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Atazanavir Crystal–Induced Chronic Granulomatous Interstitial Nephritis

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INTRODUCTION

Atazanavir (ATZV) is a common protease inhibitor used in the treatment of HIV infection, often boosted with ritonavir (RTV). Prior to the introduction of highly active antiretroviral therapy (HAART), kidney complications developed as sequelae of the viral disease itself, opportunistic infection, or other drug-related effects.[1] The spectrum of kidney disease associated with HIV infection, classified pathologically, is broad and includes glomerular dominant (podocytopathies or immune complex–mediated glomerular disease), tubulointerstitial dominant, or vascular dominant in the setting of HIV.[S1] Classic HIV-associated nephropathy manifests as collapsing glomerulopathy.[S2] Among these classifications, HAART itself should be considered as potential etiology for some forms of renal impairment. HAART-associated nephrotoxicity is primarily linked to tenofovir (TFV) or to the no-longer-used drug indinavir. However, exposure to ATZV has more recently been implicated as an additional cause of kidney-related complications in patients with HIV. Specifically, ATZV has been described as a cause of nephrolithiasis and, more rarely, as a cause of acute or chronic loss of kidney function.[S3] Herein, we describe a case of biopsy-proven ATZV crystal-induced chronic granulomatous interstitial nephritis and review previously reported cases of kidney complications associated with the use of ATZV.

CASE PRESENTATION

A 51-year-old African American man with a history of HIV presented to a nephrology clinic for evaluation of worsening kidney function. The patient had been diagnosed with HIV at age 46 years after developing a varicella-zoster infection. At that time, he was started on abacavir, lamivudine, and efavirenz. His viral load became undetectable after 6 months of HAART, but CD4 levels were persistently low. Efavirenz was subsequently discontinued and replaced by ritonavir and ATZV 3 years prior to the consultation. Four months prior to the consultation, the baseline serum creatinine was recorded as 1.8 mg/dl. One month prior to the encounter, his serum creatinine was found to be elevated at 2.7 mg/dl during a routine follow-up primary care visit, which prompted a consultation to nephrology. The patient denied poor appetite, nausea, vomiting, diarrhea, acute illness, recent use of nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, moonshine drinking, prophylactic trimethoprim-sulfamethoxazole, or recent exposure to an antibiotic, herbal medicine, recreational drug, or intravenous radiocontrast. Medications included abacavir/lamivudine, atazanavir/ritonavir, capsaicin, gabapentin, ferrous sulfate, hydrocodone/paracetamol, hydroxyzine, pregabalin, and multivitamins. The patient was a smoker and described infrequent alcohol use. There was no family history of kidney disease.

On examination, vital signs showed a blood pressure of 148/81 mm Hg, heart rate of 74 beats/min (regular), respiratory rate 18/min, and temperature 36.2 °C. Oxygen saturation was 100% on ambient room air. Physical examination was unremarkable with normal cardiovascular, respiratory, and abdominal examinations but showed a thin (body mass index [BMI], 16.99 kg/m^2) man. Laboratory investigations showed the following: serum sodium, 136 mEq/l; serum potassium, 4.3 mEq/l; serum chloride, 106 mEq/l; serum bicarbonate, 23 mEq/l; blood urea nitrogen, 50 mg/dl; serum creatinine, 2.7 mg/dl; white blood count, 5.52 × 10^9/l; and hemoglobin, 9.9 g/dl (Table 1). The CD4 count was

Table 1. Laboratory values at presentation

Laboratory measurement	Value
Serum sodium	136 mEq/l
Serum potassium	4.3 mEq/l
Serum chloride	106 mEq/l
Serum bicarbonate	23 mEq/l
Blood urea nitrogen	50 mg/dl
Serum creatinine	2.7 mg/dl
White blood count	5.52 × 10^9/l
Hemoglobin	9.9 g/dl
CD4 count	327 (undetectable HIV-1 RNA viral load)
Urinalysis	
Blood	Trace
Red blood cells	8 per high-power field
White blood cells	86 per high-power field
Protein	20 mg/dl
Leukocyte esterase	Positive (3+)
Nitrites	Negative

