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Atazanavir nephrotoxicity

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Abstract

Atazanavir is commonly used as one of the key drugs in combination antiretroviral therapy for human immunodeficiency virus (HIV). However, atazanavir has the potential to yield its crystalline precipitation in urine and renal interstitial tissues, leading to crystalluria, urolithiasis, acute kidney injury (AKI) or chronic kidney disease (CKD). In epidemiological studies, atazanavir/ritonavir alone or in combination with tenofovir has been associated with increased risk of progression to CKD. However, renal biopsies were not provided in these studies. Case reports showing an association between atazanavir use and tubulointerstitial nephritis among HIV-infected individuals provide clues as to the potential causes of atazanavir nephrotoxicity. We now review atazanavir-related kidney disease including urolithiasis, renal dysfunction and interstitial nephritis and illustrate the review with a further case of atazanavir-associated kidney injury with sequential renal biopsies. There are two forms of atazanavir-associated tubulointerstitial nephritis: acute tubulointerstitial nephritis that may develop AKI rapidly (in weeks) after initiation of atazanavir, and chronic tubulointerstitial nephritis that may develop progressive CKD slowly (in years) with granuloma and intrarenal precipitation of atazanavir crystals as well as crystalluria. Caution should be exercised when prescribing atazanavir to patients at high risk of CKD, and therapy should be reevaluated if renal function deteriorates, especially associated with crystalluria and hematuria.

Keywords: arteriolosclerosis; crystalline precipitation; infrared spectroscopy; prednisolone therapy

Background

Atazanavir is a widely used protease inhibitor for the treatment of patients infected with human immunodeficiency virus (HIV). Brewster and Perazella [1] first described acute interstitial nephritis associated with atazanavir in 2004. Izzedine *et al.* [2] reported an HIV patient with renal insufficiency due to granulomatous interstitial nephritis (GIN) characterized by the coexistence of crystalline depositions, 60% of which included atazanavir metabolites. Four case reports of crystal nephropathy associated with atazanavir use have been published [2–5]. We now review atazanavir-related kidney disease including urolithiasis, renal dysfunction and clinical outcomes and pathological characteristics of acute and chronic interstitial nephritis. We illustrate the review with a further report of atazanavir-associated GIN showing renal pathological changes before and after withdrawal of atazanavir and prednisolone therapy.

Kidney disease associated with atazanavir use

Atazanavir boosted by ritonavir (atazanavir/ ritonavir) is commonly used as one of the key drugs in combination antiretroviral therapy (cART). The Japan Ministry of Health, Labour and Welfare approved atazanavir as an efficacious drug for treatment-experienced HIV-infected patients, at a usual once-daily dose of 300 mg boosted with 100 mg of ritonavir in January 2004. Atazanavir has relatively few side effects, especially on lipid profiles, as compared with other protease inhibitors [6, 7]. Chronic kidney disease (CKD), which is diagnosed by the existence of persistent urinary protein and albumin and/or chronic impairment of glomerular function, has emerged as one of the most burdensome complications in HIV-infected individuals receiving long-term cART [8–11]. Previous cohort studies showed that cumulative exposure to atazanavir/ritonavir may induce a decrease in glomerular function, most of

which accompanies tubular dysfunction. In particular, co-use of tenofovir may facilitate the emergence of renal disease related to atazanavir/ritonavir.

