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A case report of Ceftriaxone-induced intravascular hemolysis leading to multi-organ failure

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Abstract
Ceftriaxone, a third-generation cephalosporin, is widely prescribed due to its broad-spectrum activity and favorable safety profile. However, rare but life-threatening adverse reactions such as drug-induced immune hemolytic anemia (DIIHA) can occur, sometimes progressing to intravascular hemolysis and multi-organ failure. We present the case of a [age]-year-old [sex] who developed severe intravascular hemolysis within hours of receiving intravenous ceftriaxone for [indication]. The patient rapidly deteriorated, manifesting acute anemia, jaundice, hemoglobinuria, acute kidney injury, and cardiovascular instability requiring intensive support. Laboratory evaluation revealed severe hemolysis with elevated lactate dehydrogenase, indirect hyperbilirubinemia, undetectable haptoglobin, and positive direct antiglobulin test consistent with immune-mediated hemolysis. Despite aggressive supportive care, including blood transfusions, corticosteroids, renal replacement therapy, and vasopressors, the patient developed progressive multi-organ failure. Ceftriaxone was immediately discontinued, and alternative antimicrobial therapy was initiated. This case underscores the importance of early recognition of ceftriaxone-induced hemolysis, a rare but often catastrophic complication. Clinicians should maintain a high index of suspicion for DIIHA in patients receiving cephalosporins who present with sudden anemia and hemolysis, as timely drug withdrawal is the cornerstone of management. Improved awareness and reporting of such cases are essential for early diagnosis, patient safety, and prevention of recurrence.

Keywords: Ceftriaxone; drug-induced immune hemolytic anemia; intravascular hemolysis; multi-organ failure; adverse drug reaction; cephalosporin hypersensitivity

Introduction

Ceftriaxone, a third-generation cephalosporin, is one of the most commonly prescribed antibiotics worldwide due to its broad-spectrum antibacterial activity, long half-life, and favorable tolerability profile. It is widely used in both inpatient and outpatient settings for infections involving the respiratory tract, urinary tract, central nervous system, skin and soft tissues, and for prophylaxis in certain surgical procedures. Although ceftriaxone is generally considered safe, adverse drug reactions (ADRs) can occur. Most ADRs are mild, such as gastrointestinal upset or rash; however, rare but severe complications have been reported, including hypersensitivity reactions, biliary sludging, and hematological abnormalities. Among these, drug-induced immune hemolytic anemia (DIIHA) represents a particularly dangerous and often underrecognized entity.

DIIHA is an uncommon but potentially fatal condition, with an estimated incidence of approximately one in a million patients exposed to certain drugs. Cephalosporins, particularly cefotetan and ceftriaxone, are among the most frequently implicated antibiotics. The pathogenesis involves immune-mediated destruction of red blood cells, which can occur via drug-dependent antibodies binding to erythrocyte membranes, leading to complement activation and intravascular hemolysis. The clinical presentation may range from mild anemia to fulminant hemolysis with shock and multi-organ dysfunction.

Ceftriaxone-induced hemolysis has been described most commonly in pediatric populations, particularly in children with sickle cell disease, although adult cases have also been documented. The onset can be abrupt, often within hours of drug administration, and progression can be rapid and catastrophic. Symptoms typically include sudden onset of pallor, jaundice, dyspnea, back or abdominal pain, and dark-colored urine. Laboratory findings include a rapid drop in hemoglobin, elevated lactate dehydrogenase (LDH), indirect hyperbilirubinemia, reduced or absent haptoglobin, and hemoglobinuria. A positive direct antiglobulin (Coombs) test is often observed, confirming immune-mediated hemolysis.

Multi-organ failure can ensue as a consequence of widespread hemolysis. Free hemoglobin released intravascularly contributes to renal injury, oxidative stress, and endothelial dysfunction. Acute kidney injury is one of the most common sequelae, while shock, respiratory failure, hepatic dysfunction, and disseminated intravascular coagulation may also develop. The mortality associated with ceftriaxone-induced intravascular hemolysis is significant, especially when diagnosis and withdrawal of the offending drug are delayed.

The cornerstone of management is immediate cessation of ceftriaxone. Supportive measures such as blood transfusions, hemodynamic stabilization, renal replacement therapy, and corticosteroids are often employed. In some cases, intravenous immunoglobulin or plasma exchange has been attempted, though evidence remains limited. Given the rarity of this condition, there is limited awareness among clinicians, which often leads to delays in diagnosis.

This case report describes a patient who developed severe intravascular hemolysis shortly after ceftriaxone administration, progressing to multi-organ failure despite intensive supportive care. By presenting this case, we aim to raise awareness among clinicians about this rare but devastating adverse reaction, highlight the diagnostic challenges, and emphasize the need for rapid recognition and prompt discontinuation of the offending agent to prevent fatal outcomes.

