Ceftriaxone Induced Hemolysis Complicated by Acute Renal Failure

Gaurav Kapur, MD,1* Rudolph P. Valentini, MD,1 Tej K. Mattoo, MRCP, MD,1 Indira Warrier, MD,2 and Abubakr A. Imam, MD1

Over the last decade, second and third generation cephalosporins have been the most common drugs causing hemolytic anemia (HA). Of these cases, 20% have been attributed to ceftriaxone. The clinical presentation of ceftriaxone-induced HA is usually abrupt with sudden onset of pallor, tachypnea, cardio-respiratory arrest and shock. Acute renal failure (ARF) has been reported in 41% of such cases with a high fatality rate. We report a pediatric patient with ARF complicating ceftriaxone-induced HA who survived. Ceftriaxone is a commonly used drug, and early recognition of HA and institution of supportive care, including dialysis is likely to improve the outcome.


Key words: acute renal failure (ARF); ceftriaxone; hemolytic anemia (HA)

INTRODUCTION

Drug induced hemolytic anemia (HA) is an immune mediated process in which antibodies react against the red blood cells (RBC). Risk of clinical blood dyscrasias is increased fivefold among patients receiving antibiotics and is highest with cephalosporins [1]. Since the first report of severe intravascular immune hemolytic anemia (IHA) with cefotaxime [2], second and third generation cephalosporins have been reported as the most common cause of drug-induced HA [3]. More than 50% of all reported cases of IHA associated with third-generation cephalosporins are related to ceftriaxone [4]. A fatal outcome is more common in ceftriaxone-induced HA than in IHA associated with other drugs [4]. Ceftriaxone induced HA in children is more common in patients with underlying hematological and immune dysfunction. We present a pediatric case, who survived acute renal failure (ARF) secondary to ceftriaxone-induced HA.

CASE REPORT

A 10-year-old Caucasian male with a past medical history significant for craniosynostosis was evaluated for scalp abscess on right temporal area which was incised and drained. Patient had received one dose of intravenous (I/V) ceftriaxone and two doses of...

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clindamycin and was sent home on cephalaxin 250 mg orally four times a day. The patient developed superficial infection of the skin and underlying temporal shield. He was readmitted and started on I/V clindamycin (250 mg) every 6 hr. The patient had surgical removal of the temporal shield and switched to I/V ceftriaxone (1 g twice a day). After receiving the third dose of ceftriaxone, he developed a maculopapular rash starting at the upper torso and spreading to involve the face and abdomen with itching all over the body. Patient also developed mild facial puffiness. There was no associated wheezing, shortness of breath, or arthritis. Subsequently the patient was noticed to have deterioration of his mental status associated with decreasing urine output. He became anuric 1 day later. His serum creatinine increased from 1.1 mg/dl on admission to 5.4 mg/dl over a period of 4 days. His hemoglobin dropped from 12.4 mg/dl to 8.7 mg/dl during the same period. There was no history of excessive blood loss at surgery. The patient was transferred to Children’s Hospital of Michigan for management of his ARF.

On admission the patient was drowsy, but responsive, with a pulse of 111/min, BP 122/80 and respiratory rate 15/min. Apart from mild facial puffiness, rest of the physical examination was within normal limits. His investigations revealed: Blood urea nitrogen (BUN) 34 mg/dl, creatinine 6.9 mg/dl, sodium 138 meq/L, potassium 4.6 meq/L, phosphorus 5.6 mg/dl, Lactate dehydrogenase (LDH) 3867 U/L, serum albumin 2.3 mg/dl. Rest of the blood chemistry included normal complements, liver function tests, creatinine kinase and antistreptolysinO (ASO) titer. His hematological workup revealed hemoglobin 8.4 g/dl, platelets 112 × 10³/mm³, reticulocyte count 4.5%, D-dimer 400–800 ng/ml (normal <200 ng/ml), fibrinogen 1056 mg/dl (158–416 mg/dl), activated partial thromboplastin time (APTT) 33.1 sec and prothrombin time (PT) 11.1 sec. Broad spectrum and monospecific Coombs (C3d, IgG) tests were negative. The patient’s peripheral smear showed normocytic normochromic red cells with no evidence of schistocytes or eosinophilia. His immunological workup included negative serology for antinuclear antibody (ANA), HIV and normal immunoglobulin levels. His urine analysis revealed specific gravity 1015, pH 7.0, protein 100 mg/dl, 2 + leukocyte esterase, >100 RBC/HPF, >100 WBC/HPF, and no casts or myoglobinuria. A renal ultrasound with Doppler revealed large echogenic kidneys with normal resistive indices. The patient underwent a renal biopsy for the evaluation of the cause of his renal failure and peritoneal dialysis was initiated. The renal biopsy showed acute tubular necrosis with hemoglobin casts within the tubular lumen (Fig. 1). There was no evidence of interstitial nephritis on the renal biopsy. He received peritoneal dialysis for 2½ weeks. Subsequently, his renal function and urine output gradually recovered. The patient’s serum creatinine normalized at 0.7 after 6 weeks of onset of symptoms.

