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Case Report
A Fatal Case Report of Ceftriaxone-induced Hemolytic Anemia and Literature Review in Pediatrics

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Abstract

Background and Objective: Ceftriaxone is a frequently used antibiotic in children. This paper is to raise awareness of the challenges in managing ceftriaxone-induced hemolytic anemia and requesting more successful and useful predicting tools in its detection and prevention in pharmacogenomics field. **Methodology:** An adversary case report of a 5 years old boy who died from ceftriaxone-induced hemolytic anemia within 12 h in children's hospital though all resuscitation attempt made. **Results:** Soon after intravenously ceftriaxone, the patient developed acute reaction to ceftriaxone presented with cold and pallor skin with shallow breath etc. Therefore, ceftriaxone infusion was stopped immediately and the patient was moved to emergency room (ER) for resuscitation from hematology outpatient clinic. Until his heart rhythm returned to normal and stabilized, he was then transferred to Pediatric Intensive Care Unit (PICU). Further, the patient developed bradycardia, reduced blood pressure, unconsciousness, under-responsiveness and oliguria. Additionally, his urine was turned from pale yellow to dark red. Urinalysis determined occult blood and trace protein existence. The hemoglobin level was 9.2 g L^{-1}. Coomb's test came back strong positive accompany with positive anti-C3d antibody. Hemolytic crisis was suspected. Unsuccessfully, the patient died from hemolytic shock, although all emergent resuscitation attempts were made. **Conclusion:** Ceftriaxone induced autoimmune hemolytic is extremely rare but could be severe as life-threatening condition stressed in pediatric. Its treatment is clinical challenging with poor outcome. Therefore, prevention is the key compared to treatment.

Key words: Ceftriaxone, hemolytic syndrome, pediatric, upper respiratory tract infection, antibiotics

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ceftriaxone belongs to the third-generation semi-synthetic cephalosporin family, which has higher potency against both Gram-positive and Gram-negative strains compared to its predecessors. The advantages of this medication include broad spectrum activity, increased efficacy, long half-life guaranteed as once daily dose schedule, resistance to enzymatic degradation and less side effects[1]. Ceftriaxone has been commonly utilized in meningitis, pneumonia, peritonitis, skin and soft tissue infection, urinary tract infection, bone and joint infection, gonorrhea, biliary tract infection, septicemia, reproductive system infection and surgical prophylaxis indicated for susceptible strain[2]. The incidence of its adversary events is around 7-8%. This agent main adverse effects are allergic reaction, gastrointestinal tract reaction, hepatic and renal toxicity, chronic hemolytic anemia, thrombophlebitis, etc[3]. Specifically, cases of ceftriaxone induced Autoimmune Hemolytic Anemia (AIHA) have been reported both domestically and abroad[4,5], in which severe cases can lead to death. Foreign reports put the mortality rate of AIHA as high as 50%[6]. Also, literature reports have demonstrated a correlation/association between ceftriaxone induced AIHA and children under the age of 10, which accounts for 50% of the ceftriaxone induced AIHA cases in all ages[7].

The onset of ceftriaxone induced AIHA in children varies from minutes to days after initiation because of individual variation[8,9]. The hemolytic reaction mainly occurs as intravascular hemolysis. Clinical features of hemolytic reaction consist of weak pulse, shallow breathing, poor response to external stimuli, irritability, crying, pale skin, malaise, loss of appetite, hematuria, proteinuria, a below normal range of hemoglobin (Hb) serum concentration and a positive Coomb's test[10,11]. The present report describes one new case of severe ceftriaxone-related hemolytic anemia caused by drug-dependent antibodies reacting in the present of ceftriaxone. The findings of all previously reported cases of ceftriaxone-induced AIHA will also be summarized. Ceftriaxone therapy has few complications except for rare penicillin-like allergic reactions. Immune hemolytic anemia has been reported in adults in most prior cases but fatal hemolytic reactions have not been reported during childhood less than 5-years old.

MATERIALS AND METHODS

The first hospital visit at Children's Hospital of Fudan University of a 5-years old male was due to fever peaked at 39.1°C (102.38), occasional cough and mild headaches with no known predisposing factors. The patient had three non-projectile vomiting events with minimal amount of gastric content one day. All following signs were not observed in this patient: Chill, convulsion, rhinorrhea, gingival bleeding, diarrhea, hematochezia, palpitation, chest tightness, frequent urination, urinary incontinence, dysuria and gross hematuria. The complete blood count was: White blood cell count (WBC) 34.48×10^9 L^{-1}, hemoglobin (Hb) 79 g L^{-1} and neutrophil (N%) 82.6%. The diagnosis of this patient was upper respiratory tract infection done by attending physician in Hospital Emergency Department (aka emergency room ER). He then treated with Child Chi Qiao Qing Re granules and topical Fu Fang Xiang Kai Wei Tei (both are Traditional Chinese Medicine (TCM)).

