2. Masson E, Synold TW, Relling MV, et al. Allopurinol inhibits de novo purine synthesis in lymphoblasts of children with acute lymphoblastic leukemia. Leukemia 1996;10:56–60.
3. Nelson SC, Bruggers CS, Kurtzberg J, et al. Management of leukemic hyperleukocytosis with hydration, urinary alkalinization, and allopurinol. Are cranial irradiation and invasive cytoreduction necessary? Am J Pediatr Hematol Oncol 1993;15:351–355.
4. Basade M, Dhar AK, Kulkarni SS, et al. Rapid cytoreduction in childhood leukemic hyperleukocytosis by conservative therapy. Med Pediatr Oncol 1995;25:204–207.
5. Schrappe M, Reiter A, Zimmermann M, et al. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Munster. Leukemia 2000;14:2205–2222.
6. Schwartz CL, Thompson EB, Gelber RD, et al. Improved response with higher corticosteroid dose in children with acute lymphoblastic leukemia. J Clin Oncol 2001;19:1040–1046.
7. Fiselier T, Monnens L, Moerman E, et al. Influence of the stress of venepuncture on basal levels of plasma renin activity in infants and children. Int J Pediatr Nephrol 1983;4:181–185.
8. Bhisitkul DM, Morrow AL, Vinik AI, et al. Prevalence of stress hyperglycemia among patients attending a pediatric emergency department. J Pediatr 1994;124:547–551.
9. Rose RM, Hurst MW. Plasma cortisol and growth hormone responses to intravenous characterization. J Human Stress 1975;1:22–36.
10. Mason JW, Sachar EJ, Fishman JR, et al. Corticosteroid responses to hospital admission. Arch Gen Psychiatry 1965;13:1–8.
11. Meeran K, Hattersley A, Mould G, et al. Venepuncture causes rapid rise in plasma ACTH. Br J Clin Pract 1993;47:246–247.
12. Kamada AK, Wiener MB, LaVallee NM, et al. A pharmacokinetic comparison of two oral liquid glucocorticoid formulations. Pharmacotherapy 1997;17:353–356.
13. Duzova A, Cetin M, Gumruk F, et al. Acute tumour lysis syndrome following a single-dose corticosteroid in children with acute lymphoblastic leukaemia. Eur J Haematol 2001;66:404–407.
14. Rajagopal S, Lipton JH, Messner HA. Corticosteroid induced tumor lysis syndrome in acute lymphoblastic leukemia. Am J Hematol 1992;41:66–67.
15. Tiley C, Grimwade D, Findlay M, et al. Tumour lysis following hydrocortisone prior to a blood product transfusion in T-cell acute lymphoblastic leukaemia. Leuk Lymphoma 1992;8:143–146.
16. Luna-Fineman S, Healy MV, Parker BR. Corticosteroid pretreatment for potential contrast reactions in children with lymphoreticular cancer: A word of caution. AJR Am J Roentgenol 1990; 155:357–358.
17. Smith T. Tumor lysis syndrome after steroid therapy for anaphylaxis. South Med J 1988;81:415–416.
18. Loosveld OJ, Schouten HC, Gaillard CA, et al. Acute tumour lysis syndrome in a patient with acute lymphoblastic leukemia after a single dose of prednisone. Br J Haematol 1991;77:122–123.

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, MD[1]

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. Pediatr Blood Cancer 2008;50:139–142. © 2006 Wiley-Liss, Inc.

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

[1]Division of Nephrology and Hypertension, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, Michigan; [2]Department of Pediatrics, Division of Hematology, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, Michigan

*Correspondence to: Gaurav Kapur, Department of Pediatrics, Fellow, Pediatric Nephrology, Children's Hospital of Michigan, Wayne State University School of Medicine, 3901 Beaubien Boulevard, Detroit, Michigan, 48201. E-mail: gkapur@dmc.org

Received 21 November 2005; Accepted 13 February 2006

© 2006 Wiley-Liss, Inc.
DOI 10.1002/pbc.20839

WILEY InterScience® DISCOVER SOMETHING GREAT

clindamycin and was sent home on cephalexin 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 hematology workup revealed hemoglobin 8.4 g/dl, platelets $112 \times 10^3/mm^3$, 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.