**DISCUSSION**

Adverse drug reactions are a major clinical problem accounting for 2–6% of all hospital admissions [5]. Of the total 17 reported cases of ceftriaxone-induced hemolysis, 61% have been reported in children [4,6–20]. Ceftriaxone-induced hemolysis has a 63% fatality rate in children and 40% in adults. In 41% of these patients, the clinical course has been complicated by ARF with invariably poor outcome (Table I). The review of these [4,10,13] revealed that 10 out of 11 cases had an underlying immune or hematological dysfunction and were frequently associated with a history of recurrent infections. In these cases, re-exposure or continued treatment with ceftriaxone might be critical determinants for development of drug dependent antibodies. Normal RBC morphology on peripheral smear, negative Coombs test, neonatal screening (history) and immunological workup excluded any significant intrinsic RBC or immunological disorder in our patient. Although, this workup for underlying intrinsic RBC or immune disorder was minimal, there was no obvious disorder detected.

The second and third generations of cephalosporins have been reported as the most common cause of drug-induced HA [3]. 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 [21]. 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 [22,23]. 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 [3]. Ceftriaxone appears to induce only antibodies that elicit immune complex type of in vitro reaction and is associated with a high fatality [3]. The hemolysis due to complement activation by these antibodies is abrupt and is usually intravascular. The resulting hemoglobinuria is nephrotoxic particularly when intra-tubular obstruction facilitates proximal tubular heme uptake [24].

