Case study

Case of Ceftriaxone-Induced Immune Hemolytic Anemia in an Outpatient Parenteral Antimicrobial Therapy (OPAT) Unit

Abstract:

Background: Ceftriaxone is a commonly used antimicrobial agent for the treatment of various infections. It is frequently administered once daily and is an attractive option for use in both in- and out-patient settings. Ceftriaxone-induced immune hemolytic anemia, while rare, can potentially cause severe and even fatal complications if not identified and managed early.

Case Presentation: We present the case of a 59-year-old Korean female with hypertension, hyperlipidemia, diabetes, and no known prior allergies, who was being treated for pyelonephritis in our outpatient parenteral antimicrobial therapy (OPAT) infusion unit with ceftriaxone. A few days following antibiotic exposure she was admitted to the hospital and her laboratory values were most consistent with hemolysis. All values normalized following discontinuation of ceftriaxone and initiation of ertapenem.

Conclusion: This case describes the clinical course, alternative diagnosis as well as the severity of ceftriaxone induced immune hemolytic anemia. While a rare phenomenon, it can be potentially fatal. Furthermore, it validates the importance of prompt identification and withdrawal of the offending agent may limit the progression of this disease, especially in the outpatient setting, where patients are not as closely monitored.

Key Words: Ceftriaxone, Drug-Induced Immune Hemolytic Anemia, Hemolysis, Adverse drug reactions

Abbreviations

Outpatient parenteral antimicrobial therapy: OPAT
Drug-induced immune hemolytic anemia: DIIHA
Acute kidney injury: AKI
White blood cells: WBC
Intravenous: IV

Emergency Department: ED
Computed tomography: CT
Lactate Dehydrogenase: LDH
Direct antiglobulin test: DAT
Immunoglobulin G: IgG
Red blood cell: RBC

Introduction:

Drug-induced immune hemolytic anemia (DIIHA) is an unusual condition characterized by a sudden decrease in hemoglobin following an exposure to an eliciting medication. Ceftriaxone, a broad-spectrum cephalosporin, has been infrequently associated with DIIHA. Most of these cases were diagnosed in the inpatient setting. Outpatient parenteral antimicrobial therapy (OPAT) infusion unit is a safe and effective alternative to inpatient antibiotics treatment for many infectious diseases. However, OPAT is not without risks, and adverse drug reactions can occur including drug-induced hemolytic anemia.We report a case of a patient treated for pyelonephritis in our OPAT infusion unit, who developed DIIHA while receiving ceftriaxone in the outpatient setting.Our objectives in reporting this case are to describe the clinical course, alternative diagnoses, as well as demonstrate the importance of prompt identification leading to successful response to treatment. The importance of early recognition and intervention in identifying the causative agent, may limit the progression and forestall the development of lethal events, especially in an outpatient setting, where patients are not monitored as closely as inpatient settings.

Presentation of Case:

A 59-year-old Korean female with hypertension, hyperlipidemia, diabetes, and without known allergies, presented to our hospital with fever, chills, urinary frequency, and dysuria. On examination, she was febrile, tachycardic, but otherwise had an unremarkable physical examination. Laboratory values were notable for acute kidney injury (AKI), WBC 8.32 x 10^3 K/uL, hemoglobin 11.1 g/dL, and urinalysis with large leukocyte esterase, nitrate negative, negative for bacteria, and urine white blood cells greater than 100 high power field (Table 1). She was admitted to the hospital for management of acute pyelonephritis and was administered ceftriaxone 1 gram intravenously daily. Blood and urine cultures demonstrated growth of *Escherichia coli* (*E. coli)* susceptible to ceftriaxone. Ceftriaxone dose was increased to 2 grams daily after her second hospital day. As she stabilized, she transitioned to the hospital-based OPAT infusion unit to complete her antibiotic course. Prior to this hospitalization there are no prior records of ceftriaxone exposure.

