AJKD
Teaching Case

Atazanavir-Associated Crystalline Nephropathy

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Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Crystalline nephropathy can occur following treatment with multiple therapeutic agents. We describe a human immunodeficiency virus (HIV)-infected patient treated for 2 years with combination antiretroviral therapy including atazanavir (ATV). Kidney biopsy revealed a crystalline nephropathy associated with diffuse chronic and granulomatous interstitial inflammation. Following the biopsy, treatment with ATV was discontinued and kidney function returned to pretreatment baseline levels. ATV, which has a well-established association with nephrolithiasis, is a rare but important cause of crystalline nephropathy. Recognition of this association and prompt withdrawal of the offending agent are critical to optimize outcomes.
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INDEX WORDS: Atazanavir (ATV); crystalline nephropathy; HIV; acute renal failure; combined antiretroviral therapy (cART); granulomatous interstitial inflammation; kidney function; kidney biopsy.

In the modern era of combination antiretroviral therapy (cART) for patients with human immunodeficiency virus (HIV) infection, there has been an increase in the burden of non-AIDS complications, including acute kidney injury (AKI), the incidence of which has nearly doubled in recent years.[1] The cause of AKI in the HIV-infected population includes HIV-specific and HIV-nonspecific causes.[2] Prerenal states is the most common cause of AKI in the aging HIV-infected patient population, in which the burden of chronic kidney disease, heart disease, and diabetes mellitus—all of which are risk factors for AKI—has increased. The incidence of HIV-associated nephropathy and HIV immune complex kidney disease has declined in the cART era, whereas nephrotoxicity related to antiretroviral therapies has emerged as an important HIV-specific cause of AKI.

In the context of HIV-specific AKI, kidney biopsy plays an important role in diagnosis because many of these nephrotoxicities are associated with distinct patterns of kidney injury. For example, tenofovir is associated with an often reversible acute proximal tubulopathy with characteristic mitochondrial abnormalities,[3] whereas indinavir is associated with crystalline nephropathy. Atazanavir (ATV), often boosted with ritonavir, is a commonly used protease inhibitor owing to its overall good safety profile and once-daily dosing. Since its release in 2004, ATV has been linked to crystalluria and 3 rare but distinct patterns of kidney injury: nephrolithiasis, acute interstitial nephritis (AIN), and, rarely, crystalline nephropathy. We report a case of crystalline nephropathy with granulomatous interstitial inflammation in an HIV-infected patient treated with ATV.

CASE PRESENTATION

Clinical History and Initial Laboratory Data

A 53-year-old African American man presented to the emergency department with symptoms of decreased appetite, poor oral intake, metallic taste, and generalized weakness and was found to have AKI, with a creatinine level of 10.15 mg/dL (corresponding to an estimated glomerular filtration rate [eGFR] of 7 mL/min/1.73 m^2 as calculated using the 4-variable Modification of Diet in Renal Disease [MDRD] Study equation), requiring renal replacement therapy. Medical history was significant for HIV infection (diagnosed 27 years prior in 1987), hepatitis C virus infection (treatment naive), active intravenous drug abuse, remote hepatitis B virus infection (which had resolved with seroconversion and undetectable hepatitis B surface antigen), and right nephrectomy following a stab wound many years prior. The patient had baseline chronic kidney disease over the prior 12 months, with serum creatinine levels ranging from 1.85 to 2.97 mg/dL (eGFR range, 47-27 mL/min/1.73 m^2). The patient denied chest pain, shortness

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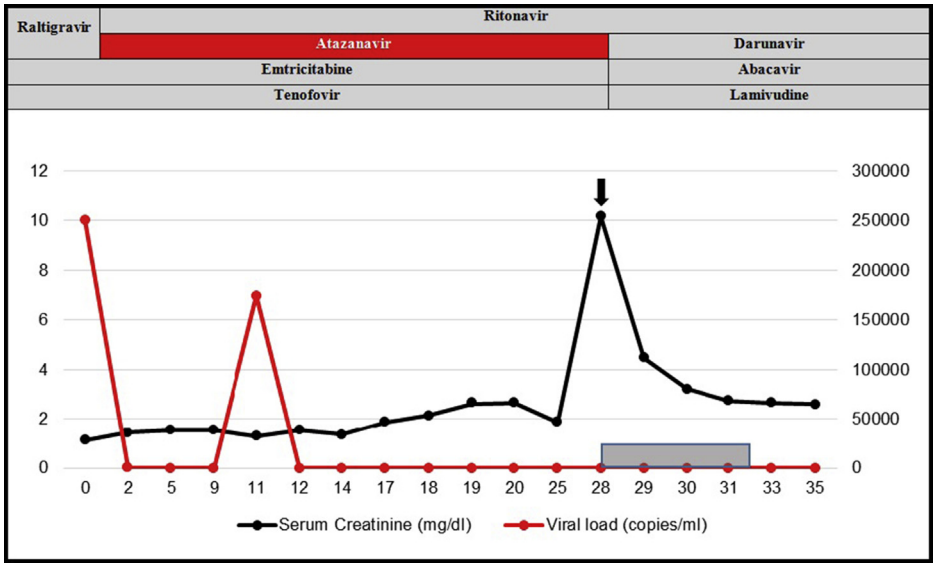

Figure 1. Timeline of therapy in weeks in relation to serum creatinine level and human immunodeficiency virus (HIV) viral load. The duration of treatment with atazanavir was approximately 2 years when the patient developed acute kidney injury, at which time a kidney biopsy was performed (arrow). The patient was maintained on hemodialysis for approximately 4 months (gray shaded area).

of breath, diarrhea, or vomiting. He had no dysuria, urgency, or gross hematuria, but reported a recent decline in urine output.