The negative DAT test in our patient could be due to the sudden massive hemolysis occurring with ceftriaxone and therefore the lack of sensitized RBC with C3d and IgG at the time of testing when the patient presented to us. Also the LDH showed a decreasing trend subsequently which showed that the hemolysis was sudden and massive and did not continue once ceftriaxone was stopped. The diagnosis of ceftriaxone-induced HA in our patient was based on laboratory evidence of hemolysis and renal biopsy showing hemoglobin-laden tubules with acute tubular necrosis. The most effective treatment of patients who develop drug dependent IHA is immediate discontinuation of the drug [22],
<table>
<thead>
<tr>
<th>Author (ref #)</th>
<th>Year</th>
<th>Age/Sex</th>
<th>Primary diagnosis</th>
<th>Repeat dose after initial reaction</th>
<th>Days on ceftriaxone (Reaction onset)</th>
<th>Clinical features</th>
<th>Complications</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric cases</strong></td>
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<tr>
<td>Borgna-Pignatti et al. [6]</td>
<td>1995</td>
<td>8/M</td>
<td>Perinatal HIV</td>
<td>Yes</td>
<td>3 (20 min)</td>
<td>Back pain, hemoglobinuria</td>
<td>DIC, ARF</td>
<td>Death</td>
</tr>
<tr>
<td>Lascari et al. [7]</td>
<td>1995</td>
<td>5/M</td>
<td>Juvenile CML</td>
<td>No</td>
<td>1 (45 min)</td>
<td>Unconsciousness, anemia, shock</td>
<td>Intravascular hemolysis</td>
<td>Death</td>
</tr>
<tr>
<td>Bernini et al. [8]</td>
<td>1995</td>
<td>2/M</td>
<td>Sickle cell anemia</td>
<td>Yes</td>
<td>1 (20 min)</td>
<td>Unconsciousness, anemia, shock</td>
<td>Multiple organ failure</td>
<td>Death</td>
</tr>
<tr>
<td>Scimeca et al. [9]</td>
<td>1996</td>
<td>3/F</td>
<td>Eosinophilic syndrome</td>
<td>No</td>
<td>1 (5 min)</td>
<td>Unconsciousness, anemia, shock</td>
<td>DIC, oliguria</td>
<td>Death</td>
</tr>
<tr>
<td>Moallem et al. [10]</td>
<td>1998</td>
<td>14/F</td>
<td>Perinatal HIV</td>
<td>No</td>
<td>1 (30 min)</td>
<td>Back pain, shock</td>
<td>Muscle spasms, anemia</td>
<td>Death</td>
</tr>
<tr>
<td>Viner et al. [12]</td>
<td>2000</td>
<td>6/M</td>
<td>Sickle cell anemia</td>
<td>No</td>
<td>6 (30 min)</td>
<td>Back pain, anemia, anemia</td>
<td>NA</td>
<td>Survive</td>
</tr>
<tr>
<td>Citak et al. [13]</td>
<td>2002</td>
<td>5/F</td>
<td>Recurrent UTI</td>
<td>No</td>
<td>3 (30 min)</td>
<td>Seizures, anemia, cardiac arrest</td>
<td>Mechanical ventilation</td>
<td>Survive</td>
</tr>
<tr>
<td>Kakaiya et al. [14]</td>
<td>2004</td>
<td>10/M</td>
<td>Sickle cell disease</td>
<td>No</td>
<td>3</td>
<td>Seizure, anemia, shock</td>
<td>Mechanical ventilation</td>
<td>Survive</td>
</tr>
<tr>
<td>Bell et al. [15]</td>
<td>2005</td>
<td>17/F</td>
<td>Hb SC with acute chest syndrome</td>
<td>Yes</td>
<td>4</td>
<td>Anemia, hemoglobinuria, altered mental status</td>
<td>ARF, hepatitis,</td>
<td>Death</td>
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<td><strong>Adult cases</strong></td>
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<tr>
<td>Garratty et al. [16]</td>
<td>1990</td>
<td>52/F</td>
<td>Recurrent staph infections</td>
<td>Yes</td>
<td>5 (Immediately)</td>
<td>Muscle spasms, anemia</td>
<td>ARF</td>
<td>Death</td>
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<tr>
<td>Lo et al. [17]</td>
<td>1993</td>
<td>67/F</td>
<td>H. influenzae septic arthritis</td>
<td>No</td>
<td>34</td>
<td>Anemia, Hemoglobinuria</td>
<td>NA</td>
<td>Survive</td>
</tr>
<tr>
<td>Punar et al. [19]</td>
<td>1999</td>
<td>38/M</td>
<td>Meningitis</td>
<td>No</td>
<td>10</td>
<td>Icterus, anemia, ARF</td>
<td>multiple organ failure</td>
<td>Death</td>
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<tr>
<td>Falezza et al. [20]</td>
<td>2000</td>
<td>79/F</td>
<td>Recurrent diverticulitis</td>
<td>Yes</td>
<td>7</td>
<td>Pain, anemia, Icterus</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Seltsam et al. [4]</td>
<td>2000</td>
<td>64/F</td>
<td>Carcinoma bile duct</td>
<td>No</td>
<td>1 (30 min)</td>
<td>Back pain, anemia, shock</td>
<td>Intravascular hemolysis</td>
<td>Death</td>
</tr>
<tr>
<td>Seltsam et al. [4]</td>
<td>2000</td>
<td>68/F</td>
<td>Tubercular meningitis</td>
<td>No</td>
<td>10</td>
<td>Lumbar pain, hemolytic crisis</td>
<td>ARF</td>
<td>Survive</td>
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</table>
which was the case in our patient. Of the reported cases, almost one third of the patients continued to receive the drug after an initial allergic reaction to ceftriaxone as they were diagnosed retrospectively.

In conclusion, ceftriaxone can cause fatal hemolysis and should be used with caution especially in patients who are immunocompromised or have an underlying hematological condition. ARF may be the presenting manifestation of ceftriaxone-induced IHA and the prognosis may be favorable for recovery with early diagnosis and initiation of supportive therapy including dialysis.

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Large Granular Lymphocyte Leukemia (LGL) in a Child With Hyper IgM Syndrome and Autoimmune Hemolytic Anemia

Brenda J. Kitchen, MD* and Laurence A. Boxer, MD

We describe a female with a history of autosomal recessive hyper-IgM (HIGM) syndrome along with a history of autoimmune hemolytic anemia and intermittent lymphadenopathy. She subsequently developed neutropenia, lymphocytosis and mild thrombocytopenia. Flow cytometry of the peripheral blood revealed the presence of a marked predominance of cytotoxic T lymphocytes, shown to be clonal, with concomitant natural killer (NK) antigen expression. She responded to weekly methotrexate therapy. Pediatr Blood Cancer 2008;50:142–145. © 2006 Wiley-Liss, Inc.

INTRODUCTION

Large granular lymphocyte leukemia (LGL) is a rare, indolent form of non-Hodgkin’s lymphoma. This clonal lymphoproliferative disease arises most frequently from T-cells and less commonly from natural killer (NK) cells [1]. The median age at presentation is 60 years old with less than 10% of patients younger than 40 years of age. Ceftriaxone was the causative agent for fatal hemolysis in this adolescent.

Key words: autoimmune hemolytic anemia; granular lymphocyte leukemia; hyper-IgM syndrome

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