

CASE REPORT

CEFTRIAZONE ASSOCIATED ACUTE CHOLECYSTITIS

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SUMMARY

Ceftriazone is a widely used third generation cephalosporin that has an antimicrobial activity against many gram-positive and gram-negative microorganisms. Long plasma half-life, good tissue penetration characteristics and broad-spectrum coverage makes it advantageous in many indications for both children and adults. Although it is generally well tolerated it has a known effect to induce reversible precipitates of ceftriazone calcium stones and sludge in the biliary system. This kind of biliary pseudolithiasis can be symptomatic and severe cases were previously reported requiring surgical intervention. In this report we present a 36 year-old female patient who was referred to our clinic from another institution after being operated for acute appendicitis. The patient was followed conservatively with medical treatment without any surgical intervention with complete recovery. As this pathology is reversible early surgical intervention should be avoided.

Key words: Biliary sludge, ceftriazone, gallstones

RÉSUMÉ

Cholécystite aiguë associée à ceftriazone

Ceftriazone est une céphalosporine de troisième génération largement utilisée en thérapeutique et elle présente une activité antimicrobienne efficace contre plusieurs micro-organismes Gram-négatifs et Gram-positifs. Grâce à une longue demi-vie plasmatique, de bonnes caractéristiques de pénétration dans les tissus et une couverture à large spectre, ceftriazone a plusieurs indications pour les enfants et les adultes. Bien que ceftriazone est généralement tolérée, elle peut former des précipités réversibles des calculs de calcium et/ou des boues biliaires. Ce type de pseudolithiasis biliaire peut avoir des cas symptomatiques; et des cas sévères ont été signalés nécessitant une intervention chirurgicale. Dans cet article on présente le cas d'une femme âgée de 36 ans qui a été transférée dans notre clinique d'un autre hôpital où elle a été opérée pour une appendicite aiguë. La patiente a été traitée de façon conservatrice avec un traitement médical sans aucune intervention chirurgicale avec récupération complète. Comme cette pathologie est réversible, l'intervention chirurgicale précoce doit être évitée.

Mots-Clés: boue biliaire, ceftriazone, calculs biliaires

INTRODUCTION

Ceftriazone is a widely used third generation cephalosporin that has antimicrobial activity against many gram-positive and gram-negative microorganisms. Long plasma half-life, good tissue penetration characteristics and broad-spectrum coverage makes it advantageous in many indications for both children and adults. Its standard dose is 1-2g intravenously daily for the adult and children older than 12 years old. This dose can be elevated in severe cases. About %50 - %60 of the drug is excreted unchanged in the urine and the remaining %40 is excreted by the bile also unchanged. (1) Ceftriazone is known to induce reversible precipitates of ceftriazone calcium in the gallbladder. (2) Tolerance for this antibiotic is

usually good, but several adverse effects have been reported, including diarrhea, rash, thrombocytopenia, eosinophilia, elevated liver enzymes, renal stones, gall stones and hemolytic anemia.

Transient gallbladder stones and/or sludge formation is reported generally in the pediatric age group of patients. It is generally a reversible finding but severe cases are also reported requiring surgical intervention. In this report we present a case of ceftriazone induced biliary sludge and acute cholecystitis during the postoperative course after of an appendectomy operation.

