Interstitial Nephritis Induced by Cloxacillin

P.C.	Paul C.	Grimm
M.R.	Malcolm R.	Ogborn
A.J.	Alfield J.	Larson
J.F.S.	John F.S.	Crocker

Department of Pediatrics, Dalhousie University and The Izaak Walton Killam Hospital for Children, Halifax, Nova Scotia, Canada

Dr. John F.S. Crocker, Professor of Pediatrics, IWK Hospital for Children, 5850 University Avenue, Halifax, Nova Scotia B3J 3G9 (Canada)

Dear Sir,

Interstitial nephritis due to drug exposure is a common cause of acute renal failure. Many members of the penicillin group of antibiotics have been implicated in this condition. Interstitial nephritis in patients receiving methicillin is the most publicized association but episodes have been reported with amoxicillin, oxacillin, flucloxacillin, dicloxacillin, carbenicillin, penicillin G, and ampicillin. We report a case of interstitial nephritis associated with the use of cloxacillin.

Case Report

The patient was a 4-year-old Caucasian male who presented to hospital with fever, irritability and decreased fluid intake and urination. He had been well until 28 days prior to admission (PTA) when he was prescribed a 10-day course of oral cloxacillin for a minor localized cellulitis on the foot. Five days after the completion of cloxacillin, he developed a fever and malaise. Eleven days PTA, the fever and listlessness recurred accompanied by a fine red truncal rash. He was seen by a pediatrician who diagnosed a bacterial cervical lymphadenitis and prescribed another course of oral cloxacillin 50 mg/kg/day $\times$ 7 days. The spiking fever subsided 8 days PTA but returned on the 5th day PTA. Anorexia, vomiting, and mild conjunctival injection were present on admission and he had been anuric for 48 h. Past history was unremarkable except for recurrent otitis media treated with amoxicillin.

On examination he was lethargic, irritable and moderately dehydrated with dry mucous membranes, a pulse rate of 90 bpm, blood pressure of 90/50 mm Hg, oral temperature of 38.8 °C, and weight of

kg. There was no skin rash, lymphadenopathy, arthritis, or renomegaly on admission. Laboratory values included a WBC of

10V1 (27,500 mm³), (88% neutrophils, 2% band, 6% monocyte, 4% lymphocytes, and no eosinophils), Hbg 96 g/l (1.49 mmol/l), with a normal peripheral blood smear; Na 124 mmol/l; K 3.7 mmol/l, urea 39.3 mmol/l (109 mg/dl) creatinine 500 μ mol/l (5.6 mg/dl). Urinalysis revealed a pH of 5.0, SG of 1.009, no glucose, protein or blood, 10–20 WBC casts/HPF, spot Na of 3 mmol/l, creatinine 4.4 mmol/l (50 mg/dl), Fractional excretion of sodium 0.3% and osmolality 253.

A tentative diagnosis of prerenal azotemia secondary to dehydration from vomiting was entertained, so he was rehydrated overnight with normal saline. In the morning his weight was

increased by 1.4 kg, he was still oliguric and then had moderate peripheral edema. He was normotensive and still febrile. Creatinine was 534 $\mu\text{mol/l}$ (6.0 mg/dl) and BUN 39.6 $\mu\text{mol/l}$ (111 mg/dl). Renal scan showed enlarged kidneys with normal blood flow but minimal excretion of radiopharmaceutical. There was no evidence of obstruction to urine flow. C3, C4, and immunoglobulins G, M, and A were normal. Cultures of urine, blood and throat were negative. Urine sediment cytology showed a high-grade eosinophiluria (5%). A repeat urinalysis showed the development of glucosuria and trace hematuria with persistent eosinophiluria. A diagnosis of acute renal failure due to interstitial nephritis was considered and the patient was given one intravenous dose of methylprednisolone and 2 daily doses of prednisone 150 mg p.o. The creatinine fell dramatically and he had a brisk diuresis. Dialysis was not required and 1 year later, he remains well with normal renal function.

Discussion

Since Councilman [1] first used the term interstitial nephritis in 1898, this condition has been reported with many drugs and specifically a number of penicillins. Appel and Neu [2] have stated that it is only a matter of time before all penicillin drugs are implicated. A search of the Medline® database and recent reviews [3, 4] failed to associate cloxacillin with interstitial nephritis. In this child there are few of the confounding variables of inter-current illness, advanced age, multiple drug use, and other treatments that are frequently present in cases of interstitial nephritis and often result in the need for renal biopsy to confirm this diagnosis. The urinary eosinophil count of 5% of the total sediment granulocytes is suggested to strongly support a diagnosis of interstitial nephritis [5]; however, this belief is somewhat controversial [6]. These urinary findings in combination with the clinical picture of a patient with recurrent spiking fever, malaise, skin rash, during and after exposure to a penicillin class drug, and rapid response to drug withdrawal and steroids

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supports a diagnosis of interstitial nephritis secondary to cloxacillin. Prerenal causes of oliguria were ruled out by the absence of a clinical response to a volume load sufficient to cause peripheral edema. The fractional excretion of sodium was less than 1%. This has been frequently reported in cases of interstitial nephritis and argues against the alternative diagnosis of acute tubular necrosis induced by some unknown factor [7].

This case represents what we believe is the first report of this complication of cloxacillin therapy and emphasizes the need for awareness of this complication in patients receiving any penicillin derivative.

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