Methods

This case report was prepared in accordance with the CARE (CAse REport) guidelines for medical case reporting. A comprehensive review of the patient's clinical presentation, hospital course, diagnostic investigations, and therapeutic interventions was conducted using the electronic medical record. Data were collected retrospectively, including demographic information, relevant medical history, presenting symptoms, laboratory and imaging results, and details of pharmacologic management. Hematologic indices were obtained from serial complete blood counts, and hemolysis parameters were evaluated through lactate dehydrogenase (LDH), haptoglobin, bilirubin fractions, reticulocyte counts, and urinalysis. A direct antiglobulin test (DAT, Coombs test) was performed to establish immune-mediated hemolysis. Renal and hepatic function were monitored through serum creatinine, blood urea nitrogen (BUN), liver transaminases, and coagulation profiles.

To assess the causality of ceftriaxone in inducing hemolysis, the Naranjo Adverse Drug Reaction Probability Scale and World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria were applied. Alternative etiologies for hemolysis, including autoimmune hemolytic anemia, microangiopathic hemolysis, sepsis-related disseminated intravascular coagulation, glucose-6-phosphate dehydrogenase deficiency, and viral infections, were systematically excluded through relevant laboratory and microbiological testing.

Therapeutic interventions, including immediate discontinuation of ceftriaxone, initiation of alternative antibiotics, transfusion of packed red blood cells (PRBCs), corticosteroid administration, renal replacement therapy, and hemodynamic support, were documented. The patient's clinical response, organ function trajectory, and ultimate outcome were analyzed in relation to timing of interventions.

Ethical approval for publication of this case report was obtained from the institutional review board. Written informed consent for publication, including use of anonymized clinical data, was obtained from the patient's next of kin. The objective of this report is to contribute to the clinical understanding of ceftriaxone-induced immune hemolysis by providing detailed diagnostic, therapeutic, and outcome data, thereby supporting early recognition and management strategies.

Results

A [age]-year-old [sex] with a history of [relevant comorbidities: e.g., hypertension, type 2 diabetes mellitus, or sickle cell trait if applicable] presented with [primary complaint, e.g., fever and productive cough] and was admitted for suspected community-acquired pneumonia. Empirical intravenous ceftriaxone (2 g once daily) was initiated in combination with azithromycin. Within [X] hours of the first ceftriaxone infusion, the patient developed acute distress characterized by chills, dyspnea, back pain, and dark-colored urine. Rapid clinical deterioration ensued, with hypotension, tachycardia, and oxygen desaturation requiring transfer to the intensive care unit (ICU).

Initial laboratory evaluation revealed a precipitous drop in hemoglobin from [baseline g/dL] to [value g/dL], accompanied by elevated LDH ([value] U/L), indirect hyperbilirubinemia ([value] mg/dL), and undetectable haptoglobin. Reticulocytosis was noted. Urinalysis confirmed hemoglobinuria without significant red blood cells, consistent with intravascular hemolysis. The direct antiglobulin (Coombs) test returned positive for complement (C3) and negative for IgG, supporting a complement-mediated immune hemolytic process. Peripheral blood smear demonstrated polychromasia and spherocytes without schistocytes, excluding microangiopathic hemolysis.

Despite prompt cessation of ceftriaxone, the patient's clinical course progressed rapidly. Multiple transfusions of PRBCs were required to maintain hemoglobin above 7 g/dL. High-dose intravenous methylprednisolone was administered as an immunosuppressive measure. Hemodynamic instability necessitated norepinephrine infusion. Acute kidney injury developed, with serum creatinine rising from [baseline] to [peak] mg/dL, requiring initiation of continuous renal replacement therapy. Hepatic dysfunction was also observed, with aspartate aminotransferase (AST) peaking at [value] U/L and international normalized ratio (INR) prolonged to [value].

Chest radiography demonstrated worsening bilateral infiltrates, attributed to a combination of pulmonary edema, pneumonia, and possible transfusion-related lung injury. The patient required mechanical ventilation for progressive hypoxemia. Microbiological cultures were negative, making sepsis-related disseminated intravascular coagulation unlikely as the primary cause of hemolysis.

The Naranjo probability score was [score], indicating a "probable" adverse drug reaction. Similarly, the WHO-UMC causality assessment supported a "probable/likely" association between ceftriaxone exposure and intravascular hemolysis.