327 with undetectable HIV-1 RNA viral load. Testing for hepatitis B and C were negative. Rapid plasma reagin was nonreactive. Complement testing and serum protein electrophoresis were within normal limits. Urinalysis showed 8 red blood cells, 86 white blood cells, 20 mg/dl protein, few eosinophils, negative leukocyte esterase, and negative nitrites. Urine protein-to-creatinine ratio was 450 mg/g. Urine culture was negative. Renal ultrasound showed a right kidney of 10.4 cm and left kidney of 11.0 cm. Both kidneys were found to have regular contour, preserved parenchymal echogenicity, no cysts, no masses, no stones, and no hydronephrosis. Despite a negative urine culture, the patient was empirically treated with levofloxacin due to sterile pyuria. Three weeks later, serum creatinine rose to 3.3 mg/dl. Given the unexplained progressive loss of kidney function (Figure 1), a decision was made to perform a percutaneous kidney biopsy. The kidney biopsy specimen showed up to 15 glomeruli present per level of section, of which 9 were globally sclerotic and 3 were segmentally sclerotic. There was severe interstitial mononuclear infiltrate with numerous eosinophils and fibrosis. There was a granulomatous process with central necrosis and neutrophils with crystal-like material within the granulomas (Figure 2).

Atazanavir-ritonavir was promptly discontinued and replaced by raltegravir. Abacavir/lamivudine was continued. The patient was treated with oral corticosteroids, which were subsequently tapered down over the course of 12 weeks. Serum creatinine improved and returned to a new baseline level of 2.0 mg/dl within 8 months (Figure 1).

DISCUSSION

We describe a case of a patient who developed ATZV crystal-induced granulomatous interstitial nephritis after 3.5 years of initiation of treatment. The prolonged exposure to ATZV preceding the rise in serum creatinine along with similarities in clinical presentation, course, laboratory abnormalities, and histopathological findings of our case to that of previous cases of ATZV-associated nephropathy make a strong case for causality (Table 2).[1–8] Our case is a valuable contribution that adds to a sparse amount of existing literature and provides further insight into its presentation and clinical course that could foster early recognition of this serious adverse effect of a commonly used antiretroviral.

ATZV-associated nephropathy appears to manifest as either acute or chronic tubulointerstitial nephritis.

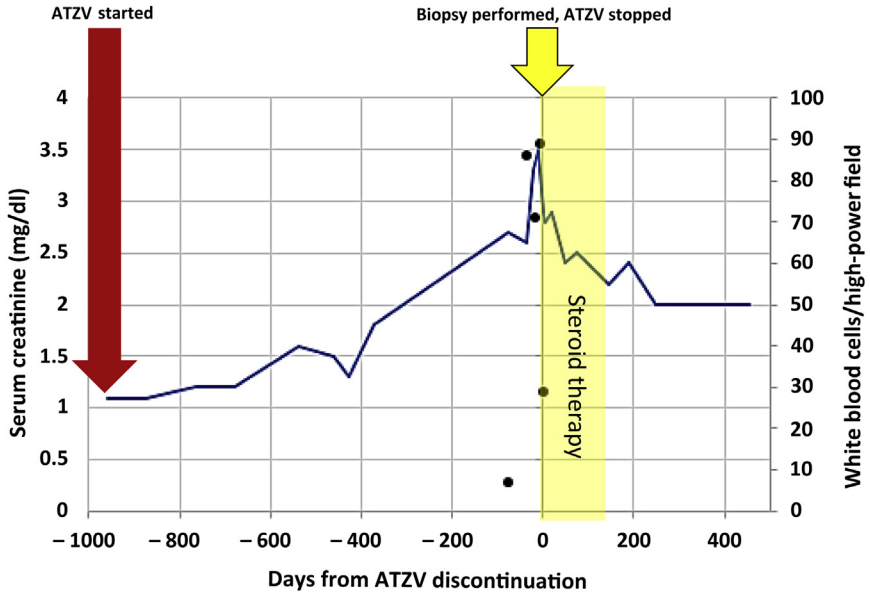

Figure 1. Serum creatinine (blue line) and pyuria (black dots) during atazanavir (ATZV) therapy and after discontinuation; corticosteroid therapy (yellow).