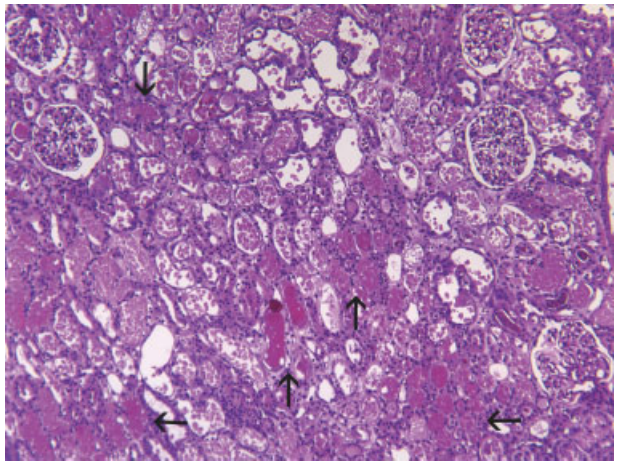

Fig. 1. Renal biopsy showing hemoglobin laden tubules and normal glomeruli. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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 intratubular 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 I. Summary of Pediatric and Adult Patients Reported With Ceftriaxone Induced Hemolytic Anemia

Author (ref #)	Year	Age/Sex	Primary diagnosis	Repeat dose after initial reaction	Days on ceftriaxone (Reaction onset)	Clinical features	Complications	Outcome
Pediatric cases								
Borgna-Pignatti et al. [6]	1995	8/M	Perinatal HIV	Yes	3 (20 min)	Back pain, hemoglobinuria	DIC, ARF	Death
Lascari et al. [7]	1995	5/M	Juvenile CML	No	1 (45 min)	Unconsciousness, anemia, shock	Intravascular hemolysis	Death
Bernini et al. [8]	1995	2/M	Sickle cell anemia	Yes	1 (20 min)	Unconsciousness, anemia, shock	Multiple organ failure	Death
Scimeca et al. [9]	1996	3/F	Eosinphillic syndrome	No	1 (5 min)	Unconsciousness, anemia, shock	DIC, oliguria	Death
Moallem et al. [10]	1998	14/F	Perinatal HIV	No	1 (30 min)	Back pain, shock	DIC	Death
Meyer et al. [11]	1999	16/F	Recurrent meningitis	Yes	7 (30 min)	Muscle spasms, anemia	Acute renal failure	Death
Viner et al. [12]	2000	6/M	Sickle cell anemia	No	6 (30 min)	Back pain, anemia, anemia	NA	Survive
Citak et al. [13]	2002	5/F	Recurrent UTI	No	3 (30 min)	Seizures, anemia, cardiac arrest	Mechanical ventilation	Survive
Kakaiya et al. [14]	2004	10/M	Sickle cell disease	No	3	Seizure, anemia, shock	Mechanical ventilation	Survive
Bell et al. [15]	2005	17/F	Hb SC with acute chest syndrome	Yes	4	Anemia, hemoglobinuria, altered mental status	ARF, hepatitis,	Death
This report	2006	10/M	Craniostenosis	No	3 (Immediately)	Maculopapular rash, anemia	ARF	Survive
Adult cases								
Garratty et al. [16]	1990	52/F	Recurrent staph infections	Yes	5 (Immediately)	Muscle spasms, anemia	ARF	Death
Lo et al. [17]	1993	67/F	*H. influenzae* septic arthritis	No	34	Anemia, Hemoglobinuria	NA	Survive
Punar et al. [19]	1999	38/M	Meningitis	No	10	Icterus, anemia,	ARF, multiple organ failure	Death
Falezza et al. [20]	2000	79/F	Recurrent diverticulitis	Yes	7	Pain, anemia, Icterus	NA	NA
Seltsam et al. [4]	2000	64/F	Carcinoma bile duct	No	1 (30 min)	Back pain, anemia, shock	Intravascular hemolysis	Death
Seltsam et al. [4]	2000	68/F	Tubercular meningitis	No	10	Lumbar pain, hemolytic crisis	ARF	Survive

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.

