Piperacillin-Induced Acute Interstitial Nephritis

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Dear Sir,

Acute interstitial nephritis (AIN) has been well documented during therapy with antimicrobial agents of the penicillin class, including penicillin G [1], ampicillin [2], oxacillin [3], methicillin [4], nafcillin [5], carbenicillin [6] and mezlocillin [7].

Piperacillin is a semisynthetic penicillin with activity against *Pseudomonas aeruginosa*, other gram-negative bacteria and some gram-positive bacteria, which has been available commercially in a great number of countries for long time. Despite a worldwide clinical experience, however, AIN associated with piperacillin has been reported just once [8].

Here we describe a patient with probably clinical AIN in association with piperacillin therapy. A 59-year-old man was admitted to our hospital for acute myelophoblastic leukemia (M2 of the FAB classification). His induction treatment was done with Adriamycin (30 mg/m² i.v. for 3 days) and cytarabine (1 g/12 h/m² for 3 days plus 100 mg/m² for 7 days). Allopurinol (200 mg/day) was added to the treatment. He had no history of drug reaction or allergies.

Two months later, the patient presented fever and pulmonary infiltrates in a chest X-ray, which were treated with antibiotics (vancomycin: 500 mg/6 h, amikacin: 500 mg/ 12 h, imipenem: 500 mg/6 h) and amphotericin B (30 mg/day). Ten days later the infiltrates and fever persisted unchanged. As we suspected tuberculous infection, antibiotics and amphotericin B were discontinued, and rifampicin (600 mg/day), isoniazid (300 mg/day), ethambutol (1,200 mg/day) and pyrazinamide (1750 mg/day) were instituted, with good response, and the fever and the infiltrates disappeared.

At this time his blood urea nitrogen (BUN) and serum creatinine levels were 56 mg/dl (19.9 mmol/l) and 2.3 mg/dl (203.3 µmol/l), respectively, the rest of laboratory data being normal [except an uric acid level of 13.4 mg/dl (0.79 mmol/l)]. The hemogram showed a normal number of leukocytes, neutrophils and red blood cells. The platelet count was 30,000/µl, and urinalysis was normal without hematuria and eosinophils.

Two weeks later, the patient developed fever again, since *Acinetobacter baumannii* grew from blood cultures. The patient was given intravenous piperacillin (4 g every 6 h), because the germ was sensible to this antibiotic. The rest of the medication was not changed.

Two days later, our patient experienced worsening of his renal function, and eosino-philia of 20% was noted without fever, rash, hematuria, arthropathy or eosinophiluria. At this moment laboratory studies showed a BUN of 79 mg/dl (28.2 mmol/l) with a serum creatinine level of 4.6 mg/dl (406.6 μ mol/l) and a hemogram with 16,100 leukocytes/ μ l with 20% eosinophils.

Wright's stain urine sediment was negative for eosinophils.

Piperacillin was stopped 3 days later because the patient's physician thought that it could be responsible for renal damage. Anti-tuberculosis drugs and allopurinol were retained at the same doses, and ceftazidime (2 g every 8 h) was instituted.

Laboratory studies performed after 2 days showed a BUN of 68 mg/dl (24.3 mmol/l), a serum creatinine level of 3.5 mg/dl (309.4 μ mol/l) and a hemogram with 14,100 leukocytes/ μ l with 14% eosinophils.

A new laboratory control made 3 days later displayed a BUN of 57 mg/dl (20.3 mmol/l) and a serum creatinine level of 2.4

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mg/dl (212.2 μ mol/l) with a normal hemogram, without eosinophils.

The diagnosis of drug-induced AIN is usually made by associating the implicated drug with acute renal failure, rash, fever, hematuria, arthropathy, eosinophilia and eosinophiluria [9].

Our patient developed a gradual renal damage after his hospital admission, produced probably by the administration of anti-neoplastic drugs and amphotericin B, and afterwards he experienced a rapid impairment of his renal function with peripheral eosinophilia after the introduction of piperacillin therapy. When piperacillin therapy was discontinued, his renal function rapidly returned to baseline values.

Although this patient only presented acute renal failure and eosinophilia without other signs and symptoms, we think that he developed AIN. No confirmatory renal biopsy was performed because the patient had a relative thrombocytopenia and his renal function quickly improved.

The patient received another potentially nephrotoxic agent that might produce delayed renal damage, but due to the immediate temporal relationship between the precipitous development of acute renal failure and the administration of piperacillin and the fast resolution after its withdrawal, it seems unlikely that an agent other than piperacillin caused the interstitial nephritis. Both humoral and cell-mediated mechanisms of renal damage have been incriminated in penicillin-related AIN [10], and probably the mechanism that produced the AIN in our patient is the same.

Further studies are required to understand better the interstitial nephritis associated with the administration of semisynthetic penicillins. Its presentation, however, is characteristic, and its diagnosis should be considered in semisynthetic-penicillin-treated patients who present acute renal failure with marked peripheral blood eosinophilia and often with urinary eosinophils, hematuria, fever, rash, proteinuria and occasional arthropathy.

This syndrome should be recognized as potentially severe, resulting in marked renal dysfunction. Because of this the suspicious drug should be discontinued, and the patient's course should be closely monitored.

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