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Ceftriaxone-Induced Hemolytic Anemia in a Jehovah's Witness

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 65
Final Diagnosis: Ceftriaxone induced immune hemolytic anemia
Symptoms: Blindness • fatigue
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual clinical course

Background: Drug-induced immune hemolytic anemia (DIIHA) is a rare condition that may result from the administration of an antibiotic, most notably the cephalosporin class, commonly used in both the adult and pediatric populations. A delay in recognition by a provider may lead to continuation of the offending agent and possibly result in fatal outcomes.

Case Report: We report the case of a 65-year-old woman on ceftriaxone infusions after being diagnosed with acute mitral valve endocarditis 3 weeks prior, which presented with severe anemia and bilateral transient vision loss. Being a Jehovah's Witness, the patient refused blood product transfusions and was managed with alternative therapies. The etiology of the symptoms was suspected to be a hemolytic anemia directly related to her ceftriaxone infusions.

Conclusions: This report demonstrates the importance of close vigilance while prescribing drugs known to cause hemolytic anemia. Although rare, drug-induced immune hemolytic anemia caused by ceftriaxone may be a potentially fatal condition, but with early recognition and withdrawal of the offending agent, successful treatment may ensue. Serological tests should be utilized to obtain a definitive diagnosis.

MeSH Keywords: Anemia, Hemolytic • Ceftriaxone • Jehovah's Witnesses

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903507

Background

Drug-induced immune hemolytic anemia (DIIHA) is a rare but potentially life-threatening disorder that should be considered if a patient develops hemolysis under drug treatment [1]. DIIHA occurs in approximately 1 in 1 million people, but is likely underdiagnosed despite its potential lethality [2]. Second- and third-generation cephalosporins, especially cefotetan and ceftriaxone, are increasingly associated with severe, sometimes fatal, immune hemolytic anemia [3]. The first case of fatal ceftriaxone-induced immune hemolytic anemia (CIIHA) was reported by Garratty et al. in 1991 [4,5]. Estimates of fatality in CIIHA are reported as high as 40% [5–7]. DIIHA should be classified as involving either drug-dependent (DDAB) or drug-independent antibodies (DIAB) to more appropriately treat the condition. When involving DDAB, hemolysis typically appears within 2 weeks of starting the causative drug with the patient developing a progressive anemia [2]. Cessation of the offending agent is standard treatment, along with blood product transfusions for symptomatic anemia.

Case Report

A 64-year-old white woman presenting with complaints of recent transient bilateral vision loss was found to be severely anemic upon arrival to the emergency department. She described her new-onset vision changes as a complete vision loss during which she saw pitch black for a few hours. She stated this occurred immediately after the last 2–3 sessions of her daily intravenous ceftriaxone infusions, as she was being treated for a recent group B streptococcal bacteremia with associated acute endocarditis. She stated her vision loss would improve within a few hours when she would get home and lay down. Over the past 2 weeks, she had noted an increase in fatigue, which worsened with even minimal exertion and was associated with mild shortness of breath. At the time of presentation, she denied chest pain, hemoptysis, hematochezia, change in stool, fever, chills, abdominal pain with associated nausea/vomiting/diarrhea, and urinary symptoms. She denied any recent falls or trauma.

Past medical/surgical history included right-sided breast cancer status post right mastectomy with reconstruction with latissimus dorsi myocutaneous flap, diastolic congestive heart failure, mild aortic stenosis, hypertension, sciatica, and a recent hospitalization (discharged about 3 weeks prior) for group B streptococcal bacteremia with associated acute endocarditis, which was deemed most likely to be a result from a urinary tract infection (UTI). Past social history included being a Jehovah's Witness. She denied any alcohol, tobacco, or recreational drug use. Past family history included a father with history of lung cancer and mother with unspecified liver cirrhosis. For her previous hospitalization (roughly 3 weeks prior), she presented with complaints of low back pain and foul smelling urine for 2 days. She was found to be febrile at 105.1°F (40°C), tachycardic, and hypotensive. After proper fluid hydration of 30 cc/kg, she was started on pressor support. She was started empirically on vancomycin and ceftriaxone for a likely urinary tract infection, with the urine culture eventually reporting as no growth. Cerebrospinal fluid studies were negative. Blood cultures ×2 grew group B streptococcus. No obvious source of the bacteremia was found, but was hypothesized to be due to a UTI. Ultimately, her lactic acidosis/septic shock resolved within 48 hours, but due to continued leukocytosis, a transesophageal echocardiogram (TEE) was obtained, which revealed a medium-sized, 8.6 mm (L)×7.3 mm (W), irregular vegetation on the anterior leaflet of the mitral valve (Figure 1). She was discharged home with plans for intravenous infusion of ceftriaxone 2 grams IV daily for a total of a 6-week course with ESR, CRP, CMP, and CBC scheduled every Monday, which followed infectious disease recommendations.