REFERENCES

1. Huerta C, Garcia-Rodriguez L. Risk of clinical blood dyscrasias in a cohort of antibiotic users. Pharmacotherapy 2002;22:630–636.
2. Salama A, Gottsche B, Schleiffer T, et al. Immune complex mediated intravascular hemolysis due to IgM cephalosporin-dependent antibody. Transfusion 1987;27:460–463.
3. Arandt PA, Leger RM, Garratty G. Serology of antibodies to second and third generation cephalosporins associated with immune hemolytic anemia and/or positive direct antiglobulin tests. Transfusion 1999;39:1239–1246.
4. Seltsam A, Salama A. Ceftriaxone-induced immune hemolysis: Two case reports and a concise review of the literature. Intensive Care Med 2000;26:1390–1394.
5. Maraspin V, Lotric-Furlan S, Strle F. Ceftriaxone associated hemolysis. Wien Klin Wochenschr 1999;111:368–370.
6. Borgna-Pignatti C, Bezzi TM, Reverberi R. Fatal ceftriaxone induced hemolysis in a child with acquired immunodeficiency syndrome. Pediatr Infect Dis J 1995;14:1116–1117.
7. Lascari AD, Amyot K. Fatal hemolysis by ceftriaxone. J Pediatr 1995;126:816–817.
8. Bernini JC, Mustafa MM, Sutor LJ, et al. Fatal hemolysis induced by ceftriaxone n a child with sickle cell anemia. J Pediatr 1995;126:813–815.
9. Scimeca PG, Weinbatt ME, Boxer R. Hemolysis after treatment with ceftriaxone. J Pediatr 1996;128:163.
10. Moallem HJ, Garratty G, Wakeham M, et al. Ceftriaxone related fatal hemolysis in an adolescent with perinatally acquired human immunodeficiency virus infection. J Pediatr 1998;133: 279–281.
11. Meyer O, Hackstein H, Hoppe B, et al. Fatal immune hemolysis due to a degradation product of ceftriaxone. Br J Hematol 1999;105: 1084–1085.
12. Viner Y, Hashkes PJ, Yakubova R, et al. Severe hemolysis induced by ceftriaxone in a child with sickle cell anemia. Pediatr Infect Dis J 2000;26:1390–1394.
13. Citak A, Garratty G, Uscel R, et al. Ceftriaxone-induced hemolytic anemia in a child with no immune deficiency or hematological disease. J Pediatr Child Health 2002;38:209–210.
14. Kakaiya R, Cseri J, Smith S, et al. A case of acute hemolysis after ceftriaxone: Immune complex mechanism demonstrated by flow cytometry. Arch Pathol Lab Med 2004;128:905–907.
15. Bell MJ, Stockwell DC, Luban NL, et al. Ceftriaxone-induced hemolytic anemia and hepatitis in an adolescent with hemoglobin SC disease. Pediatr Crit Care Med 2005;6:363–366.
16. Garratty G, Postway N, Schwellenbach J, et al. A fatal case of ceftriaxone (Rocephin)—induced hemolytic anemia associated with intravascular immune Hemolysis. Transfusion 1991;31:176–179.
17. Lo G, Higginbottom P. Ceftriaxone induced hemolytic anemia. Transfusion 1993;33:25S.
18. Longo F, Hastier P, Buckley MJ, et al. Acute hepatitis, autoimmune hemolytic anemia and erythroblastopenia induced by ceftriaxone. Am J Gastroenterol 1998;93:836–837.
19. Punar M, Ozsut H, Eraksoy H, et al. An adult case of fatal hemolysis induced by ceftriaxone. Clin Microbiol Infect 1999;5:585–586.
20. Falezza GC, Picolli PL, Franchini M, et al. Ceftriaxone-induced hemolysis in an adult. Transfusion 2000;40:1543–1545.
21. Wright MS. Drug-induced hemolytic anemias: Increasing complications to therapeutic interventions. Clin Lab Sci 1999;12:115–118.
22. Mueller-Eckhart C, Salama A. Drug-induced immunecytopenias: A unifying concept with special emphasis on the role of drug metabolites. Transfus Med Rev 1990;4:69.
23. Habibi B. Drug induced red blood cell autoantibodies co-developed with drug specific causing hemolytic anemia. Brit J Hematol 1985; 61:139–143.
24. Zagar RA, Gamelin LM. Pathogenic mechanisms in experimental hemoglobinuric acute renal failure. Am J Physiol 1989;256:F446–F455.

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, lymphocyostosis 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.

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

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

Division of Hematology/Oncology, Department of Pediatrics and Communicable Diseases, University of Michigan, Mott Children's Hospital, Ann Arbor, Michigan

*Correspondence to: Brenda J. Kitchen, Women's Hospital Rm L2110, 1500 E. Medical Center Dr., Box 0238, Ann Arbor, MI 48109.
E-mail: nkbrenda@umich.edu.

Received 5 January 2006; Accepted 18 April 2006

© 2006 Wiley-Liss, Inc.
DOI 10.1002/pbc.20902

WILEY InterScience® DISCOVER SOMETHING GREAT