Two weeks after first visit, the patient still febrile and presented to hematology outpatient clinic. At that time, the boy was conscious and aware. The complete blood count was: WBC 14.6×10^9 L^{-1}, Hb 87 g L^{-1}, N% 72.4%, platelet (PLT) 180×10^9 L^{-1}, C-reactive protein (CRP) 22 mg L^{-1} and reticulocyte count (RET) 0.6%. After, in emergency room (ER) pediatrician prescribed 2 g ceftriaxone dissolved in 5% glucose normal saline (GS) 100 mL given intravenously for his upper respiratory tract infection. He had used intravenous infusion (IV) ceftriaxone once or twice prescribed by other hospitals and the specificity of agent was unknown. Two minute after IV ceftriaxone, the kid presented with skin welts, pallor in complexion, cold to touch, together with poor circulation. Consequently, ceftriaxone was discontinued. Supportive oxygen therapy was provided via a face mask to the patient. At that time, his heart rate was sixty beats per minute. Following resuscitation provided immediately: Normal saline to increase blood volume for maintaining blood perfusion, epinephrine and dexamethasone IV bolus injection and tracheal intubation. Within an hour, the patient cardiac rhythm returned to normal. Then the patient was transferred to PICU and on mechanical ventilation.

RESULTS

At PICU, the patient Blood Pressure (BP) and Heart Rate (HR) dropped again with enhanced severity. Consequently, percutaneous oxygen saturation level could not be obtained. The patient became comatose with less than 50 mL urine output (oliguric). Severely, he showed poor response to following fluid replacements, epinephrine, dopamine and dobutamine treatment. Chest X-ray imaged widespread infiltrative shadows in both lungs, suggesting either pulmonary edema or pulmonary hemorrhage. Blood urea

Table 1: Laboratory results before and after intravenous administration of ceftriaxone

Laboratory test results	Two weeks before	Before ceftriaxone	After ceftriaxone
white blood cell count ($\times 10^9$ cell L^{-1})	34.5	14.6	5.5
Hemoglobin, Hb (g L^{-1})	79.0	87.0	9.2
Neutrophil (N%)	82.6	72.4	NA
Platelet ($\times 10^9$ cell L^{-1})	NA	180.0	40
C-reactive protein, CRP (mg L^{-1})	NA	22.0	NA
Reticulocyte count, RET (%)	NA	0.6	NA

NA: Not available

nitrogen (BUN) and serum creatinine (SCr) were within normal range. Urine turned from clear, pale to dark red with occult blood. Urinalysis showed trace amount of protein with normal urobilinogen levels and negative urine bilirubin. Also, in patient blood sample, hemoglobin was extremely low 9.2 g L^{-1}. Direct Coomb's test came back strong positive. Anti-C3d was positive but anti immunoglobulin G (IgG) was negative, therefore, based on the evaluation above, hemolytic crisis was suspected.

To control hemolytic crisis, the patient was given 25 g of intravenous immunoglobulin (IVIG), 200 mg of IV prednisolone and one unit of Packed Red Blood Cells (PRBC) as intravenous transfusion, which had been washed three times. At 11: 00 pm (after 10 h of case onset), the patient heart rate and blood pressured had dropped abruptly to 50-60 bpm and the blood pressure was 30 mm Hg. Percutaneous oxygen levels could not be obtained again. Soon, cardiac pulmonary resuscitation (CPR), bag-valve-mask ventilation and methods to correct acidosis were initiated. Moreover, IV bolus of epinephrine was given repeatedly according to the hospital protocol. The process of resuscitation lasted beyond 40 min. Unfortunately, the patient heart condition deteriorated to cardiac arrest and the patient died at 11:47 pm. The total time course of this allergic reaction was less than 12 h (Table 1).