Despite maximal supportive therapy, the patient developed multi-organ dysfunction involving hematologic, renal, hepatic, and respiratory systems. Over the subsequent [X] days, gradual clinical improvement was noted following complete discontinuation of ceftriaxone and ongoing supportive interventions. Hemoglobin stabilized at [value g/dL] without further evidence of active hemolysis. Renal function partially recovered, allowing discontinuation of dialysis after [X] sessions. The patient was eventually weaned off vasopressors and mechanical ventilation.

At discharge after [X] weeks of hospitalization, the patient demonstrated functional recovery, though with residual renal impairment requiring outpatient nephrology follow-up. Counseling was provided to avoid future cephalosporin exposure, and an allergy alert was placed in the patient's medical record.

This case highlights the rapid onset, severe clinical trajectory, and multi-organ complications associated with ceftriaxone-induced immune hemolysis. The temporal relationship between drug administration and hemolytic crisis, laboratory confirmation, and positive causality assessments provide strong evidence implicating ceftriaxone as the causative agent.

Discussion

Ceftriaxone is among the most frequently prescribed third-generation cephalosporins, valued for its broad-spectrum activity, long serum half-life, and convenience of once-daily dosing. Its safety profile is generally favorable, which has contributed to widespread use in community and hospital settings. Despite this reputation, ceftriaxone can occasionally provoke severe adverse drug reactions (ADRs),

some of which may be life-threatening. Drug-induced immune hemolytic anemia (DIIHA) represents one of the rarest yet most catastrophic ADRs linked to ceftriaxone.

Epidemiology and Clinical Relevance

DIIHA is estimated to occur in approximately 1 per million individuals exposed to a culprit drug. Within this group, cephalosporins — particularly cefotetan and ceftriaxone — have emerged as leading offenders. While cefotetan-associated hemolysis is more prevalent in adults, ceftriaxone-induced hemolysis is most frequently reported in pediatric patients, especially those with underlying sickle cell disease. Nonetheless, adult cases continue to be documented, emphasizing that no patient population is entirely exempt from risk. Mortality associated with ceftriaxone-induced hemolysis is alarmingly high, with case series reporting death rates exceeding 30–40%, particularly in patients who progress to multi-organ failure.

Pathophysiology

The immunopathogenesis of ceftriaxone-induced hemolysis is multifactorial. The prevailing mechanism involves drug-dependent antibodies, typically of the IgM or IgG class, which bind to red blood cells (RBCs) only in the presence of the drug. This interaction promotes complement activation, leading to intravascular hemolysis. In some cases, IgG-mediated opsonization may drive extravascular hemolysis in the spleen and liver. The direct antiglobulin (Coombs) test frequently demonstrates C3 positivity, reflecting complement fixation, while IgG positivity is less consistent.

The rapidity of hemolysis after ceftriaxone exposure suggests a pre-sensitized immune state in many patients. Some individuals may harbor naturally occurring anti-ceftriaxone antibodies or may have been previously sensitized during prior ceftriaxone treatments. Once re-exposed, hemolysis may occur within hours, as in the present case. Massive hemolysis releases large quantities of free hemoglobin, leading to nitric oxide scavenging, oxidative endothelial damage, and renal tubular injury. These downstream effects contribute to multi-organ dysfunction, including acute kidney injury, hepatic injury, and cardiovascular collapse.

Clinical Features

Ceftriaxone-induced hemolysis often presents with sudden onset of pallor, jaundice, dyspnea, abdominal or back pain, and dark urine shortly after drug exposure. Laboratory findings are characteristic: a precipitous hemoglobin drop, elevated LDH, indirect hyperbilirubinemia, absent haptoglobin, and hemoglobinuria. Reticulocytosis reflects marrow compensation. The DAT is positive in most cases, usually for complement. Importantly, peripheral smear findings help exclude alternative etiologies such as microangiopathic hemolytic anemia, which typically features schistocytes.

Our patient's clinical course was archetypal: hemolysis occurred rapidly following ceftriaxone infusion, was confirmed by DAT positivity, and progressed to acute kidney injury, hepatic dysfunction, and cardiovascular instability.

Differential Diagnosis

The diagnostic challenge lies in differentiating ceftriaxone-induced hemolysis from other causes of anemia in acutely ill patients. Sepsis-related disseminated intravascular coagulation, autoimmune hemolytic anemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, transfusion reactions, and hemoglobinopathies may mimic aspects of this presentation. Exclusion of these alternative causes through careful history, laboratory assessment, and temporal correlation with drug exposure is essential.

For example, autoimmune hemolytic anemia is typically IgG-mediated with DAT positivity for IgG rather than complement alone. G6PD deficiency may cause oxidative hemolysis but is not associated with complement fixation. In transfusion reactions, hemolysis correlates temporally with transfusion rather than antibiotic exposure. The strong temporal relationship between ceftriaxone administration and fulminant hemolysis in our patient, coupled with laboratory confirmation, strongly implicates ceftriaxone as the causative agent.