For her current admission, the patient's initial vitals were blood pressure 108/62 mmHg, heart rate 91, respirations 18,

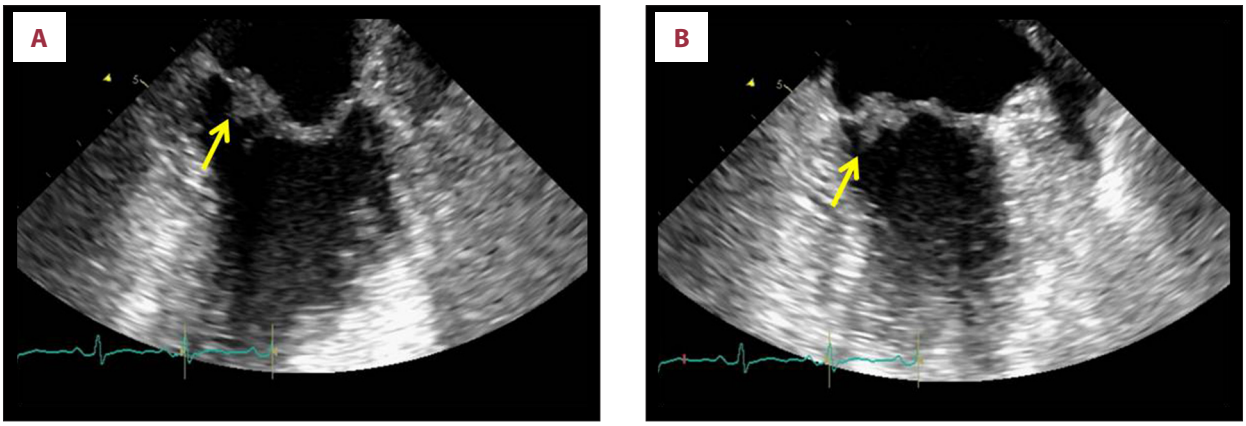

Figure 1. (**A, B**) These 2 transesophageal echocardiogram (TEE) images show the vegetation on the anterior leaflet of the mitral valve. The vegetation was not seen on the standard 2-D transthoracic echocardiogram (TTE).

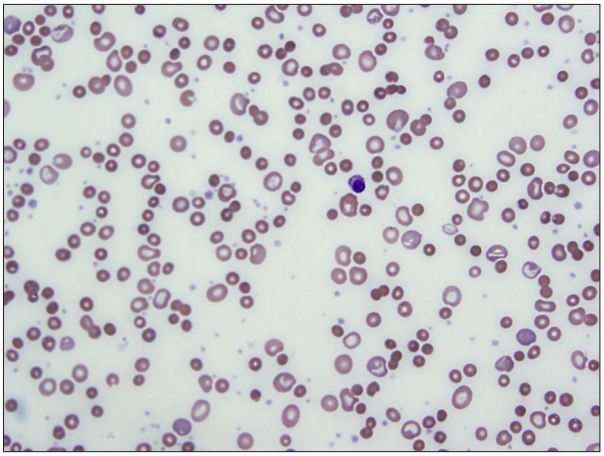

Figure 2. This blood smear demonstrates the presence of numerous spherocytes (smaller, more dense cells), abundant immature reticulocytes (larger cells with significant central pallor), and the lack of schistocytes or "bite" cells.