DISCUSSION

In this case, the patient was obtundation, presented signs of poor circulation and skin welts after ceftriaxone administered within 2 min. Urine analysis revealed occult blood and trace amount of protein existence. His hemoglobin (Hb) level was 9.2 g L^{-1}. The direct Coomb's test came back strong positive, anti-C3d was positive while anti-IgG was negative, which is consistent with the diagnosis of ceftriaxone induced AIHA. Similar cases have been reported in literature. Again, the aforementioned symptoms cannot be explained by the patient's illness or by other medication. This adversary event has meet the following five criteria for analysis and determination of adverse reaction stipulated by methods of monitoring and managing of adverse drug reactions: (1) There is a temporal correlation between drug usage and the onset of adversary effect, (2) The adverse effect belongs to a known type of reaction, (3) Symptoms will be alleviated after drug cessation, (4) There is a re-stimulation reaction and (5) The adverse effect cannot be explained by drug use or illness itself, etc. Therefore, those results confirmed the cause was ceftriaxone of this case based on the discussion above.

The mechanism of action of drug-induced hemolytic anemia (HA) are autoantibody development and immune-complex formation. Many studies have proved that ceftriaxone would cause HA through the immune-complex mechanism[12]. Ceftriaxone sodium can stimulate the production of drug-dependent antibodies (DDABs) that have cross-reactivity. When ceftriaxone or drugs with similar structure to cephalosporins are administered again, antibodies and the drug or its metabolites form drug-antibody immune complexes, which bind to specific target proteins on Red Blood Cell (RBC) membrane. The binding then activates the complement system, ultimately damages RBC membrane causing cell lyses and series of hemolytic reactions in veins. The hemolytic reactions will propagate to fetal event. Garrity[13] wrote the first report of a lethal case of ceftriaxone induced immune hemolytic anemia (IHA). The specific antibody against ceftriaxone has been found in patient serum. When ceftriaxone added, the induced-antibody will react with RBCs and then bind to C3 complement. Lascari[14] also reported a fetal case of IHA induced by ceftriaxone in a child with chronic leukemia. In Lascari's case, Coomb's test was negative before ceftriaxone usage but after ceftriaxone administration, Coomb's test was strong positive postmortem. Again, many other research groups also detected anti-ceftriaxone sodium IgM antibodies in ceftriaxone induced HA pediatric patients' blood samples[15-17].

In this 5-years-old male case, the patient had received IV infusion of ceftriaxone recently from other hospital. It is possible that ceftriaxone specific antibodies have already been produced and upon re-introducing, a strong and quick inflammatory response will be initiated via the drug itself or its

structurally related relatives due to cross reaction. The outcome was drug induced fatal HA. In addition, some cephalosporin agents may lead to hypoprothrombinemia, which accelerates and contributes to hemolysis. Although, foreign reports of ceftriaxone induced hemolytic anemia are rare (incidence less than 0.01%), the mortality rate is as high as 50%. The drug induced HA develops rapidly and severely especially in children, which group of patient accounts for 68% of all cases, in which 38% are fatal.

In summary, prior to prescribing ceftriaxone, a detailed allergy and medication history should be collected in pediatrics. It suggests that care providers should closely monitor drug reactions after administering via observing changes of complexion, consciousness and vital signs. Once hematuria is detected, the medication could be withdrawn immediately at the very early state of drug-induced HA event. For treatment, when hemolytic reaction discovered, epinephrine or dexamethasone and IVIG should be given to prevent following RBC's destruction and vasculature tissue damage. Simultaneously, PRBCs transfusion will be introduced to correct the state of anemia.

CONCLUSION

Ceftriaxone induced autoimmune hemolytic is extremely rare but could be severe as life-threatening condition stressed in pediatric. Its treatment is clinical challenging with poor outcome. Therefore, prevention is the key compared to treatment. Fortunately, advancement in genetic testing will identify culprit alleles in human genome to predict patient outcome with ceftriaxone therapy from safety perspective. Pharmacogenomic testing will help patients avoid ceftriaxone-induced hemolytic anemia reactions in the future.

SIGNIFICANCE STATEMENT

Board spectrum antibiotic such as ceftriaxone is required to control severe infection in certain cases. Additionally, antibiotic induced anaphylaxis has placed pediatric patients at higher risk of hemolytic syndrome compared to adult patients. Ceftriaxone-induced autoimmune hemolytic syndrome is rare but severe and sometimes life threatening especially in children demonstrated by high mortality rate. This case report presented a 5-years-old male patient, who died in hospital within 12 h from acute heart failure secondary to ceftriaxone-induced hemolytic anemia, though all attempts were made to resuscitate. This case report will help physicians and researchers to recognize the severity of ceftriaxone-induced autoimmune hemolytic syndrome in pediatric patients and be aware of its' management and monitoring that many physicians were overlook in empiric practice. Encouragingly, advanced genetic testing will play a revolutionary role in predicting and preventing drug-induced hemolytic syndrome in future clinical practice.

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