Ceftriaxone-Induced Hemolytic Anemia: A Rare Case Report

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ABSTRACT

Introduction: Drug-induced immune hemolytic anemia (DIIHA) is a rare complication of any drug therapy, which if not recognized early can be fatal. It is usually underdiagnosed. Ceftriaxone is a commonly used antibiotic in routine practice and is one of the most common drugs to cause DIIHA.

Case Presentation: We report a case of ceftriaxone-induced immune hemolytic anemia in a 62-year-old woman who had a negative result of a direct antiglobulin test.

Discussion: A review of the literature highlights the salient features of DIIHA and underscores the importance of keeping the suspicion of DIIHA high in the relevant clinical settings because ceftriaxone has been associated with particularly severe outcomes of DIIHA. In cases of unclear hemolysis and despite a negative result of a direct antiglobulin test, the treating physician must keep suspicion of DIIHA high and meticulously look for the possible culprit drugs. Treatment with suspected drugs must be stopped promptly to prevent severe complications and fatal outcomes.

INTRODUCTION

Drug-induced immune hemolytic anemia (DIIHA) is rare complication of any drug therapy. The estimated incidence of DIIHA is around 1 in 1 million per year.[1,2] If not recognized early, DIIHA can be fatal. Ceftriaxone is a commonly used antibiotic in routine practice and is also one of the most common drugs to cause DIIHA. We report a case of ceftriaxone-induced immune hemolytic anemia and present a review of the literature to highlight its salient features and potential severity. The case is worth featuring because the result of the direct antiglobulin test (DAT) was negative in the patient, which is unusual.

CASE PRESENTATION

Presenting Concerns

A 62-year-old woman, with known type 2 diabetes mellitus receiving oral antidiabetic drugs, presented to our Emergency Department with fever and pain in the right flank region for the past 2 days. On examination, her vital signs were stable and physical findings were unremarkable except for mild tenderness of the right side of the costovertebral angle. Her blood glucose level measured by glucometer was 557 mg/dL, and urine for ketones was 2+, albumin 2+, and glucose 4+ on a dipstick test. Microscopic analysis revealed a field full of neutrophils. Her blood tests yielded the following values: Hemoglobin, 10.7 g/dL; white blood cell count, 17,980/mm^3 (× 10^3/μL); platelets, 200,000/mm^3; reticulocytes, 0.5%; hematocrit, 32.8%; serum urea nitrogen, 41 mg/dL; serum creatinine, 1.1 mg/dL; sodium, 136 mEq/L; potassium, 4.8 mEq/L; total bilirubin, 1.1 mg/dL; aspartate aminotransaminase, 20 U/L; alanine aminotransaminase, 21 U/L; and alkaline phosphatase, 116 U/L. Results of an arterial blood gas analysis revealed high anion gap metabolic acidosis. Results of an ultrasonogram of the abdomen were suggestive of pyelonephritis.

Therapeutic Intervention and Treatment

The patient was admitted, with a diagnosis of diabetic ketoacidosis with a urinary tract infection. She was started on a regimen of intravenous insulin and fluids for the management of diabetic ketoacidosis and intravenous ceftriaxone for urinary tract infection treatment. After 2 days, the patient recovered from diabetic ketoacidosis and was shifted to a basal-bolus regimen of subcutaneous insulin. The antibiotic treatment was continued for a urinary tract infection.

Five days after the initiation of ceftriaxone therapy, her hemoglobin level dropped from 10.5 g/dL to 6.4 g/dL, hematocrit decreased from 32.8% to 29.3%, and the total bilirubin level rose from 1.1 mg/dL to 1.8 mg/dL, with the indirect bilirubin level rising from 0.6 mg/dL to 1.3 mg/dL. There was no evidence of active bleeding to suggest disseminated intravascular coagulation. The coagulation profile was normal. With suspicion of DIIHA high, ceftriaxone therapy was immediately discontinued and was shifted to imipenem.