Crystalluria and urolithiasis

Atazanavir/ritonavir has the potential to cause crystalluria and often induces urolithiasis. Frequency of urolithiasis ranges from 7.3 to 23.7 cases per 1000 person-years [12, 13]. The incidence of urolithiasis among HIV-infected patients receiving atazanavir/ritonavir was higher than that among those receiving other protease inhibitors [12, 13]. The definite mechanism for the formation of lithiasis still remains unknown; however, its related factors have been suggested: preexisting hepatic or renal impairment, past history of urolithiasis, high serum bilirubinemia indicating a slower metabolization of atazanavir, alkaline urine and chronic active hepatitis C [12–15]. Most of all, cumulative exposure to atazanavir/ritonavir is likely linked with the formation of urolithiasis, as the patients who manifested urolitiasis had received atazanavir/ritonavir over several years, averaging nearly 2 years after the start of atazanavir/ritonavir [13–16]. Sudden symptoms of urolithiasis including acute lumbar or flank pain and incident gross hematuria may prompt us to suspect the existence of atazanavir/ritonavir-related urolithiasis. On the other hand, it could be difficult to identify atazanavir/ritonavir-related urolithiasis prior to emergence of such clinical manifestations, partly because the sensitivity of common urinalysis is insufficient to detect crystalline precipitates in urine. Such crystals are reported to be found only in 8.9% of asymptomatic patients receiving atazanavir/ritonavir [17]. As the crystals, which are usually 8–20 nm sized, rod like-shaped and mildly birefringent, contain atazanavir components, the infrared spectrophotometry should be appreciated as an efficient tool for the diagnosis. Atazanavir slightly dissolves in water at the concentration of 4–5 mg/mL, and its solubility becomes maximal at pH 1.9 with decreasing degree of acidity. Although sufficient and persistent acidification of urine is recommended from the prophylactic perspective of urolithiasis, it would be practically unfeasible, especially in those who are receiving concomitant therapy with sulfonamide derivatives. Increased daily diuresis and discontinuation of atazanavir/ritonavir are more feasible in patients who have experienced urolithiasis, as they are at higher risk of recurrence. Prospective studies should address the risk of CKD in patients who develop urolithiasis and continue atazanavir.

Impairment of glomerular and tubular function

The Euro SIDA group reported that exposure to atazanavir as well as tenofovir and indinavir was associated with a high incidence of CKD in the nonrandomized cohort study including 6843 HIV-positive persons [median age, interquartile range (IQR), 43 (38–50) years] [18]. Calza *et al.* [19] reported that a reduction in eGFR during a 12-month follow-up period was significantly greater in the patients receiving atazanavir/ritonavir (−7.6 mL/min/1.73 m^2) than in those receiving either efavirenz (−5.1 mL/min/1.73 m^2) or lopinavir/ritonavir (−4.8 mL/min/1.73 m^2), and that the reduction accompanied a higher incidence of proximal tubular damage in the prospective cohort study including 235 patients [median age (IQR): 43.7 (34.3–54.2), 42.6

