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A rare case report of ceftriaxone induced immune hemolytic anemia - A fatal condition

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Abstract
Ceftriaxone is an empiric antibiotic widely used in children and is likely to cause ceftriaxone-induced immune hemolytic anemia (CIIHA). This adverse reaction to ceftriaxone may result in fatal and severe complications if not diagnosed early. Herein, we describe management of a rare case of CIIHA. A 5-year-old boy, with sickle cell disease (SCD), presented with signs of vaso-occlusive crises (VOC), osteomyelitis (OM), in form of; shoulder pain, swelling and fever treated with ceftriaxone infusion. Post-infusion patient experienced severe pale, tachycardia, rapid breathing and lethargic with dark color of urine. Lab investigations confirmed a sudden drop in hemoglobin indicated severe anemia, hemolysis and thrombocytopenia. Immediately, the ceftriaxone infusion was stopped, and supportive care was given.
Further, the patient was treated with packed RBCs which stabilize him. This case demonstrates a rare event that occurs after ceftriaxone administration to a boy with SCD. Understanding clinical signs and correct diagnosis of CIIHA along with immediate cessation of ceftriaxone therapy can be useful in the successful clinical management of such patients.

Keywords: Hemolytic anemia, adverse drug reaction, sickle cell disease, ceftriaxone-induced immune hemolytic anemia, ceftriaxone

Introduction
Ceftriaxone-induced immune hemolytic anemia (CIIHA) is a rare episode with potentially fatal complication of ceftriaxone administration. CIIHA occurs at an estimated incidence rate of 1/million/year and mortality rate due to CIIHA was suggested as high as 30 % [1, 2]. Ceftriaxone is an antibiotic of choice for acute febrile episodes in children with sickle cell disease (SCD). It can cause severe immune complex-type reaction through formation of anti-ceftriaxone antibodies (acAb) causing intravascular hemolysis [3].
Given the benefit of rarity to CIIHA, it is difficult for clinicians to differentiate between overlapping signs of CIIHA and underlying disease in patients. To take an immediate action for the management of CIIHA, clinicians should correctly diagnose the CIIHA to prevent the patient from severe complication events. Here in the present study, we described a rare case of CIIHA to demonstrate the clinical features and its management with future perspectives.

Case Presentation
A 5-year-old boy, with sickle cell disease (SCD), was presented on 2nd April night to Emergency department in King Saud Medical City, Riyadh, Saudi Arabia with signs of vaso-occlusive crises (VOC), osteomyelitis (OM), in form of; shoulder pain, swelling and fever. He had a history of blood transfusion for many times and treatment with hydroxyurea.
On presentation, his baseline vitals were as follows, temperature (39.1°C), respiratory rate (22 beats/min), heart rate (120 pulses/min), SpO2 (98%), hemoglobin (8.3 g/dL) and platelet count (200*109/µL). The white blood cells count at the time of presentation was 12,000/µL. The treatment was initiated immediately, and the patient received intra-venous infusion of ceftriaxone (75 mg/kg/day) for twenty minutes to treat infection.
After few minutes from infusion of ceftriaxone, the patient experienced severe pale, tachycardia, rapid breathing and lethargic with dark color of urine. Post ceftriaxone reaction demonstrated temperature, heart rate, respiratory rate, and SpO2 of 36.7°C, 190 pulses/min, 28 beats/min and 90-92 %, respectively. The history indicated the patient had received ceftriaxone multiple times prior this occasion without any consequences. The laboratory investigations were performed and showed severe drop in Hb of 3.2 g/dL and severe metabolic acidosis. We found elevated levels of bilirubin evident by dark color of urine. This indicated severe anemia and thrombocytopenia followed by which the cetriaxone infusion was discontinued.
Supportive care was immediately provided, including oxygen and a normal saline bolus until the patient was stabilized. Following that, a unit of packed red blood cells (PRBCs) was administered. After PRBCs transfusion the patient was normalized. On discharge, his vital signs showed; temperature was 37.1°C, respiratory rate was 20 beats/min, heart rate was 109 pulses/min, and SpO2 was 97 %. Table *1* shows the result of lab investigations of case 1 indicated improvement in the health condition of the patient after discontinuation of ceftriaxone.