Two days later, the hemoglobin level further dropped to 4.8 g/dL, hematocrit decreased to 25.2% with increased reticulocyte count to 7.1%, and the total and indirect bilirubin levels rose to 3.3 mg/dL and 2.4 mg/dL, respectively. Serum lactic acid dehydrogenase levels measured at this stage were 607 U/L (normal < 250 U/L). A DAT and an indirect antiglobulin test (both immunoglobulin [Ig] G and complement based, polyspecific reagent) done at this time yielded negative results. A peripheral blood smear showed red blood cells (RBCs) as reduced in number and microcytic hypochromic, with anisopoikilocytosis and absent schistocytes. There was no derangement in kidney function test results throughout the admission. There was no bleeding manifestation in the patient. Taken together, all these findings were suggestive of hemolytic anemia, possibly drug (ceftriaxone) induced. At this time, 1 unit of packed RBCs was transfused.

Further laboratory tests excluded other causes of anemia with the following values: Ferritin, 1659 ng/mL (reference range = 10.0-120.0 ng/mL); iron, 166 μg/dL (50.0-170.0 μg/dL); total iron-binding capacity, 234 μg/dL (230.0-425.0 μg/dL); transferrin saturation, 70.0% (15%-50%); vitamin B_{12}, 226 pg/mL (180.0-914.0 pg/mL); folate, 5.5 ng/mL (3.0-17.24 ng/mL);

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and negative antinuclear antibody. Results of a serologic workup were negative for HIV, hepatitis B, and hepatitis C. Glucose-6-phosphate dehydrogenase levels were within the normal range. Flow cytometry results for CD55 and CD59 for detection of paroxysmal nocturnal hemoglobinuria were within normal limits.

Follow-up and Outcomes

Seven days after discontinuation of ceftriaxone therapy, her hemoglobin level improved to 7.5 g/dL, and bilirubin and lactic acid dehydrogenase levels normalized without any corticosteroid therapy. The patient was discharged on a regimen of insulin and folic acid and subsequently followed-up on an outpatient basis. On day 40, her hemoglobin level was 11.5 g/dL, and the patient had returned to her routine life. A case timeline appears in Table 1.

DISCUSSION

DIIHA is rare complication of any drug therapy, which if not recognized early can be fatal. It is usually underdiagnosed, with the incidence estimated to be around 1 in 1 million per year.[1,2] It is pertinent to differentiate DIIHA from autoimmune hemolytic anemia so that discontinuation of the drug can be considered at the earliest time, thereby avoiding drastic consequences.

More than 130 drugs have been reported to cause DIIHA, with antibiotics and platinum-based chemotherapies being the most common causative agents.[3,4] Among antibiotics, the second- and third-generation cephalosporins have been reported as the most common causes of DIIHA.[5] In a study by Garratty,[6] ceftriaxone was the second most common drug to cause DIIHA after cefotetan. It has also been noticed that ceftriaxone causes more severe clinical courses and more outcomes that are fatal than do other drugs responsible for DIIHA.[3,7] Ceftriaxone-induced hemolysis is more common in children than adults.[8]

Several mechanisms causing DIIHA have been described. According to Kapur et al[9]: *The mechanisms that have been proposed to explain drug induced HA include: (1) drug adsorption; (2) immune complex; (3) membrane modification and (4) true antibody formation. A unifying hypothesis proposes that drug/drug metabolites interact with the RBC membrane causing composite immunogenic epitopes that are recognized as foreign by the immune system. The antibodies produced may react with the drug (in penicillin induced HA), the drug–RBC complex (in ceftriaxone induced HA) or the membrane alone (in methyldopa induced HA). Recently it has been reported, that except for ceftriaxone, the second and third generation cephalosporins appear to induce all three-antibody populations. Ceftriaxone appears to induce only antibodies that elicit immune complex type of in vitro reaction and is associated with a high fatality [rate].* In ceftriaxone-induced immune hemolytic anemia, the DAT result is usually positive for C3 and, in some cases, also for IgG.[4,7]

In pediatric cases, ceftriaxone-induced hemolysis has been seen in the presence of underlying hematologic or immunologic disorders such as sickle cell anemia and HIV. There has also been an association of the hemolysis with a history of previous ceftriaxone use. This has not been established in the literature for adult cases. Our patient denied previous ceftriaxone use. The implication of underlying hematologic or immune disorders or previous ceftriaxone therapy in the DIIHA process remains to be proved.[8]

In our patient, the acute hemolysis, as evidenced by an acute drop in the hemoglobin level, increased reticulocyte count, rise in the indirect bilirubin level, and increased lactic acid

Table 1. Timeline of the case

Relevant medical history and interventions
The patient is a 62-year-old woman with type 2 diabetes mellitus, who was receiving oral antidiabetic drugs.