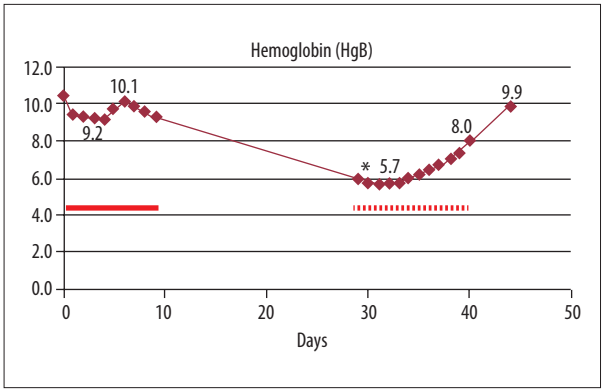

Figure 3. This graph depicts the patient's Hgb levels from her first hospitalization through the post second hospitalization outpatient followup. Hgb measured in g/dL. (*) designates day 1 of cessation of ceftriaxone and transition to vancomycin. Solid bar designates hospitalization 1 and dotted bar designates hospitalization 2.

temperature 99.3°F (37°C), and oxygen saturation 96% on room air. Primary exam revealed a pale, well-developed, alert, and oriented female in no acute distress, lying flat in bed. Cardiac exam revealed a +3/6 systolic murmur without radiation to the carotid arteries. Rectal exam was unremarkable, with stool Hemoccult-negative. No splinter hemorrhages were appreciated on nail beds. Head, ears, eyes, nose, throat (HEENT)/neck/pulmonary/abdomen/skin/neurological exams were all grossly unremarkable. An initial electrocardiogram (EKG) was unremarkable. Chest x-ray revealed a right-sided PICC in proper placement, but was otherwise unremarkable. A computer tomography (CT) scan of the head revealed moderate diffuse cerebral volume loss with chronic microvascular ischemic changes. CT abdomen/pelvis revealed a large right-sided pleural effusion and incidental cholelithiasis, but otherwise unremarkable with no retroperitoneal hematoma.

Laboratory assessments on admission were as follows: white blood cell count (WBC) 5.8; hemoglobin/hematocrit (Hgb/Hct) 6.0/17.0; platelets 560; reticulocyte count 12.4%; sodium 129; potassium 3.8; chloride 100; carbon dioxide 23; blood urea nitrogen (BUN) 13; creatinine 0.7; alkaline phosphatase 71; total bilirubin 1.5; aspartate transaminase (AST) 38; alanine transaminase (ALT) 17; lactate dehydrogenase (LDH) 348; haptoglobin 101; direct coombs positive including positivity for both IgG and C3d; activated partial thromboplastin time 24.4; protime 13.8; INR 1.2; lactic acid 0.9; and an overall negative urinalysis. Blood cultures were negative. Peripheral blood smear revealed lymphocyte 45%, monocyte 48%, eosinophil 6%, basophil 1%, nucleated red blood cell 10%, +2 anisocytosis, and polychromasia (Figure 2).

The patient was admitted to a telemetry floor for her symptomatic, likely hemolytic, anemia. Our infectious disease service was consulted, who recommended a change from ceftriaxone to vancomycin due to a likely ongoing drug-induced immune hemolytic anemia. The patient adamantly refused blood products and requested to be treated conservatively. She was started on daily 325 mg ferrous sulfate, daily 1 mg folic acid, and 1000 mcg intramuscular vitamin B12 injections for 7 days. A prednisone taper was initiated, starting at 40 mg daily (starting hospital day 2) for 4 days and then decreasing by 5 mg until off. Epoetin Alfa was initiated on hospital day 2 at 4000 units subcutaneous scheduled every other day. The dose was increased to 8000 units on hospital day 6, 10 000 units on hospital day 8, and 12 000 units on hospital day 10. The patient's Hgb eventually plateaued at 5.7 and slowly improved with the cessation of ceftriaxone.

Outcome and follow-up

Figure 3 shows the gradual improvement in hemoglobin (Hgb) throughout the second hospital stay and post-hospital stay. The patient's severe anemia was successfully treated conservatively and she was safely discharged to home with assistance from family. The patient finished her outpatient antibiotic course of intravenous vancomycin and continues to follow up on a routine basis. The multiple episodes of transient vision loss, which the patient suffered prior to admission, never returned and were explained as being directly related to her severe anemia; i.e., ischemic optic neuropathy.

