutrition such as our patient, the risk of stone formation is incrementally increased.[8-11] Our patient met all the previously reported risk factors for biliary precipitate with CTX use, namely, age >12 months, daily dose >100 mg/kg/d, and duration of treatment >5 days.[8] However, most previously reported cases were asymptomatic and did not need surgical intervention, unlike ours.

The incidence of CTX-induced biliary pseudolithiasis in children ranges from 10.1% to 46.5%[12,13] Most CTX-associated gallbladder dysfunction leads to a clinical entity known as pseudolithiasis, which is rarely associated with clinical symptoms, or if it is, they resolve without intervention and without demonstrating dilatation of the biliary system and in many cases is reversible after discontinuation of CTX.[11,13] Prevalence of CTX-associated gallbladder dysfunction is seen in 0.13% to 0.3% of patients receiving this antibiotic. In a retrospective study of 254 children with gallbladder dysfunction, 20% had exposure to CTX, with 7 of 51 acquiring cholecystitis. Use of CTX was associated with spontaneous resolution.[14] Murata et al followed 60 pediatric hospitalized patients and noted that pseudolithiasis occurred in 11 of them (18.3%). Presentation occurred during the first 10 days of therapy, and none of them reported having symptoms.[11] Within days of discontinuing CTX, all findings were resolved.[11] Finally, a case series of 38 patients with similar dosing to our case showed abnormal ultrasound in 36.8% of patients by day 10 of therapy on CTX, with only 1 patient developing cholelithiasis.[15]

In our patient, the combination of severe SP-HUS and prolonged use of CTX could have led to hepatocyte dysfunction, hepatic congestion, and cholestasis in the setting biliary dyskinesia, resulting in clinically significant cholelithiasis requiring surgical intervention.

Conclusion

Cholelithiasis can be independently seen in patients with SP-HUS and CTX use but symptomatic gallbladder disease requiring intervention is unusual in both cases. Given that cephalosporin use is often the mainstay treatment of *S pneumoniae* infections, this case highlights the importance of its judicious use especially in the presence of other underlying conditions (such as HUS) which heighten the risk of complications.

Author Contributions

CMA: Contributed to conception and design; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
DRH: Contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
BB: Contributed to conception and design; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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