Date	Summaries from initial and follow-up visits	Diagnostic testing (including dates)	Interventions
December 6, 2018	Presented to ED with fever and pain in right flank region for past 2 d. Patient was diagnosed with DKA with UTI	Hb, 10.7 g/dL; hematocrit, 32.8%; TLC, 17,980 cells/mm3; total bilirubin, 1.1 mg/dL; indirect bilirubin, 0.6 mg/dL	Patient was started on intravenous insulin and fluids for the management of DKA, and received ceftriaxone injection
December 11, 2018	Evidence of drug-induced hemolysis noted	Hb dropped from 10.5 g/dL to 6.4g/dL; hematocrit dropped from 32.8% to 19.3%; total bilirubin raised from 1.1 mg/dL to 1.8 mg/dL; indirect bilirubin raised from 0.6 mg/dL to 1.3 mg/dL	Ceftriaxone discontinued. Imipenem started
December 13, 2018	DAT and indirect Coombs test were negative. Other causes of hemolytic anemia were ruled out	Hb dropped to 4.8g/dL; hematocrit dropped to 15.2% with increased reticulocyte count to 7.1%; total bilirubin rose to 3.3 mg/dL; indirect bilirubin rose to 2.4 mg/dL; serum LDH was 607 U/L (normal < 250 U/L)	At this time, 1 PCV was transfused
December 18, 2018	Patient showed signs of recovery	Hb improved to 7.5 g/dL with normalization of bilirubin and LDH level following discontinuation of ceftriaxone	Patient was discharged on insulin and folic acid and subsequently followed on OPD basis
January 15, 2019	Patient was healthy at the time of 1-month follow-up	Hb was 11.5 g/dL	Treatment for diabetes mellitus continued

DAT = direct antiglobulin test; DKA = diabetic ketoacidosis; ED = Emergency Department; Hb = hemoglobin; LDL = low-density lipoprotein; OPD = Outpatient Department; PCV = packed cell volume; TLC = total lymphocyte count; UTI = urinary tract infection.

dehydrogenase level, as well as the normal results of a workup for other causes of anemia support the diagnosis of DIIHA. An increased serum ferritin level may be a marker of inflammation. Moreover, the temporal association with ceftriaxone therapy and improvement after discontinuation of the ceftriaxone regimen without corticosteroid therapy further supports the diagnosis. However, the DAT result was negative in our case.

Usually DAT is positive in ceftriaxone-induced IHA; however, a negative DAT result has also been described in ceftriaxone-induced immune hemolytic anemia, probably because of massive hemolysis resulting in a lack of intact complement/antibody-loaded erythrocytes to mount a positive response.[9] Therefore, a false-negative DAT result does not preclude the diagnosis of DIIHA. Other possible explanations for the negative DAT result include a lack of sensitivity to detect low levels of a small yet still relevant number of RBC-bound IgG below the threshold of the DAT, low-affinity autoantibodies that wash out during the process, and/or presence of IgA or IgM antibody subtypes.[10] In consequence, an initial negative DAT result should not rule out an immune cause, especially when the clinical suspicion is high and findings of investigations do not suggest a valid nonimmune cause.[10] The negative DAT test in our patient may be caused by the same reason studied by Kapur et al.[9] Massive hemolysis may have occurred with ceftriaxone and therefore there was a lack of C3 and IgG at the time of testing.[9] Although DAT-negative autoimmune hemolytic anemias represent 5% to 10% of all autoimmune hemolytic anemias,[11] the percentage of DAT-negative DIIHA is not available in the literature.

CONCLUSION

This case is reported to highlight ceftriaxone, a frequently used antibiotic in hospitalized patients, as a cause of DIIHA. Ceftriaxone is one of the most commonly implicated drugs of DIIHA and has been associated with particularly severe outcomes. In the relevant clinical settings, patients should be carefully monitored for any evidence of hemolysis. Patients may be briefed about the possible deterioration in health with the addition of or change in antibiotics.

In cases of unclear hemolysis and despite a negative DAT result, the treating physician must keep suspicion of DIIHA high and meticulously look for the possible culprit drugs, because there are no suitable definitive tests. Treatment with suspected drugs must be stopped promptly to prevent severe complications and fatal outcomes. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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