Renal Complications in HIV Disease

At the New York course in fall 1998, Paul E. Klotman, MD, presented two cases of renal disorders in individuals with HIV disease. The first, concerning HIV-associated nephropathy, was summarized in the December 1998 issue of this publication. The details of the second case presentation are summarized below, followed by a discussion of diagnosis and management.

Case Description

Presentation:

A 28-year-old white woman, HIV-seropositive for 8 years with a history of *Pneumocystis carinii* pneumonia presented to the emergency room with shortness of breath. Her CD4+ cell count was 200/µL; plasma HIV RNA level was 1.8 x 10^4/mL. The patient was antiretroviral-experienced with presumed drug-resistant viral strains. She began taking the investigational antiretroviral drug adefovir through the expanded access program at a dose of 120 mg/d 30 weeks prior to coming to the emergency room. She had responded with a 1-log decrease in her plasma HIV RNA level and an increase in her CD4+ cell count to 220/µL.

Physical findings

- 4-lb weight loss
- Afebrile
- Respiratory rate of 25
- Pulse, 64 bpm
- Blood pressure, 124/82 mm Hg
- Rhonchi that cleared with coughing
- Cardiovascular exam findings were normal

Laboratory findings

- Na^+: 135, Cl^-: 115, K^+: 3.2, and HCO_3: 14 mEq/L
- Creatinine: 1.5 mg% (6 months prior it was 1.3 mg%)
- Urinalysis: urine pH: 5, glucose 1+, protein 2+, no cellular sediment
- White blood cell count: 5000/µL
- Chest X-ray: increased interstitial markings but no change from before

Diagnosis

The patient's respiratory rate was clearly increased raising the possibility of a primary pulmonary problem or an acid-base disorder. The low bicarbonate and the absence of an anion gap are suggestive of metabolic acidosis, but the blood gas was required to sort out a primary from a secondary disorder. The pH defined the problem as primarily an acidosis (nephrologists often refer to this as an acidemia) that represents a mixed acid-base disorder: a primary metabolic acidosis with a compensating respiratory alkalosis. Thus, the high respiratory rate is appropriate for the underlying metabolic disorder. The acid-base disorder was not recognized, however, and the patient underwent a ventilation perfusion scan (low probability for embolic disease) followed by bronchoscopy and lavage for *Pneumocystis carinii* (which was negative). Had the metabolic disorder been recognized, these tests could have been avoided.

Additional chemistries revealed the following: glucose 102 mg/dL, blood urea nitrogen 22 mg/dL, phosphate 1.2 mg/dL, calcium 8.5 mg/dL, uric acid 6.2 mg/dL, and alkaline phosphatase 346 U/L (normal range, 30–110). Because she had an elevated creatinine and a profound acidosis, a 24-hour urine collection was obtained and showed a creatinine clearance of 60 mL/min and a protein excretion 1.5 gm/24 hour. Liver function tests were normal. After reviewing these tests, it was apparent that the patient had experienced a decline in renal function associated with the development of a non-anion gap acidosis. The overall renal functional impairment was not sufficient to account for the profound loss of bicarbonate, and the absence of cellular elements in the urine suggested that this was not an allergic interstitial nephritis.

The presence of what appears to be a renal tubular acidosis with glycosuria and possibly phosphaturia strongly suggests a Fanconi syndrome. Fanconi syndrome is a combination of a type II or proximal renal tubular acidosis with general tubular dysfunction that is characterized by hyperchloremic non-anion gap metabolic acidosis. Tubular acidoses are often accompanied by hypokalemia as well. Under normal conditions, the proximal tubule reabsorbs 85% of the filtered load of bicarbonate through carbonic anhydrase-mediated resorption. If as a result of injury, toxicity, or an inherited defect the proximal tubule cannot manage the filtered load, then bicarbonate (and sodium) is delivered to the distal tubule where the capacity to reabsorb bicarbonate is low. Thus, urine pH rises as bicarbonate and sodium (and potassium as well) are lost in the urine. Eventually the filtered load of bicarbonate is reduced and the dysfunctional proximal tubule, even with its diminished capacity for reabsorption, can once again resorb 85% of the diminished amount of bicarbonate that appears in the filtrate. At this point, the distal nephron can deal with the remaining bicarbonate and urine pH falls in the face of a metabolic acidosis. As a result, one of the hallmarks of proximal renal tubular acidosis is the ability to excrete an acid urine when serum bicarbonate is sufficiently reduced. In contrast, a distal renal tubular acidosis does not allow effective urinary acidification because the proton gradient cannot be maintained in the distal nephron and any hydrogen gradient is quickly dissipated. In distal renal tubular acidoses, an acid urine is almost never generated.

