A Fatal Case of Ceftriaxone-Induced Autoimmune Hemolytic Anemia

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Most cases of drug-induced autoimmune hemolytic anemia (AIHA) are attributed to the second- and third-generation cephalosporins cefotetan and ceftriaxone. Cefotetan-induced AIHA is more common, but ceftriaxone-induced AIHA leads to more fatalities. If a patient treated with ceftriaxone develops hemoglobinuria, hemolyzed blood specimens, and/or a decreased hemoglobin level, then ceftriaxone-induced AIHA should be suspected. Ceftriaxone-induced AIHA is associated with a positive direct antiglobulin test (DAT), revealing the presence of IgG in all cases and C3d (complement) in most cases. In adults, activation of the complement system usually generates a severe intravascular reaction and typically occurs days to weeks after exposure to ceftriaxone. Because there are reported cases of ceftriaxone-induced AIHA in which the patient's serum reacted only in the presence of a drug metabolite, the use of drug metabolite should be considered if the DAT is negative in the presence of the native drug. This article reports a fatal case of AIHA and discusses detection and diagnosis of ceftriaxone-induced AIHA.

Ceftriaxone-induced autoimmune hemolytic anemia (AIHA) is an immune-mediated phenomenon caused by ceftriaxone, leading to the destruction of red blood cells (RBCs) and secondary anemia. Approximately 30 years ago, methyldopa and penicillin were the 2 medications most commonly associated with drug-induced AIHA. Currently, most cases of drug-induced AIHA are attributed to second- and third-generation cephalosporins, most commonly cefotetan and ceftriaxone. Although cefotetan-induced AIHA is more common, ceftriaxone-induced AIHA has been associated with higher fatality rates, with over 50% of reported fatalities caused by cephalosporin-induced AIHA specifically attributed to ceftriaxone.[1–5] This article reports the case of a man who was diagnosed with ceftriaxone-induced AIHA that proved to be fatal. A review of ceftriaxone-induced AIHA is also provided.

CASE PRESENTATION

Initial Presentation and History

A 55-year-old man presented to the outpatient primary care clinic with complaints of fever, chills, and left knee pain. The patient reported that he injured his left knee a few weeks prior to presentation, which resulted in bruising and pain. Past medical history was notable for obesity, hepatitis C, posttraumatic stress disorder, hypertension, microscopic hematuria, peptic ulcer disease, current smoking, and alcohol abuse. In addition, the patient was diagnosed with left leg cellulitis and bacteremia caused by group G streptococcus 5 years prior to presentation, which was treated with intravenous (IV) ceftriaxone (2 g/day) for 4 weeks. He underwent a left total knee arthroplasty (TKA) 3 years ago, followed by a second left TKA 2 years ago due to septic arthritis caused by *Streptococcus agalactiae*. This infection was treated with IV ceftriaxone (1 g every 12 hr) for at least 1 week. The patient's current medications included fluoxetine, lisinopril, loratadine, morphine (sustained-release and immediate-release), omeprazole, propranolol, ranitidine, and acetaminophen/oxycodone.

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Physical Examination

On physical examination, the patient was alert, oriented, and in acute distress. He weighed 310.2 lb and height was 77.2 in. Vitals signs on admission revealed a temperature of 102.2°F, a heart rate of 98 bpm, and a blood pressure of 112/68 mm Hg. The knee was slightly swollen, erythemic, warm to the touch, and tender to palpation and movement. A radiograph of the left knee revealed an intact left knee prosthesis and prominence of suprapatellar soft tissue but no definitive joint effusion. Due to the presence of fever and dry cough, a chest radiograph was also performed, which revealed no acute pulmonary findings. Blood cultures were drawn on admission and returned negative on hospital day 7.

Clinical Course

On hospital admission, IV ceftriaxone (1 g/day) and vancomycin (1 g every 12 hr) were administered for suspected left knee septic arthritis. Joint aspiration was completed on hospital day 1, and culture results of synovial fluid revealed the presence of *S. agalactiae* on hospital day 2. Therefore, IV vancomycin was discontinued and IV ceftriaxone was increased to 1 g every 12 hours. In addition, arthroscopy with irrigation and debridement was performed.

Over the next few days, the patient stabilized. Since the patient deferred another TKA, his treatment plan consisted of 8 weeks of IV ceftriaxone 2 g/day on an outpatient basis. After 5 days of hospitalization, the patient was ready for discharge, but due to travel arrangements he stayed in the hospital for another night. On the evening of hospital day 6, the patient complained of back pain (pain severity, 7/10), and on the morning of hospital day 7 he also complained of abdominal pain (pain severity, 5/10). He voided 700 mL of dark bloody urine consistent with hemoglobinuria; his abdomen, arms, and legs appeared mottled; and he began to develop jaundice. The patient's breathing became shallow and labored, and his oxygen saturation dropped to 76%. Complete blood work was ordered, but the patient's blood specimens hemolyzed. The hematology team was consulted for a complete work-up of acute hemolytic anemia. Computed tomography scans of the thorax, abdomen, and pelvis were unremarkable.