(33.2–53.1), and 42.9 (32.8–52.9) years, respectively]. The rate of GFR loss reported for atazanavir/ritonavir is close to that observed in untreated diabetic nephropathy. Dauchy *et al.* [20] showed that atazanavir/ritonavir use was significantly associated with proximal tubular dysfunction, tested with the following markers: phosphate diabetes, non-diabetic glucosuria, metabolic acidosis, urinary β_2-microglobulinuria (β_2M)/Cr ratio >0.3 mg/L, and low serum uric acid with uric acid fractional excretion >15%, in a cross-sectional analysis of 26 patients receiving cART with proximal tubular dysfunction [median age (IQR), 51.5 (46.8–59.1) years] and 373 patients receiving cART without proximal tubular dysfunction [median age (IQR), 47.2 (42.2–53.4) years]. These two reports indicated that atazanavir/ritonavir may cause renal tubular damage, responsible for ensuing glomerular dysfunction. Young *et al.* [21] demonstrated that the use of tenofovir *plus* atazanavir/ritonavir contributes to a greater decrease in eGFR, as compared with the use of tenofovir *plus* efavirenz in the cohort comprising recipients of tenofovir combined with either efavirenz [484 patients; median age (IQR), 40 (34–47) years] or atazanavir/ritonavir [187 patients; median age (IQR), 38 (32–46) years]. Rasch *et al.* [22] showed that patients with baseline eGFR <90 mL/min/1.73 m^2 exposed to tenofovir and atazanavir in combination had a higher risk of incident CKD (adjusted incidence rate ratio 26.75 (95% CI 9.54–75.05), when CKD was defined as eGFR values < 60 mL/min per 1.73 m^2 persisting for >3 months, in the Danish cohort comprising 2044 HIV-infected patients with a therapy period over 16 years [median age (IQR), 38.7 (31.9–46.8) years]. Furthermore, Ryom *et al.* [23] showed that exposure to atazanavir/ritonavir was an independent predictor of chronic loss in glomerular function of HIV individuals who had normal renal function at baseline, and that this adverse effect was independent of the presence or absence of tenofovir use [22 603 HIV-infected patients; median age (IQR), 39 (33–44) years]. Among 18 055 HIV-positive persons from the Data on Adverse Drugs (D:A:D) study with baseline eGFR >60 mL/min/1.73 m^2, the number needed to harm (NNTH) when evaluating CKD (eGFR <60 mL/min/1.73 m^2) in patients starting atazanavir was 1395, 142 or 20, respectively, among those with low, medium or high risk and in patients starting atazanavir/ritonavir were 603, 61 and 9 for those with a low, medium or high risk [24]. High-risk groups were defined according to a score that included older age, intravenous drug use, HCV-positive antibody status, lower baseline eGFR, female gender, lower CD4 nadir, hypertension, diabetes and cardiovascular disease. These studies indicated a possibility that atazanavir/ritonavir alone or with tenofovir may cause renal tubular damage and chronic impairment of glomerular function. Thus, it has been proposed that these more potentially nephrotoxic drugs should be avoided in high-risk patients [24].

Acute interstitial nephritis and chronic crystal-associated GIN

There are eight case reports, showing an association between atazanavir/ritonavir use and tubulointerstitial nephritis including GIN [1–5, 25]. Table 1 reviewed clinical characteristics of all cases that manifested atazanavir/ritonavir-related interstitial nephritis.

Among these previous cases, four were diagnosed as GIN [2–5], as they showed the formation of granuloma

Table 1. Summary of clinical characteristics of cases that manifested atazanavir (ATV)/ritonavir-related interstitial nephritis

| Reference | Age/sex | Peak of serum Cr, mg/dL | Time to diagnosis, years | Renal pathological findings of biopsy specimens | | Renal outcome |
				Diagnosis	Granuloma/crystal formation	
Brewster and Perazella [1]	49/M	11.1	0.1	AIN	−/−	Remission after ATV cessation
Schmid *et al.* [25]	51/M	10.3	0.3	AIN	−/−	Remission after ATV cessation
Schmid *et al.* [25]	44/F	3.4	0.1	AIN	−/−	Remission after ATV cessation
Schmid *et al.* [25]	63/M	7.0	0.3	AIN	−/−	Remission after ATV cessation
Izzedine *et al.* [2]	61/M	3.63	Unknown	GIN	+/+	Remission with steroids after ATV cessation
Viglietti *et al.* [3]	60/M	2.3	4.1	GIN	+/+	Partial remission with steroids after ATV cessation
Kanzaki *et al.* [4]	50/M	2.18	5.2	GIN	+/+	Unknown
Coelho *et al.* [5]	71/M	7.1	2.8	GIN	+/+	No remission with steroids after ATV cessation. Chronic hemodialysis.
Present case[a]	66/M	2.2	5.6	GIN	+/+	No remission with steroids therapy after ATV cessation

ATV, atazanavir; M, male; F, female; Cr, creatinine; AIN, acute interstitial nephritis; GIN, granulomatous interstitial nephritis.
[a]Re-renal biopsy was performed after stopping atazanavir and steroid therapy only in this case.

with multinuclear giant cells surrounding needle-shaped crystals. In three of them, it took 2.8–5.2 years from atazanavir/ritonavir initiation to the diagnosis of GIN (no data shown for the remaining case) and in some slowly progressive CKD was documented. Crystal deposition is the likely trigger of the disease. Izzedine *et al.* [2] identified urine crystals as a mixture of atazanavir metabolite and calcium phosphate using polarized light microscopy analysis of his patient. On the other hand, we identified that urinary crystals included atazanavir by infrared spectroscopic analysis (see case report). From these previous and new findings, we believe that the crystals accumulated in tubular epithelial cells were atazanavir crystals, which were clearly identified by electron microscopy.