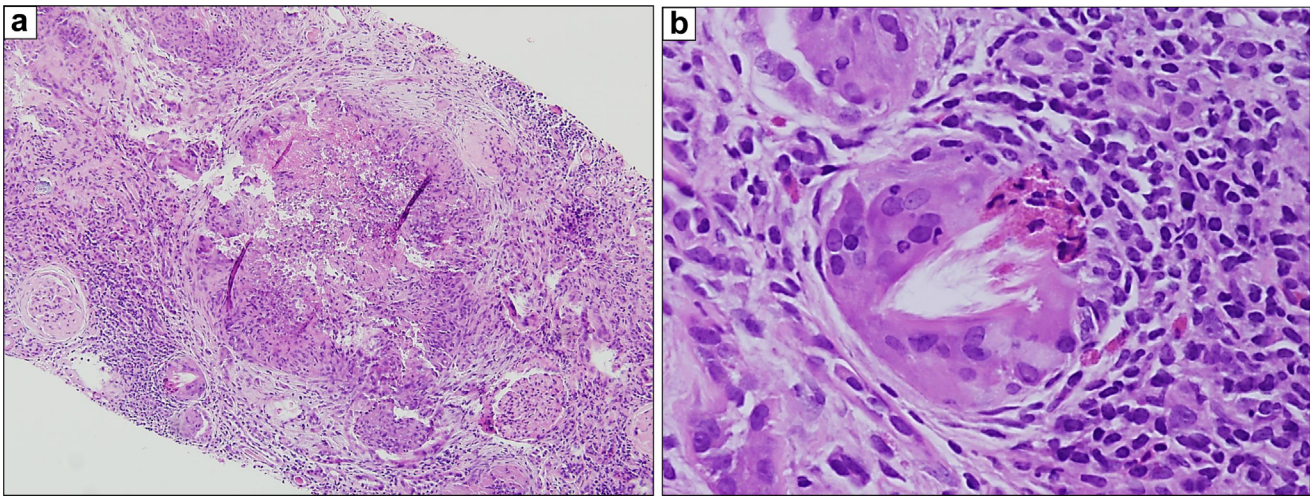

Figure 2. (a) Low magnification (original magnification ×100; hematoxylin and eosin stain) view of the kidney biopsy showing a central granuloma in a background of interstitial fibrosis and tubular atrophy. (b) Higher magnification (original magnification ×400; hematoxylin and eosin stain) showing a multinucleated giant cell with clefts where crystalline material was present. The crystals were lost during processing. Eosinophils are present at the right edge of the giant cell.

The acute form presents as a hypersensitivity-type reaction occurring within a few weeks to months of initiation of therapy.[2] The chronic form of tubulointerstitial nephritis seems to typically be granulomatous in nature and associated with crystal deposition in the renal parenchyma. These chronic cases can occur within 3 to 5 years after initiating ATZV,[2] but there is significant variability in timing of presentation. Crystal formation is thought to activate the NLRP3 inflammasome in myeloid cells, which triggers an inflammatory response. The inflammasome component forms a cytosolic multimolecular platform complex with adaptor protein ASC and caspase-1, subsequently activating caspase-1 and leading to a release of cytokines including interleukin-1B and interleukin-18.[S4]

Overall, a variety of renal syndromes have been reported in association with exposure to ATZV including acute kidney injury (AKI), progressive chronic kidney disease (CKD)—such as in our case—and obstructive uropathy/urolithiasis (Tables 2 and 3). As mentioned above, cases of either AKI or progressive CKD associated with ATZV exposure involve a form of tubulointerstitial nephritis. We found equal occurrence of AKI and progressive CKD. Importantly, sterile pyuria has been reported in half the cases and could be considered a urinary abnormality that should raise suspicion for this entity. The identification of sterile pyuria was a critical factor that stimulated the treating nephrology team to raise suspicion for a tubulointerstitial lesion and to entertain further diagnostic investigation.

Discontinuation of ATZV, as was done in our case, has been reported to lead to partial or complete renal recovery (Table 2). Our patient presented with significant loss of kidney function, and the biopsy specimen revealed substantial proportion of globally sclerotic glomeruli. Thus, the reversibility of the renal lesion seems to relate to the timing of recognition. Although

Table 2. Reports of ATZV crystal-induced nephropathy

Case	Kanzaki *et al.*[1]	Brewster and Perazella[2]	Izzedine *et al.*[3]	Hara *et al.*[4]	Santiorelli *et al.*[5]	Viglietti *et al.*[6]	Schmid *et al.*[7]	Schmid *et al.*[7]	Schmid *et al.*[7]	Coelo *et al.*[8]	Varghese *et al.* (current report)
sCr at biopsy	2.0	11.1	3.6	2.2	10.2	2.2	10.3	3.4	7.0	7.1	3.3
UPCR (g/g)	0.38	N/A	0.3	0.25	N/A	N/A	0.75	0.5	1.0	N/A	0.45
Pyuria	–	+	–	–	+	+	–	+	–	+	+
ATZV duration	3.5 yr	4 wk	N/A	5.6 yr	2 yr	4.1 yr	3 mo	6 wk	4 mo	8 mo	3.5 yr
Select HAART	RTV, TFV	–	RTV	RTV	RTV, TFV	RTV	RTV, TFV	RTV, TFV	RTV, TFV	RTV, TFV	RTV
Pathology	CGIN	AIN	CGIN	CGIN	CGIN	CGIN	AIN	AIN	AIN	AIN	CGIN
Syndrome of kidney dysfunction	CKD	AKI	AKI	CKD	CKD	CKD	AKI	AKI	AKI	CKD	CKD
Corticosteroid use	N/A	–	+	+	+	+	N/A	N/A	N/A	+	+
Renal recovery	Complete	Complete	Partial	No recovery	Partial	Partial	Complete	Complete	Complete	No recovery	Partial