	Reference Range	Initial Presentation	Discharge	Second Admission	After change in Antibiotics
WBC Count	4.0 – 11.0 K/uL	8.32	10.84	38.00	12.52
Hemoglobin	11.5 – 15.8 g/dL	11.1	11.2	4.4	8.0
Hematocrit (%)	35 – 45%	34.0	34.6	11.9	23.4
Mean Corpuscular Volume	78.0-100.0 fL	93.9	94.5	103.5	86.0
Mean Corpuscular Hemoglobin	26.0 – 34.0 pg	30.7	30.6	38.3	29.4
Mean Corpuscular Hemoglobin concentration	31.0-37.0	32.6	32.4	37.0	34.2
Red blood cell count	4.50 -m5.20 M/uL	3.62	3.66	1.15	2.72
Platelet Count	140 – 400 K/uL	131	114	474	441
Sodium	136 – 145 mmol/L	132	139	134	140
Potassium	3.5 - 5.1 mmol/L	5.3	4.0	4.8	4.5
Bicarbonate	22 – 29 mmol/L	16	19	16	20
Anion Gap	5 – 17	15	12	20	16
Glucose	74 – 106 mg/dL	286	218	290	139
BUN	6.0 – 20.0 Mg/dL	18.2	19.1	23.5	17.9
Creatinine	0.50 – 0.95 mg/dL	1.21	1.26	1.07	1.04
eGFR	>= 60 mL/min/1.73 m2	49	47	57	59
Total Bilirubin	0.0 – 1.2 mg/dL	1.7		3.7	2.6
Direct Bilirubin	0.0 – 0.2 mg/dL	0.8		1.6	
Indirect Bilirubin	0.0 – 0.9 mg/dL	0.9		2.1	
AST	5 – 32 U/L	24		24	40
ALT	5 – 33 U/L	26		20	
Alkaline phosphatase	35 – 105 U/L	127		179	161
LDH	135 – 225 U/L			498	
Haptoglobin	30 – 200 mg/dL			< 10	
Ferritin	13.00 – 150.00 ng/mL	443			
Iron Saturation	20 – 55 %	6			
Iron Total	37-145 ug/dL	9			
TIBC	255 – 450 ug/dL	160			
Reticulocyte Count	0.50 – 2.00 %			3.26	
Lactate	0.50 – 1.60 mmol/L			4.31	

Table 1: Laboratory results with reference range from initial hospitalization (initial presentation and at time of discharge) and from second admission, and after change in antibiotic regimen.

Eight days into her 14-day treatment course, she was noted to be diaphoretic and hypotensive to 98/67 mmHg shortly after completing her daily dose in OPAT. Intravenous (IV) normal saline was administered with improvement of her blood pressure to 117/71 mmHg, and she was discharged home. The following day, during her ceftriaxone infusion, she was found to be pale, diaphoretic, and endorsed shortness of breath. Vitals at that time showed a blood pressure of 107/72 mmHg with an oxygen saturation of 100% on room air. A non-rebreather was placed at 15 liters/minute, with gradual improvement in symptoms which returned upon removal of non-rebreather, and she was transferred to the emergency department (ED) for further evaluation.

In the ED, initial laboratory values were most notable for new onset severe anemia with a hemoglobin decrease from two days prior 10.4 g/dL to 4.4 g/dL accompanied by worsening white blood cell count from 10 K/uL two days prior to 38 K/uL (with a neutrophilic predominance and moderate polychromasia present on blood smear. She received two packed red blood cell transfusions emergently, with improvement of her hemoglobin to 8.2 g/dL. Occult blood test was negative. Liver function tests were notable for elevated, total, direct and indirect bilirubin (4.2mg/dL, 1.4 mg/dL, and 2.8 mg/dL respectively) (Table 1). CT chest, abdomen and pelvis was performed to further evaluate for aortic dissection and other possible signs of active bleeding. Results were unremarkable for the source of blood loss; however splenomegaly was noted. She was admitted for in-patient management of presumed ceftriaxone-induced hemolytic anemia. Ceftriaxone was discontinued and meropenem was initiated to complete her course of treatment for her initial acute pyelonephritis.

While inpatient, laboratory values were most notable for undetectable haptoglobin (< 10 mg/dL), elevated lactate dehydrogenase (LDH; 498 U/L; normal range 135-225 U/L), and peripheral blood smear with increased reticulocytes (3.26%) and premature red blood cells. The direct Combs (DAT) test was negative for DAT immunoglobulin G (IgG) and positive for direct antiglobulin to C3, which was most consistent with drug induced hemolysis (Table 2). After discontinuation of ceftriaxone and four packed red blood cell transfusions, her hemoglobin stabilized between 8 to10 g/dL. She was discharged back to OPAT to complete her course of treatment with ertapenem which she successfully did and maintained a stable hemoglobin and experienced no further symptoms.