Brewster and Perazella speculated that a hypersensitivity-type reaction may be the underlying mechanism in the relationship between atazanavir/ritonavir and tubulointerstitial nephritis, lacking the granuloma formation [1]. Also, Schmid *et al.* [25] suggested that the intrarenal activation of cytotoxic T cells, which are mostly differentiated from $CD8^+$ T cells, may be one of the pathomechanisms of interstitial nephritis, as they dominated in the interstitial lymphocytes. Both cases clinically manifested acute kidney injury (AKI) in 4–16 weeks after the administration of atazanavir/ritonavir, and showed no granuloma formation pathologically.

These findings may allow us to speculate that there are two types of atazanavir-related interstitial nephritis: acute interstitial nephritis that may develop AKI, rapidly (in weeks) after the administration of atazanavir, and chronic GIN that may develop progressive CKD, slowly (years), associated with the intratubular precipitation of atazanavir crystals. GIN patients had a higher average age than the AIN patients; i.e. the average age for AIN patients was 51.8 years, while GIN patients was 61.6 years. In addition, most GIN patients had hematuria, proteinuria and crystalluria. These indicate that the patients with advanced age and such abnormal urinary findings under atazanavir/ritonavir use have a likelihood of being diagnosed with GIN. Table 2 summarized similarities and differences between the two forms of atazanavir-related interstitial nephritis.

Therefore, periodic careful monitoring of urinalysis including hematuria and crystalluria is most pivotal in early identification of GIN in patients receiving atazanavir/ritonavir. Cessation of atazanavir/ritonavir should be considered in

Table 2. Comparison of clinical features between the two forms of atazanavir/ritonavir-related interstitial nephritis

|	AIN ($n = 4$)	GIN ($n = 5$)
Mean age, years	51.8	61.6
Sex male, %	75	100
Presence of hematuria, %	50	60
Presence of proteinuria, %	100	100 (excluding one case undescribed [3])
Presence of crystalluria, %	0	100 (excluding one case undescribed [3])
Mean peak value for serum Cr, mg/dL	7.95	3.48
Mean time to diagnosis, years	0.20	4.42
Renal outcome	Remission in all cases.	Two cases remission, two cases did not achieve remission (one required chronic hemodialysis), and the outcome of the remaining case was unknown.

AIN, acute interstitial nephritis; GIN, granulomatous interstitial nephritis; Cr, creatinine.

particular when hematuria is sustained concurrently with crystalluria. Overlooking GIN has to be avoided especially in elderly patients over 60 years old, since remission of CKD was only observed in half the cases after atazanavir withdrawal and chronic hemodialysis was required in one patient. The utility of steroids is unclear. One GIN case achieved complete resolution of renal function [2], whereas another showed partial improvement of renal function after steroid therapy [3]. Initiation of steroid therapy for GIN may have been too late in the case reported below, as compared with the three previous GIN patients who received steroids within 1 month of atazanavir withdrawal [2–4]. As is the case in a patient who was started on steroids after he developed AKI twice [5], this treatment delay might be associated with the incomplete recovery of renal function despite the almost complete cure of severe interstitial inflammation. In general, therapy for acute interstitial nephritis should be implemented as soon as the diagnosis is made in order to restore renal function and inhibit the progression to CKD [26]. As illustrated below, the only patient with a reported repeat biopsy to date, in at least some cases, withdrawal of the drug plus steroids is associated

with disappearance of intrarenal crystals and granuloma but persistence of tubular atrophy and interstitial fibrosis.