CASE REPORT

A 36 year-old 48 kg female patient was seen at the

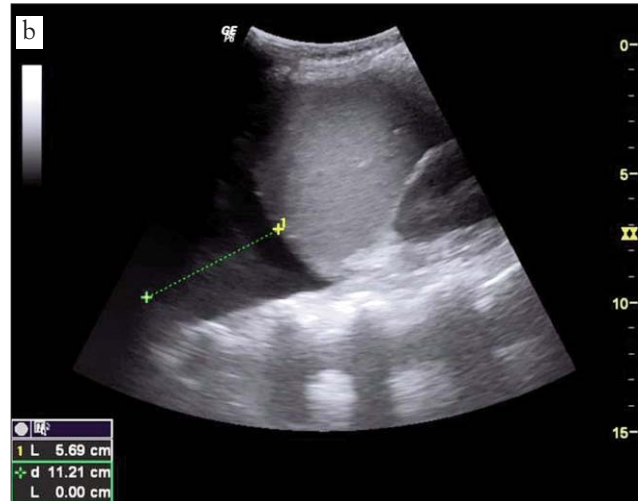


Figure 1 a, b - Abdominal ultrasonography during admission

emergency polyclinic with the complaint of postoperative right upper quadrant pain. She was very uncomfortable and her vitals showed a blood pressure of 110/70 mmHg and fever of 38°C. Right upper quadrant pain and muscular defense was present in her abdominal examination. She had been operated for acute appendicitis four days earlier in another institution. In her reports it was seen that she went to that hospital with right lower abdominal pain. She had also fever, nausea and vomiting and received ceftriaxone intravenously 2 grams per day. Her blood work up at the admission showed elevation of white blood cell count (WBC) $11.07 \mu 10^3/L$ which became $19.22 \mu 10^3/L$ after one day. Blood biochemistry was within normal limits. Abdominal ultrasonography was normal and appendix vermiformis could not be visualized. Gall bladder and other intraabdominal organs were normal. As the abdominal pain became worse during the follow-up and there was an elevation of WBC, the attending surgeon decided to operate the patient with the possible diagnosis of acute appendicitis through a Mc Burney incision. Appendix was found to be slightly inflamed and other findings were normal. The abdominal findings became worse after the postoperative day two despite the fall of WBC counts within normal ranges. The pain was right sided, predominantly on the right upper quadrant this time and she had fever of 40°C from axillary measurement. A repeat abdominal ultrasonography confirmed thickening of gallbladder wall, sludge and fluid collection around the liver and gallbladder. Cholecystectomy had been planned but the patient refused and she was referred to our institution for further evaluation and treatment.

After the evaluation in our emergency department the patient was admitted to the surgical ward with the diagnosis of acute postoperative cholecystitis. Her blood work up showed WBC: $8150 \mu 10^3/L$, CRP 6.75mg/dL, AST 38 U/L. Other variables were within normal ranges.

Abdominal US showed gallbladder wall thickening, biliary sludge and fluid around the liver and gallbladder. Intra and extrahepatic biliary ducts were normal. Abdominal CT showed findings related to acute cholecystitis, per-



Figure 2 - Abdominal CT during admission

ihepatic, interloop ascitis and right pleural effusion (fig. 1 a-b and fig. 2).

Acute cholecystitis and pseudolithiasis due to ceftriaxone was suspected. Ceftriaxone was stopped, the patient was followed with *n/po*, intravenous fluid therapy and ceftazidime was administered. The patient was stable and clinical findings were better starting from the first day. Oral feeding was gradually started from the second day of admission. Ultrasonographic follow up confirmed the resolution of intraperitoneal fluid and relieving the findings of acute cholecystitis. The patient was discharged on the fifth day with complete recovery. Her first control on the first month was totally normal as well as her abdominal ultrasonography (fig. 3). At this control gall bladder looked totally normal without any evidence of biliary lithiasis and/or sludge formation.

DISCUSSION

Ceftriaxone is a widely used safe parenteral antibiotic. Although it is generally well tolerated it is known to induce reversible precipitates of ceftriaxone calcium in the gallbladder (1). This so-called reversible biliary pseudolithiasis due to ceftriaxone was first described by Schaad et al. in children (2). Biliary pseudolithiasis has been reported to occur in %20-%46 of the patients treated with ceftriaxone but only a minority of these patients become symptomatic and it seldom poses any problem



Figure 3 - Control abdominal USG

such as acute cholecystitis (3-5). The risk of this complication increases with high doses, prolonged administration, rapid bolus injection, parenteral nutrition, slow gallbladder emptying time. Biliary sludge may cause complications including cholangitis, pancreatitis and cholecystitis being also reported in the literature (6,7). As this is a reversible problem, prompt surgical intervention should be delayed with discontinuation of the drug.

Physicians should be aware of this side effect of ceftriaxone and follow their patients with ultrasonography in case of physical findings to avoid unnecessary surgical intervention. Surgery should be reserved if conservative management fails.

REFERENCES

1. Mc Namara PJ, Stoeckel K, Ziegler WH. Pharmacokinetics of ceftriaxone following intravenous administration of a 3 g dose' European Journal of Clinical Pharmacology 1982; 22:1,71-75.
2. Schaad UB, Tschappeler H, Lentze MJ. Transient formation of precipitations in the gallbladder associated with ceftriaxone therapy. *Pediatric Infectious Disease* ;1986,5:6,708-710.
3. Becker CD, Fischer RA. Acute cholecystitis caused by ceftriaxone stones in an adult. *Case Reports in Medicine* ;2009, Article ID 132452, 2 pages, 2009. doi:10.1155/2009/132452.
4. Pigrau C, Pahissa A, Gropper S, Sureda D, Martinez-Vazquez JM. Ceftriaxone-associated biliary pseudolithiasis in adults. *Lancet*; 1989,15:2(8655),165.
5. Shiffman ML, Keith FB, Moore EW. Pathogenesis of ceftriaxone associated biliary sludge. In vitro studies of calcium-ceftriaxone binding and solubility. *Gastroenterology*; 1990, 99:6,1772-1778.
6. Tamai Y, Kobayashi K. Acute cholangitis associated with ceftriaxone therapy. *Internal Medicine*;2013, 52:3,403-404.
7. Sasaki Y, Aoki S, Aoki K, Achiwa K, Yama T, Kubota M, et al. Acute pancreatitis associated with the administration of ceftriaxone in an adult patient. *Nihon Shokakibyo Gakkai Zasshi*; 2009, 106:4,569-575.