The patient had been nonadherent to antiretroviral therapy until 3 years prior. His current cART regimen included tenofovir, emtricitabine, ATV, and ritonavir. He had been taking ATV, 300 mg, daily for more than 2 years when he presented with AKI. A timeline of his anti-HIV therapy is provided in Fig 1.

On physical examination, the patient was afebrile with stable vital signs. He had mild pallor, no oral thrush, and normal cardiac, pulmonary, and abdominal findings. Laboratory evaluation was notable for the following values: potassium, 4.9 mEq/L; serum bicarbonate, 13 mEq/L; sodium, 142 mEq/L; chloride, 113 mEq/L; anion gap, 16 mEq/L; albumin, 2.8 g/dL; hemoglobin, 8.2 g/dL; white blood cells, 6.3 $\times 10^3/\mu L$; platelets, 202 $\times 10^3/\mu L$; lactate dehydrogenase, 144 IU/L; uric acid, 5.4 mg/dl; and total bilirubin, 1.1 mg/dl. Urinalysis revealed a protein concentration of 100 mg/dL, pH 6.0, no red blood cells, 4 to 6 white blood cells per high-power field, and no detectable crystals. The patient had normal C3 and C4 serum complement levels and negative serologic test results, including antineutrophil cytoplasmic antibodies, serum cryoglobulins, anti–glomerular basement membrane antibody, and rapid plasma reagin. Renal ultrasound showed a cystic lesion in the left kidney, but no hydronephrosis. The patient's CD4 count was 126 cells/μL and HIV viral load was undetectable. A kidney biopsy was performed.

Additional Investigations

Sampling for light microscopy included 34 glomeruli, 3 of which were globally sclerotic. Glomeruli appeared histologically unremarkable. Specifically, no collapsing lesions of focal segmental glomerulosclerosis, typical of HIV-associated nephropathy, were identified. The predominant abnormalities involved the tubules, which contained abundant intraluminal and intracellular crystals ranging from optically clear to mildly opaque with a slightly basophilic rim and a radial/spoke-like appearance (Fig 2A-E). Tubular crystals were weakly polarizable on hematoxylin and eosin–stained sections and strongly birefringent in unstained tissue sections viewed under polarized light (Fig 2F). Tubular crystals were accompanied by acute tubular degenerative changes, including luminal ectasia, cytoplasmic simplification, irregular luminal contours, and prominent nucleoli. In some areas, crystals extended through tubular basement membranes into the interstitium, where they were associated with a prominent foreign body–type giant cell reaction (Fig 2B and E). Giant cells containing partially digested crystals also were seen within a few tubular lumina. The interstitium contained a moderate diffuse inflammatory infiltrate of lymphocytes, monocytes, scattered plasma cells, and rare neutrophils, associated with foci of lymphocytic tubulitis. Moderate underlying tubular atrophy and interstitial fibrosis were noted. Vessels exhibited moderate arteriosclerosis and arteriolosclerosis. Special stains for acid-fast bacilli and fungi were negative.

Immunofluorescence analysis gave negative results for all immune reactants. Electron microscopy revealed <10% foot-process effacement, the absence of immune deposits or endothelial tubuloreticular inclusions, and findings of acute tubular injury. The crystals dissolved during tissue processing, leaving behind only cleft-like empty spaces in the tubular lumina and within some tubular epithelial cells. Dysmorphic mitochondria typical of tenofovir toxicity were not identified.

Diagnosis

Atazanavir-associated crystalline nephropathy.

Clinical Follow-up

Following the kidney biopsy, ATV treatment was discontinued and replaced with darunavir. The patient was given a brief course of treatment with prednisone, 60 mg, daily for 1 week, which he was unable to tolerate, leading to discontinuation. Serum creatinine level improved to 3.8 mg/dL (eGFR, 20 mL/min/1.73 m^2) at 6 weeks after kidney biopsy and 2.7 mg/dL (eGFR, 30 mL/min/1.73 m^2) at 4 months, at which time the patient discontinued dialysis. One year postbiopsy, creatinine level remains at 2.7 mg/dL (eGFR, 30 mL/min/1.73 m^2).

DISCUSSION

Our patient was a 53-year-old HIV-infected African American man receiving long-term ATV therapy who presented with AKI and underwent kidney biopsy,