In conclusion, atazanavir, especially when boosted with ritonavir, has been associated with a high risk of progression to CKD, as well as to crystalluria and urolithiasis. A few case reports have evidenced acute interstitial nephritis, possibly of immunoallergic origin, within a few weeks of starting atazanavir. Three cases were reversible.
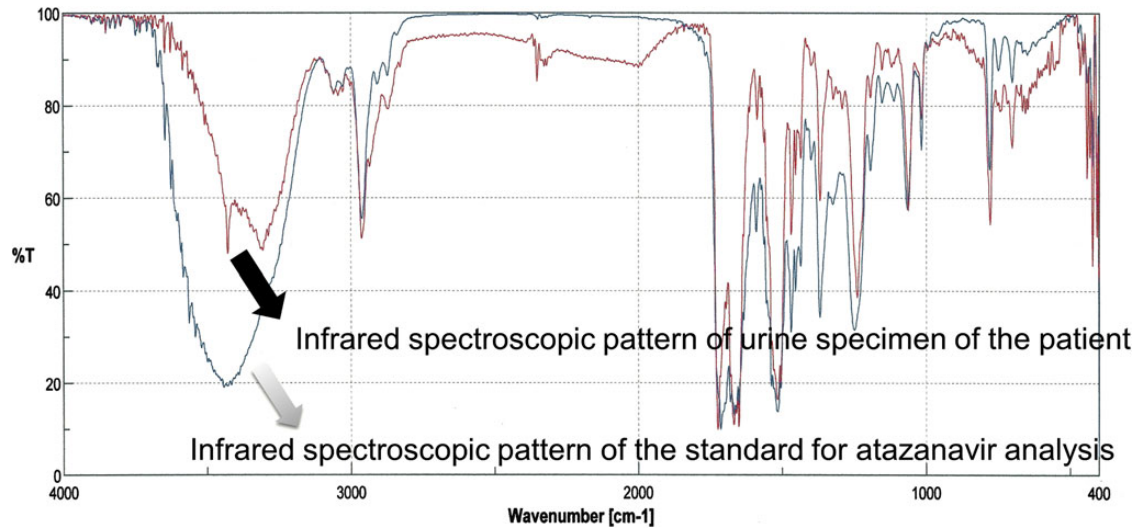
Fig. 1. Infrared spectroscopic analyses. Spectrum patterns were compared between a urine specimen from the patient and the standard for atazanavir analysis. The patterns almost overlapped.
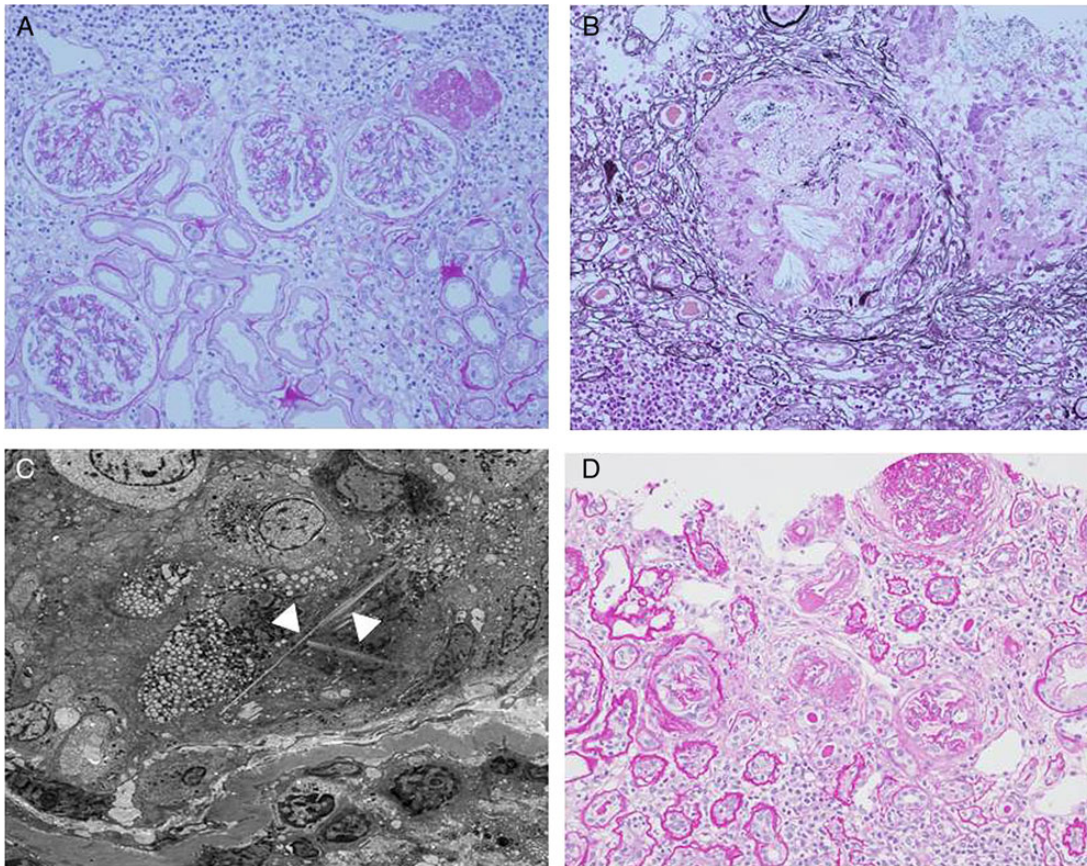
Fig. 2. Renal pathological findings in the first (A–C) and second (D) biopsy. The second biopsy was performed 1 year and 3 months from first renal biopsy. (A) Light microscopy of renal biopsy specimens, showing histologically unremarkable changes of glomeruli except global sclerosis of the glomerulus, interstitial nephritis, infiltration of lymphocyte and plasma cells into interstitial tissues (periodic acid–Schiff stain). (B) Needle-shaped crystals surrounded by multinuclear giant cells in the tubular epithelium (periodic acid–methenamine–silver stain). (C) Needle-shaped crystalline precipitation is seen within the tubular epithelial cells (arrowheads) (electron microscopy). (D) Sclerotic changes of arterioles, tubular atrophy and interstitial fibrosis had developed in the second biopsied tissues (hematoxylin and eosin stain).