Laboratory Evaluation

Hematologic testing revealed a positive direct antiglobulin test (DAT). Similarly, immunohematologic testing performed at an outside laboratory identified the presence of ceftriaxone-dependent antibodies in the patient's serum and the DAT was positive, demonstrating the presence of IgG (1+) and C3d (4+) (complement) bound to the patient's RBCs. An eluate prepared from the patient's RBCs showed no reactivity with all cells tested. When tested with untreated RBCs in the presence of ceftriaxone, the patient's serum reacted after incubation at room temperature (37°C) and testing by indirect antiglobulin test. Likewise, the patient's eluate reacted at room temperature in the presence of the drug. Of interest, the DAT was negative and serum was nonreactive in the presence of ceftriaxone when blood samples drawn on hospital day 2 (after 2 doses of ceftriaxone) were tested. This finding shows that the patient was not hemolyzing after 2 doses of ceftriaxone, which is consistent with drug-induced AIHA in adults. Specific laboratory parameters for the case patient are listed in the **Table**.

Laboratory results revealed acute liver impairment with elevated alanine aminotransferase, aspartate aminotransferase, direct and indirect bilirubin, γ-glutamyltransferase, and lactate dehydrogenase levels. The patient had baseline liver impairment due to chronic alcohol consumption and hepatitis C infection. Laboratory tests also revealed acute renal failure necessitating the placement of a dialysis access catheter. Urinalysis revealed the presence of bacteria, blood, protein, and bilirubin. Hemolysis was suspected due to low hemoglobin, hematocrit, and haptoglobin levels.

Treatment and Outcome

On hospital day 7, the patient was transferred to the intensive care unit due to hypoxia, lethargy, diaphoresis, and pallor. Due to a high suspicion of ceftriaxone-induced AIHA and a positive DAT, ceftriaxone was discontinued and a single dose of IV piperacillin/tazobactam 3.375 g and IV vancomycin 2 g/day were initiated. The patient was transfused with RBCs, and a single dose of IV methylprednisolone 1 g was given. He became hypotensive, hypoxic, and severely acidotic, requiring ventilator support. A vascular access line for dialysis was emergently established but never used due to the rapidly declining condition of the patient. Early on the morning of hospital day 8, the patient died despite several attempts at cardiac resuscitation. An autopsy did not reveal any underlying lymphoproliferative disorder, solid neoplasm, or other conditions known to be associated with AIHA. These findings lend further support to the serologic confirmation of drug-induced AIHA.

CEFTRIAXONE-INDUCED AIHA

Cephalosporin-induced AIHA is rare, with an estimated 81 cases reported as of 2005, despite the frequent

Table. Laboratory Results for the Case Patient

Study (Unit)	Normal	Baseline*	Hospital Day 1	Hospital Day 7	Hospital Day 8
Alanine aminotransferase (U/L)	7–56	65	63	110	N/A
Aspartate aminotransferase (U/L)	5–34	45	32	161	Specimen severely hemolyzed
Bilirubin, direct (mg/dL)	0– 0.5	N/A	N/A	4.8	N/A
Bilirubin, total (mg/dL)	0.2–1.3	0.6	0.8	9.8	Specimen severely hemolyzed
Creatinine clearance (mL/min)	Low, 60	73.9	66.8	93.1	30, 27.4†
Creatinine, serum (mg/dL)	0.7–1.3	1.1	1.2	1.0	2.4, 2.6, 2.9†
Haptoglobin (mg/dL)	36–196	N/A	N/A	N/A	< 5.83
Hematocrit (%)	42–52	42.6	39.7	21.8	14.4, 13.5†
Hemoglobin (g/dL)	13.5–17.5	14.3	14.1	7‡	N/A
γ-Glutamyltransferase (U/L)	12–64	54	N/A	94	Specimen severely hemolyzed
Lactate dehydrogenase (U/L)	125–243	189	N/A	1719	Specimen severely hemolyzed
Prothrombin time (sec)	10–12.2	N/A	N/A	15.9	47.7
White blood cells (cells/μL)	4800–10,800	10.2	17.2	46.7	91.1, 61.6†
Urinalysis					
Bacteria	Negative			4+	
Blood	Negative			4+	
Protein	Negative			4+	
Red blood cells (cells/HPF)	Negative			0–1	
Bilirubin	Negative			3+	
Direct antiglobulin test					
Polyspecific	Negative			Positive (4+)	
Anti-IgG	Negative			Positive (1+)	
Anti-C3d	Negative			Positive (4+)	
Saline control	Negative			Negative	
Eluate	Negative			Negative	

HPF = high-power field; N/A = not available.

*Baseline laboratory results were obtained 4 months prior to this presentation.

†Multiple laboratory draws per day.