Test	Patient Values
Direct Coombs Test, IgG	Negative
Direct Coombs Test Complement, C3	Positive

Table 2: Direct Coombs Test

Discussion

Drug-induced immune hemolytic anemia (DIIHA) is a rare but serious complication affecting 1-4 cases per million persons and as such is vastly underdiagnosed despite its fatal consequences.[1] There are more than 130 drugs reported to be associated with hemolytic anemia, with the most common medications being beta-lactam antimicrobial agents. Ceftriaxone is a broad-spectrum cephalosporin that is used for treatment of diverse bacterial infections. Recently, ceftriaxone has been one of the most important drugs shown to be responsible for DIIHA, possibly due to its increased use in both in- and out-patient settings.[2] Adults with ceftriaxone induced hemolytic anemia present with marked decrease in hemoglobin and high rates of mortality (as high as 30%).[3] Pediatric cases present with a more severe clinical picture and have worse prognosis as compared to adults.[4,5]

Clinical presentation of DIIHA is frequently nonspecific and primarily related to the degree of anemia. Symptoms of fatigue, dizziness, dyspnea, and jaundice are common.[6] Physical examination may reveal pallor or jaundice, hepatosplenomegaly and adenopathy. Laboratory evaluation is significant for a sudden decrease in hemoglobin (hemoglobin levels < 7 g/dL) from baseline associated with mild leukocytosis.[7] Prolonged hemolytic anemia can be accompanied by compensatory increased reticulocyte count and mean corpuscular volume. Lactate dehydrogenase, indirect bilirubin and haptoglobin are generally elevated. A peripheral blood smear may reveal poikilocytosis, schistocytes, spherocytes, and anisocytosis or polychromasia.[3,8] Our patient presented with symptoms consistent with those prior described including fatigue and dyspnea. Her laboratory values were most significant for an elevated leukocytosis, increased reticulocyte count (3.26 %, range: 0.50 - 2.00%) and increased mean corpuscular volume (95.6 fL at baseline increased to 103.5 fL). Imaging was remarkable for splenomegaly.

Pathophysiology of DIIHA involves two types of antibodies: drug-independent and drug-dependent. Drug-independent antibodies are present without the addition of any drug and have similar characteristics to that of red blood cell (RBC) autoantibody. These antibodies cannot be distinguished from autoantibodies mediated from warm antibody hemolytic anemia. On the other hand, drug-dependent antibodies will only react when in the presence of a drug (or drug metabolite), leading to predominantlyimmunoglobulin G(IgG) mediated extravascular hemolysis. Typically, drugs will form covalent bonds with the RBC membrane, allowing for IgG to recognize and target the complex, further inducing Fc-mediated extravascular hemolysis.[9] Specifically, Ceftriaxone forms loose bonds with the RBC membrane forming an immune complex. The immune complex activates the formation of IgM-antibodies, complement system, and intravascular hemolysis. Intravascular hemolysis is more commonly associated with higher rates of fatal outcomes.[10]

To confirm the diagnosis of DIIHA, a direct antiglobulin test (DAT) determines if IgG and/or C3 is bound to the RBC membrane. A positive DAT can determine if the hemolytic anemia is due to immune or non-immune-mediated etiology. If IgG and C3 are positive, this can be suggestive of warm antibody hemolytic anemia which is the most common form of autoimmune hemolytic anemia. However recent studies have demonstrated that DAT in cephalosporin induced IHA is positive for only anti-C3 antibodies in 100% of patients, while anti-IgG is only present in 47% of patients.[11,12] This was seen in our patient who was positive for C3-antibodies and had a negative IgG. The main antibody seen in ceftriaxone-induced hemolytic anemia is immunoglobulin M (IgM).

The management of DIIHA is based on the severity of symptoms and degree of hemolysis with early identification and treatment being crucial to improved outcomes. Discontinuation of the presumed offending drug should occur emergently with most mild to moderate cases having significant improvement after discontinuation of the offending drug. This was seen in our patient who had significant improvement in her laboratory values after the immediate discontinuation of ceftriaxone during her second admission. This prompt identification and discontinuation was vital in our approach to treatment.Despite anemia, DIIHA often induces a hypercoagulable state

and the use of thrombophylactic should be strongly considered. Steroids have proven to lack benefit in the management of DIIHA.

Conclusion

Considering ceftriaxone's important role as a once-daily, broad-spectrum antibiotic, health care providers (and especially those managing OPAT patients) should be aware of this rare, but potentially, serious adverse event associated with the use of ceftriaxone. In cases of unclear hemolysis etiology, physicians should be aware of DIIHA and check the patient's medications carefully. Early recognition of DIIHA and institution of supportive care, discontinuation of inciting agents and transfusion, is likely to improve the outcome.

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Competing Interests

The authors have declared that no competing interests exist.

Author Contributions

Jaslyn Maurer: Participated in the writing, editing and review of the manuscript. Samantha Ruddy: Participated in the diagnostic process and data collection. Monica Bapna: Participated in the diagnostic process, review and editing of the manuscript. George Rodriguez: Participated in the writing, review and editing of the manuscript. Sorana Segal-Maurer: Participated in the writing, review and editing of the manuscript.

Consent:

All authors declare that 'written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Informed Consent: Obtained

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