However, renal biopsy has confirmed crystal-associated chronic GIN in a few patients. The clinical course was of progressive CKD with frequent crystalluria, hematuria and proteinuria in older patients. Withdrawal of atazanavir or even steroid administration does not always lead to recovery of renal function. Thus, caution should be exercised when prescribing atazanavir to high-risk individuals. Whether the reported cases of chronic crystal-associated GIN represent the most severe cases of a more widespread phenomenon that may underlie some of the decrements in GFR associated with atazanavir/ritonavir in epidemiological studies requires further research.

Case report

A 65-year-old Japanese man was diagnosed with HIV infection in October 2005. There were no comorbidities, including hypertension, diabetes mellitus and dyslipidemia. cART, comprising lamivudine, abacavir and atazanavir/ritonavir (300 mg of atazanavir boosted by 100 mg of ritonavir), was started to treat his low CD4+ T-cell count (205 cells/μL) and high HIV-RNA (230 000 copies/mL) in June 2006. Soon after the initiation of cART, both proteinuria and hematuria emerged (1+ and 1+ on dipstick test, respectively) and his renal function started to decline slowly, yet there were no crystalline precipitates in the urine. Serum creatinine (Cr) increased from 0.6 to 1.0 mg/dL in June 2009, and to 1.4 mg/dL in February 2012, with persistent proteinuria (1+) and occult hematuria (2+) on a dipstick test. As serum Cr increased to 1.7 mg/dL, he was admitted to the Department of Nephrology in April 2012. The cART regimen remained unchanged, since the control of HIV infection was good at the time.