Discussion

The patient was determined to have a subacute, progressive hemolytic anemia due to her infusions of ceftriaxone. It was

concluded that her type of anemia was due to an extravascular hemolysis due to the presence of spherocytes/lack of red blood cell fragments on smear, positive DAT, increase in serum LDH, and absence of urine hemoglobin. The patient's normal haptoglobin points away from an intravascular hemolysis and may be due to the progressive nature of the anemia. Normal haptoglobin levels may be present in extravascular hemolysis. In the United States, ceftriaxone appears to be the second most common drug causing DIIHA [6,8]. A positive DAT is the most reliable laboratory finding in DIIHA [2].

For clinical management of a DIIHA, it is useful to categorize the involved antibody as drug-dependent (DDAB) or drug-independent (DIAB) [2]. Ceftriaxone, along with other cephalosporin antibiotics, are most commonly associated with DDAB formation [2,9]. Extravascular hemolysis may result from the production of non-complement-activating, drug-dependent antibodies (DDAB) [10]. DDAB-related hemolysis usually demonstrates a positive DAT and a negative elution, which may be performed to characterize the antibody coating the RBCs [2]. The DAT was positive in our patient, with both IgG and C3d positivity. Unfortunately, there was no elution completed on our patient, which in retrospect may have been helpful in clarifying the final diagnosis. Another possibility would have been to have an immunohematology laboratory, which specializes in DDAB detection, confirm the presence or absence of specific anti-ceftriaxone antibodies.

For drug-dependent hemolysis, cessation of the drug (usually cefotetan, ceftriaxone, or piperacillin) is critical and this is equally true for drug-independent hemolysis, but because of the true autoantibody in drug-independent hemolysis, patients should additionally be treated as for warm antibody autoimmune hemolytic anemia (WAIHA) (i.e., with steroids, IVIG, and/or plasma exchange) [2,8]. It was decided to initiate intravenous steroids in the patient due to the lack of contraindication and possibility of benefit in that WAIHA could not be ruled out secondary to the lack of antibody analysis. Differentiation between DIIHA and WAIHA can be fairly challenging. The only reliable confirmation of DDAB-mediated DIIHA over WAIHA requires testing the patient's serum after drug cessation and clearance of any circulating drug or drug-antibody complexes, indicated by a clear decrease in serologic reactivity [2]. There is no need at the present time for this continued testing in the patient due to the lack of DDAB verification during the acute event. Retrospectively, confirmation of the presence of DDAB should be been sought.

Most cases of WAIHA are idiopathic, with no direct cause found. It is usually associated with splenomegaly, severe anemia, fever, and jaundice, and is mostly associated with extravascular hemolysis [11]. Our patient did not have splenomegaly, fever, or jaundice, but did have spherocytes and polychromatophilic red cells on the repeat blood smear completed on hospital day 4. Hemolysis associated with ceftriaxone typically appears within 2 weeks of starting the drug and presents with progressive anemia [2], which exactly fits the clinical picture of our patient, leading to the conclusion that this case was likely a DIIHA, specifically a CIIHA. This again can only be concluded with a relative amount of certainty in that the serological evaluation was limited and therefore not allowing for a definitive diagnosis.

The differential diagnosis initially included G6PD deficiency, which was deemed doubtful due to the standard timing of G6PD presentation being 2–4 days after initial drug ingestion, as well as the lack of red blood cells fragments or "bite" cells on peripheral smear. Acute transfusion reaction could easily have been eliminated from the list of differential diagnosis in our patient. Infectious etiology, with the patient's recent (3 weeks prior) endocarditis history, was initially debated as the cause of the acute hemolysis. It is important to mention that the only positive blood cultures documented were the initial set during the initial hospitalization, which grew group B streptococcus. The presence of fragmented erythrocytes (on smear) suggests mechanical destruction of the RBCs [12], even regarding a native heart valve. There were no RBC fragments seen on smear, and with the clinical picture pointing toward an extravascular hemolysis, an infectious cause was considered unlikely.

Conclusions

The presented case highlights the importance of close vigilance while prescribing drugs known to cause hemolytic anemia. Most published cases to date involving CIIHA are in children [13] and most include blood product transfusions as the standard of treatment. The presented case is very unique in that this patient with severe hemolytic anemia was a Jehovah's Witness and was able to be successfully treated without blood product transfusion. In retrospect, further antibody evaluation should have been sought, which would have eliminated the need to speculate on the definitive diagnosis.

Competing Interests

None.

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