AIN, acute interstitial nephritis; AKI, acute kidney injury; ATZV, atazanavir; CGIN, chronic granulomatous interstitial nephritis; CKD, chronic kidney disease (progressive); HAART, highly active antiretroviral therapy; N/A, not available; RTV, ritonavir, TFV, tenofovir, sCr, serum creatinine; UPCR, urine protein-to-creatinine ratio.

Table 3. Reports of ATZV nephro-urolithiasis or obstructive uropathy

Case	Koblic *et al.*[S10]	Grant *et al.*[S11]	Chang *et al.*[S12]	Wang *et al.*[S14]	Pacanowski *et al.*[S15]	Anderson *et al.*[S16]	Savini *et al.*[S17]
sCr at presentation	0.95	1.48	1.6	2.42	N/A	N/A	N/A
Syndrome	Chalky white urine, dysuria	Right flank pain	Abdominal pain, chills, nausea, vomiting	Left flank pain, nausea, vomiting	Renal colic	Severe right flank pain	Full bladder with difficulty emptying, dysuria, flank pain
Imaging	Mild left pelvicaliectasis with diffuse thickening of the renal pelvis and ureter (ultrasound)	Mild right hydronephrosis with perinephric stranding and no evidence of stone (CT)	Right ureteral stone with hydronephrosis (CT)	Left hydroureteronephrosis to the pelvic brim (CT)	Calculi in the right kidney with no signs of hydronephrosis (ultrasound)	Hydroureteronephrosis with some perinephric stranding with no calculi (CT)	Left ureteral calculus with hydronephrosis and ureteral dilatation (CT)
ATZV duration	11 mo	9 yr	N/A	5 yr	2 yr	6 yr	6 mo

ATZV, atazanavir; CT, computed tomography; N/A, not available; sCr, serum creatinine.

the granulomatous inflammatory lesion may be treatable with drug discontinuation with or without corticosteroids, global glomerular sclerosis may be irreversible. Accordingly, our patient achieved only partial recovery of kidney function.

It remains unclear whether corticosteroids should always be used to maximize renal recovery. It has been recommended that a short duration of oral corticosteroids should be considered if there is no significant improvement in kidney function within 2 weeks of ATZV cessation.[2] We chose to prescribe corticosteroids, given the severity and activity of the lesions observed in kidney biopsy along with the high risk for progression to end-stage kidney disease. In addition, clinicians in endemic areas for tuberculosis should ensure that a biopsy specimen is acid-fast bacilli negative before considering corticosteroids. Tuberculosis may similarly cause granulomatous interstitial nephritis, making it difficult to distinguish from drug reaction.[S5]

Nearly all cases that we examined involved simultaneous use of ritonavir (RTV) and, in some cases, tenofovir (TFV) (Table 2). RTV has been reported to be potentially acutely nephrotoxic but, it has not been linked to a pathological lesion of chronic granulomatous crystal-induced nephropathy.[S6,S7] Kanzaki *et al.* describe how the concomitant use of TFV was found to accelerate and to facilitate renal disease.[1] Our patient was also exposed to RTV. There is evidence that ritonavir may contribute to an increasing risk of chronic kidney disease.[S8] Therefore, we cannot discard the possibility of a contributing role of RTV in the pathogenesis that led to progressive loss of kidney function in our patient.