Table 1: Results of lab investigations of the case

Lab investigations	At presentation	Post reaction to ceftriaxone infusion	At discharge
Hb (g/dL)	8.3	3.2	9.4
WBCs (cells/µL)	12,000	*	12,200
Platelets (cells/µL)	200*109	180*109	200*109

* WBC count post reaction to ceftriaxone could not be obtained due to insufficient sample with low hemoglobin

Discussion
Ceftriaxone is a pre-dominated and widely used antibiotic in the treatment of fatal infections in pediatric and adult population due

to its broad-spectrum coverage, long elimination half-life and safety profile [4]. It is safe and highly prescribed antibiotic for hospitalized children with sickle cell disease (SCD) [5]. Recently, in many case reports and observational studies, ceftriaxone has been identified to cause severe immune complex-type reaction leading to hemolysis and fatal complications, termed as ceftriaxone-induced immune hemolytic anemia (CIIHA) [6]. CIIHA is a rare event which could be potentially devastating, especially in pediatric group of patients, if not diagnosed early [3]. Children with underlying diseases such as sickle cell disease (SCD) and HIV may predispose to CIIHA due to abnormal structure of RBCs and multiple exposure to ceftriaxone therapy [7-9]. Majority of CIIHA cases reported worldwide were attributed to formation of drug-dependent anti-ceftriaxone antibodies (acAb) causing immune complex-type reaction, complement activation followed by intravascular hemolysis [3].

A sharp decrease in hemoglobin, formation of acAb, multi-organ involvement and history of previous ceftriaxone exposure are characteristic features of CIIHA [6]. In our patient, a fall in Hb from 8.3 g/dL (on admission) to 3.2 g/dL was observed post ceftriaxone infusion indicated positive case for CIIHA [1, 10]. This was as ideal first finding confirming CIIHA. Neuman *et al* (2014) reported a sudden drop in Hb could led to severe complications such as shock, circulatory arrest, organ ischemia, renal failure, disseminated intravascular coagulation (DIC), and acute respiratory distress syndrome (ARDS) in 27 cases [3]. Also, some of the other clinical features of CIIHA include acute back pain, altered mental status, intravascular hemolysis (dark urine, elevated lactate dehydrogenase, bilirubin). We also observed in our case study, the patient has pale dark urine indicating the stage of hemolysis with hemoglobinuria. Post-reaction, the ceftriaxone infusion was discontinued which is considered as the primary treatment measure reported by Northrop and Agarwal (2015) [11]. Termination of ceftriaxone therapy would be of great support in reducing mortality. Laboratory investigations were suggested for confirmation of CIIHA include Coombs' direct antiglobulin test (DCT) for detecting C3 complement, IgG type and IgM antibodies [6, 12]. In this case study, we did not measure the acAb due to absolute confirmation with Hb levels.

Transfusion of red blood cells, erythropoietin and intravenous immunoglobulins are the first line treatment of CIIHA [13, 14]. In our case, the patient was managed with infusion of packed RBCs resulted into remarkable recovery from CIIHA evident with increase in Hb, platelet and WBC count as shown in Table *1*. In some cases, steroids are also favored as supportive care due to their inherent immune modulating properties. However, there is no obvious reason to recommend steroid in CIIHA [2, 6, 15]. The patient was further restricted to ceftriaxone or same class antibiotic to prevent recurrence of drug induced immune reaction.

Further, we should consider the other treatment options available in near future. Also, early diagnosis of CIIHA would also benefit the patients from fatal outcomes.

Conclusions

In summary, our case reported a rare event that occurs after ceftriaxone administration to a boy with sickle cell disease. Clinicians should be attentive of history of any prescribed medication prior to start of ceftriaxone therapy. We would recommend the immediate cessation of therapy if CIIHA is sought. Alternate treatment for CIIHA should always be considered by clinicians for better outcomes.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

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