On admission, his blood pressure was 102/78 mmHg and pulse rate 98 beats per minute. His height was 154 cm and his weight was 35.4 kg (body mass index, 14.9 kg/m^2). There were no particular abnormalities on physical examination. The blood data were as follows: white blood cell count 6400/μL; red blood cell count 387 × 10^4/μL; hemoglobin 12.5 g/dL; platelet count 27.0 × 10^4/μL; serum urea nitrogen 21 mg/dL; serum Cr 1.7 mg/dL; serum sodium 139 mEq/L; serum potassium 4.5 mEq/L; serum chloride 103 mEq/L and serum C-reactive protein 0.49 mg/dL. Urine dipstick test showed pH 6.0, proteinuria (1+), and occult blood (3+). The urinary concentrations of biomarkers for tubular damage, which was corrected for urinary Cr concentrations, were as follows: N-acetyl-β-D-glucosaminidase (NAG), 12.0 IU/gCr (normal level of NAG concentration, 0.0–7.0 IU/L) and β2M, 391 μg/gCr (normal level of β2M concentration, 27–265 μg/L), respectively. The daily amount of urinary protein was 250 mg. Urinary sediments included 50–99 red blood cells/high power field (HPF), 20–29 white blood cells/HPF and small amounts of crystalline precipitation (no detail for its shape). Infrared spectroscopic analysis was implemented to test whether the urinary crystalline precipitation included atazanavir crystals. In brief, the patient's urine was stored for 24 h, and some of the urine was centrifuged for 2 min at 2000 rpm. The supernatant was used for infrared spectroscopic analysis, and the spectrum of the infrared absorbance was compared with that of the standard for atazanavir analysis (Santa Cruz Biotechnology, Inc., Dallas, TX, USA). This analysis strongly indicated that the urinary crystalline precipitation of the patient included atazanavir crystals (Figure 1). The first renal biopsy was performed in May 2012. The kidney tissue contained eight glomeruli, one of which (12.5%) was globally sclerotic. The remaining glomeruli showed no convincing histological changes indicating renal failure. In contrast, interstitial nephritis, accompanied by diffuse inflammatory infiltrates consisting of lymphocytes and plasma cells, was noted (Figure 2A). Moreover, needle-shaped crystalline precipitation, likely in the epithelia of the tubule, surrounded by multinuclear giant cells, was very characteristic (Figure 2B). Immunohistochemistry was negative. Electron microscopy showed no electron-dense deposits in the glomeruli; however, crystalline precipitation was confirmed within the tubular epithelial cells (Figure 2C). In June 2012, atazanavir was replaced by raltegravir, but renal function did not improve. From November 2012, 6 months after the first renal biopsy, oral prednisolone was started at the initial dose of 0.75 mg/kg daily for 4 weeks, and was slowly decreased in the subsequent 5 months. However, serum Cr remained constant at 1.5 mg/dL. In August 2013 (1 year and 3 months after the first renal biopsy), a second renal biopsy contained 28 glomeruli, 5 of which (17.9%) were globally sclerotic. The remaining 23 glomeruli had unremarkable changes. Needle-shaped crystals surrounded by lymphocytes and multinuclear giant cells in the tubulointerstitial compartment were completely removed. Sclerotic findings of glomeruli and intrarenal arterioles including interlobular arteries were more prominent than those observed in the first renal biopsy. Additionally, tubular atrophy and interstitial-fibrosis developed further, although the severe interstitial inflammation was almost cured (Figure 2D). Immunohistochemistry and electron microscopy showed no characteristic findings.

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