‡Estimated.

use of second- and third-generation cephalosporins.[4] Of these, 19 cases (23%) were fatal. Of 23 cases attributed to ceftriaxone, 10 (43%) were fatal. In contrast, only 9 (16%) of the 58 reported cases of AIHA caused by other cephalosporins (excluding ceftriaxone) were fatal.[4] However, it has been speculated that milder cases of drug-induced AIHA are underdiagnosed and underreported, which in turn could cause overestimation of the fatality rate.[4,5]

Pathophysiology

The mechanism by which ceftriaxone induces AIHA is not completely understood. However, it is known that the production of antibodies does not occur in response to ceftriaxone-treated RBCs and can only be replicated when serum-containing antibodies, ceftriaxone, and untreated or enzyme-treated RBCs are combined. It is theorized that ceftriaxone (the antigen) may bind loosely to RBCs in vivo, thus becoming immunogenic and stimulating the production of antibodies. After antibody production is initiated, immune complexes form (consisting of antibody and drug) and these complexes in turn bind nonspecifically to other RBCs, ultimately activating the complement system. This "immune complex" mechanism usually generates a severe intravascular reaction, with a DAT positive for C3d (complement) in all cases of drug-induced AIHA and positive for IgG in approximately 75% of cases of ceftriaxone-induced AIHA.[1–3,5]

The concept of serologic cross-reactivity between cephalosporin-dependent antibodies and RBCs in the presence of another cephalosporin or penicillin has been investigated, and in vitro testing of cefotetan and

ceftriaxone has revealed little cross-reactivity.[4,6] Caution is advised when attempting to extrapolate in vitro results to in vivo cases.[4] Different hypotheses relating to mechanisms of drug-induced AIHA are further discussed in the literature.[7]

Diagnosis

The case reported here clearly documents the immune etiology of ceftriaxone-induced hemolytic anemia and emphasizes the importance of close laboratory monitoring in any patient receiving ceftriaxone. A high level of vigilance is required on the part of clinicians whenever a patient has prior exposure to or prolonged initial therapy with ceftriaxone, since clinical and laboratory signs of hemolysis (ie, hemoglobinuria, decreased hemoglobin and haptoglobin levels, positive DAT, and hemolyzed blood specimens) can develop at any time during therapy in adult patients. In adults, immune hemolysis typically develops days to weeks after exposure to the medication, whereas it usually develops within minutes in children. Prior or prolonged exposure to ceftriaxone is commonly apparent.[1,4,5] Because there are no published data on detailed laboratory monitoring for this rare reaction, monitoring is a clinical decision that should be made by the treating physician.

The standardized approach to laboratory analysis for most cases of drug-induced AIHA is to perform a DAT to determine whether complement and/or IgG bind to the patient's RBCs. If the DAT is positive, then the patient's serum should be tested with drug-treated RBCs or untreated and enzyme-treated RBCs in addition to the drug of interest. If clinical signs and symptoms of hemolysis are present and the DAT is positive, an eluate prepared from the patient's RBCs should be tested against drug-treated RBCs with the drug present.[2,8] In the event that intravascular hemolytic anemia develops in conjunction with a positive DAT, the clinician needs to promptly investigate and identify the cause of AIHA. The physician should review the medication profile, any diagnostic work-up for neoplasms or lymphoproliferative disorders, and whether the patient has received recent blood transfusions.

In contrast, the standardized laboratory analysis for ceftriaxone-induced AIHA excludes the use of drug-treated RBCs since ceftriaxone antibodies have not been shown to react with drug-treated RBCs.[2] In some cases, a patient's serum will only react in the presence of a drug metabolite. Therefore, if drug antibodies are not detected using the native drug, the use of drug metabolites should be considered. Drug metabolites can sometimes be obtained from drug manufacturers (well characterized) or in ex vivo samples (eg, urine or plasma from volunteers who have recently ingested the drug in question [uncharacterized]).[5,9] Three cases of drug-induced AIHA have been described in which ceftriaxone antibodies were not detected when the native drug was used for testing but were detected when ex vivo urine samples containing ceftriaxone metabolites were used; 1 of these cases resulted in fatality.[9–11] Between one third and two thirds of unmetabolized ceftriaxone is excreted in the urine, with approximately 1% as a trace metabolite. The remaining drug is secreted in the bile and eliminated through the feces.[9]

Management

Management generally consists of discontinuing ceftriaxone along with administering corticosteroids and/or blood transfusions. The hemolytic anemia usually resolves with discontinuation of the offending medication. Resolution of the hemolysis can take days to months. In severe cases, corticosteroids may provide some benefit. Blood transfusions should be used with caution because the donor RBCs may also be hemolyzed, leading to further anemia.[12]

CONCLUSION

Although ceftriaxone-induced AIHA is rare, it is associated with a higher fatality rate as compared with AIHA caused by other cephalosporins. Ceftriaxone-induced AIHA should be suspected in patients treated with ceftriaxone who develop hemoglobinuria, hemolyzed blood specimens, or severe anemia. Confirmation of the diagnosis requires a hematology consult for a DAT. As the mechanism by which ceftriaxone induces AIHA continues to be investigated, the concept of cross-reactivity and the possibility that metabolites of ceftriaxone may cause severe drug-induced hemolysis remain to be clarified. In addition, increased reporting of these occurrences and further investigation of compiled data are necessary to better understand the mechanism of these fatal reactions. **HP**

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