The patient presented here was receiving adefovir and the most likely diagnosis, then, is adefovir nephrotoxicity manifested by a Fanconi-like syndrome and a reduction in glomerular filtration rate. The precise mechanism of the nephrotoxicity of adefovir is unknown. Adefovir exhibits low protein binding (<3%) and is excreted unchanged in urine. The drug clearance rate exceeds glomerular filtration rate by 3-fold, suggesting tubular secretion. The mechanism

of transport both into and out of the renal epithelial cell remains unknown but probenecid partially inhibits its excretion. Adefovir nephrotoxicity usually involves the proximal tubule but may involve other segments as well. There is currently no evidence that the glomerulus is affected by adefovir.

The patient had evidence of renal glycosuria, phosphaturia, and an increase in alkaline phosphatase of bone origin, probably as a result of the acidosis and hypophosphatemia. Adefovir toxicity is clearly related to duration of exposure and has been observed in 30% to 49% of patients receiving the 120 mg/d dose for more than 6 months. The toxicity usually resolves with discontinuation of therapy. In a study of 403 patients receiving adefovir at a dose of 120 mg/d, 6% had a serum creatinine concentration that had not returned to baseline and 9% had a serum phosphate concentration less than 2 mg/dL at the end of the study. In all of these patients, the trends of the creatinine and phosphate concentrations have been to return toward baseline. Unfortunately, follow-up is inadequate at this time to demonstrate that all laboratory values return to their initial values following the discontinuation of the drug. As a result of the frequency in renal toxicity, the current recommendation is that patients receive the 60 mg/d dose.

MANAGEMENT

Management of adefovir toxicity can be accomplished by reducing the dosage by 50% or by discontinuation of the drug if renal parameters do not resolve. In this case, the dose was reduced to 60 mg/d and bicarbonate, potassium, and phosphate supplementation was initiated. For patients who are now initiated on the 60 mg/d dose, the reduction would be to 30 mg/d if toxicity occurred. In general, the treatment of Fanconi syndrome includes maintaining the bicarbonate above 20 mEq/L with sodium bicarbonate or sodium/potassium citrate (3 mEq/kg/d), potassium supplementation to maintain the potassium above 3.2 mEq/L, and supplementing phosphorous with neutral phosphate solutions or oral K-Phos tablets (250 mg phosphate with 4:1 Na^+:K^+) if the patient is hypokalemic. Additional vitamin D and phosphorous supplements may be required. The most important parameter to follow is the serum creatinine, and if the creatinine increases to greater than 0.5 mg% above baseline, adefovir should be discontinued.

The nephrotoxicity clearly limits the duration of use of adefovir in many patients and will impact upon the patients who will likely receive the drug. Its benefits are profound for the experienced patient with drug-resistant HIV-1. The once-daily formulation is also an advantage. The major disadvantage is that as many as 50% of patients may have to change therapy due to nephrotoxicity. The long duration of time required to develop toxicity, however, should allow the physician sufficient time to anticipate and then recognize the problem. In the vast majority of patients, the renal impairment is reversible. In the experienced patient with few other options, adefovir should prove to be a useful addition to the antiretroviral armamentarium as long as physicians are aware of the potential toxic effects of the drug.

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Suggested Reading

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