One study demonstrated that the crystals deposited in kidney tissue were composed of ATZV and confirmed by spectroscopic analysis.[3] ATZV is poorly soluble with solubility decreasing as pH increases.[9] The drug is eliminated primarily in the feces but up to 13% of elimination occurs through the urine.[S9] These properties explain the propensity of ATZV to crystallize. Not surprisingly, ATZV has also been associated with nephrolithiasis at varying durations of use (Table 3). Stone formation associated with ATZV has been reported to occur as early as 6 months and as late as 11 years after the commencement of therapy. The stones were primarily composed of ATZV metabolites but occasionally contained other components (RTV metabolites, calcium oxalate).[S10–S12] Several drugs are known to cause crystal nephropathy (Table 4). Relevant to our case, there are case reports that document crystal nephropathy from levofloxacin but without description of chronic granulomatous interstitial lesions.[S13] Moreover, because of the temporal disconnect between the initial rise of serum creatinine and the transient use of levofloxacin, we conclude that the

Table 4. Common causes of crystal-induced nephropathy

Medications reported to cause crystal-induced nephropathy[S18]
• Acyclovir
• Atazanavir
• Ciprofloxacin
• Indinavir
• Levofloxacin
• Methotrexate
• Oral sodium phosphate
• Orlistat
• Sulfadiazine
• Triamterene

Table 5. ATZV crystal–induced nephropathy teaching points

- Antiretrovirals are associated with various kidney-related complications in the HIV population.
- ATZV can cause (granulomatous) interstitial nephritis/crystalline nephropathy or urolithiasis, which can present as either progressive chronic kidney disease, acute kidney injury, obstructive uropathy or renal colic.
- Sterile pyuria and/or worsening kidney function in a patient on ATZV should raise suspicion for development of chronic (granulomatous) interstitial nephritis.
- When ATZV is suspected to cause crystalline nephropathy, it should be promptly discontinued, an alternative agent should be used, and kidney biopsy should be pursued. Corticosteroids may be considered as adjuvant therapy.

ATZV, atazanavir.

kidney dysfunction was unlikely to be due to levofloxacin.

In conclusion, ATZV crystal-induced granulomatous interstitial nephritis and secondary glomerulosclerosis could result from chronic exposure to the antiretroviral. Kidney biopsy findings of crystal-like material with a background of neutrophils and eosinophils can be seen. If left unrecognized, this adverse effect of ATZV can lead to progressive irreversible loss of kidney function. Thus, an unexplained rise in serum creatinine and sterile pyuria in a patient actively treated with ATZV should raise suspicion for this entity and prompt practitioners to pursue further investigation. Discussions with HIV specialists regarding potential consideration for alternative antiretroviral selection is encouraged. Individuals treated with HAART should be carefully monitored, as they are at significant risk for kidney dysfunction. Our case adds to the growing base of literature, should increase awareness, and provides learning points regarding ATZV as an etiology of crystal-induced granulomatous interstitial nephritis (Table 5).

DISCLOSURE

JCQV has participated in Advisory Board meetings for Mallinckrodt Pharmaceuticals and Retrophin and is a member of the Speaker Bureau for Otsuka Pharmaceuticals (drugs related to those engagements are not discussed in this article). All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

REFERENCES

1. Kanzaki G, Tsuboi N, Miyazaki Y, et al. Diffuse tubulointerstitial nephritis accompanied by renal crystal formation in an HIV-infected patient undergoing highly active antiretroviral therapy. *Intern Med*. 2012;51:1543–1548.
2. Brewster UC, Perazella MA. Acute interstitial nephritis associated with atazanavir, a new protease inhibitor. *Am J Kidney Dis*. 2004;44.
3. Izzedine H, M'rad MB, Bardier A, et al. Atazanavir crystal nephropathy. *AIDS*. 2007;21:2357–2358.
4. Hara M, Suganuma A, Yanagisawa N, et al. Atazanavir nephrotoxicity. *Clin Kidney J*. 2015;8:137–142.
5. Santoriello D, Al-Nabulsi M, Reddy A, Salamera J, D'Agati VD, Markowitz GS. Atazanavir-associated crystalline nephropathy. *Am J Kidney Dis*. 2017;70:576–580.
6. Viglietti D, Verine J, Castro ND, et al. Chronic interstitial nephritis in an HIV type-1-infected patient receiving ritonavir-boosted atazanavir. *Antiviral Ther*. 2011;16:119–121.
7. Schmid S, Opravil M, Moddel M, et al. Acute interstitial nephritis of HIV-positive patients under atazanavir and tenofovir therapy in a retrospective analysis of kidney biopsies. *Virchows Archiv*. 2007;450:665–670.
8. Coelho S, Aparício S, Manso R, Soto K. Quiz page June 2012. *Am J Kidney Dis*. 2012;59.
9. National Center for Biotechnology Information. Atazanavir. PubChem Compound Database. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Atazanavir. Accessed February 11, 2020.