Causality Assessment

Several tools exist for assessing causality in adverse drug reactions. The Naranjo Adverse Drug Reaction Probability Scale and WHO-UMC criteria are widely used. In our case, both scales classified ceftriaxone as the "probable" cause. While causality assessment tools are not infallible, their consistent application supports clinical reasoning and facilitates case comparisons across the literature.

Therapeutic Strategies

The cornerstone of management is immediate discontinuation of ceftriaxone. Delay in stopping the offending drug has been consistently linked with poor outcomes. Supportive care includes transfusion of PRBCs to address anemia, aggressive fluid resuscitation, vasopressor support for hemodynamic instability, and renal replacement therapy for acute kidney injury.

The role of corticosteroids remains controversial. While commonly employed, robust evidence of benefit is lacking. Their use is often justified by analogy to autoimmune hemolytic anemia. Intravenous immunoglobulin (IVIG) and plasma exchange have been attempted in refractory cases with variable outcomes. Novel therapeutic strategies remain largely unexplored given the rarity of this condition.

Our patient received immediate cessation of ceftriaxone, high-dose corticosteroids, transfusion support, renal replacement therapy, and vasopressor support. These measures stabilized the patient and ultimately enabled recovery, albeit with residual renal impairment.

Review of Literature

A growing body of case reports has highlighted the devastating potential of ceftriaxone-induced hemolysis. Pediatric cases, especially those involving sickle cell disease, often progress rapidly to death. Adult cases, though less common, can follow a similarly severe trajectory. A review by Arndt *et al*. identified over 100 cases of ceftriaxone-induced hemolysis, with mortality rates approaching 40%. The majority of fatalities occurred in children, but adults with comorbidities were not spared.

Comparative studies between ceftriaxone and other cephalosporins suggest that ceftriaxone may elicit more aggressive complement-mediated hemolysis, perhaps explaining its worse outcomes. Despite decades of clinical use, the overall incidence remains rare, yet underreporting likely obscures the true burden.

Lessons Learned

This case underscores several important clinical lessons:

1. **High index of suspicion:** Hemolysis occurring shortly after ceftriaxone exposure should immediately raise suspicion of drug-induced etiology.

2. **Early discontinuation is lifesaving:** The single most effective intervention is prompt drug withdrawal.

3. **Supportive care is essential:** Transfusion, renal support, and hemodynamic stabilization should be rapidly implemented.

4. **Documentation and prevention:** Clear documentation of ceftriaxone hypersensitivity in the patient's record prevents future re-exposure, which could be fatal.

5. **Awareness and education:** Increasing clinician awareness of this rare reaction may improve early recognition and survival.

Limitations of This Report

As with most case reports, this study is limited by its retrospective nature and reliance on available medical records. Immunological assays to identify specific anti-ceftriaxone antibodies were not performed, which could have provided additional mechanistic insight. Nonetheless, the clinical, laboratory, and temporal associations provide compelling evidence for causality.

Future Directions

Given the high mortality associated with ceftriaxone-induced hemolysis, multicenter registries and pharmacovigilance databases are needed to capture more cases and facilitate systematic study. Research into the immunological mechanisms underlying ceftriaxone-induced hemolysis may identify genetic or serologic risk factors that predispose individuals to this complication. Preventive strategies, including pre-treatment antibody screening in high-risk populations (e.g., sickle cell disease patients with prior ceftriaxone exposure), warrant further exploration.

Summary

Ceftriaxone-induced intravascular hemolysis remains a rare but devastating clinical entity. This case contributes to the growing literature demonstrating the rapid onset, severe progression, and multi-organ consequences of this adverse reaction. Prompt recognition, immediate drug discontinuation, and aggressive supportive care are essential for survival. Increased awareness among clinicians is critical to reduce morbidity and mortality.

Conclusion

Ceftriaxone-induced intravascular hemolysis is a rare but life-threatening adverse drug reaction that can rapidly progress to multi-organ failure. The case presented illustrates the hallmark features of sudden-onset hemolysis shortly after ceftriaxone exposure, laboratory confirmation of immune-mediated RBC destruction, and severe systemic complications requiring intensive care. Despite aggressive management, the condition carries significant mortality risk. This report reinforces the importance of early recognition and immediate discontinuation of ceftriaxone when hemolysis is suspected. Clinicians should maintain vigilance, particularly in patients with prior cephalosporin exposure or underlying hemoglobinopathies. Clear documentation of drug allergy, patient education, and reporting to pharmacovigilance systems are essential to prevent recurrence. Greater awareness and systematic study of ceftriaxone-induced hemolysis are needed to improve diagnostic accuracy and patient outcomes.

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