Diffuse Tubulointerstitial Nephritis Accompanied by Renal Crystal Formation in an HIV-infected Patient Undergoing Highly Active Antiretroviral Therapy

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Abstract

This report presents a human immunodeficiency virus (HIV) patient that developed a slowly progressive renal impairment over years under highly active antiretroviral therapy (HAART). The renal biopsy showed diffuse tubulointerstitial nephritis accompanied by crystal formations that were surrounded by multinuclear giant cells. Furthermore, rod-like crystals were detected in the urinary sediments. Tenofovir and Atazanavir were thought to be the causative drugs for the renal injury. Therefore, the possibility of HARRT-induced nephrotoxicity should be considered in HIV-infected patients, even though the activity of HIV is controlled by such therapies.

Key words: human immunodeficiency virus, highly active antiretroviral therapy, Tenofovir, Atazanavir, tubulointerstitial nephritis, crystal nephropathy


Introduction

Various new antiretroviral agents have been introduced for the treatment of human immunodeficiency virus (HIV) infection. Patients with HIV infection are effectively treated with highly active antiretroviral therapy (HARRT). Renal disease can develop in HIV-infected patients, through the direct effects of HIV infection, opportunistic infections, or drug-related effects. Prior to the introduction of HAART, most of the renal diseases in HIV-infected patients were HIV-associated nephropathy (HIVAN) (1, 2). HAART has prevented HIVAN and has led to a decline in the mortality of HIV infection. However, the frequency of chronic renal disease has paradoxically increased in HIV-positive patients despite receiving HAART, and also a variety of adverse renal effects of HAART have been recognized (3, 4). Some antiretroviral drugs may have life threatening side effects, especially if underlying renal abnormalities exist. Therefore, renal insufficiency in HIV patients on HAART should be evaluated thoroughly (5). This report presents a case of an HIV-infected patient whose renal insufficiency was likely caused by antiretroviral drugs.

Case Report

The patient was a 50-year-old Japanese man with a medical history of sleep apnea syndrome when he was 40 years old. He was a homosexual and did not have a history of smoking, drinking or drug abuse. He had an episode of brain toxoplasmosis that revealed his HIV infection for the first time in March 2005, and his urinalysis was negative for protein and occult blood at that time. He received pyrimethamine plus sulfadiazine and folinic acid for the treatment of brain toxoplasmosis. After this therapy, his serum creatinine had been stable around the level of 0.9 mg/dL. His clinical course is shown in Fig. 1. The HAART of Zidovudine (ZDV), Lamivudine (3TC) and Efavirenz (EFV) was initiated in May 2005 for his HIV infection. In June 2005, his urinalysis showed increased red blood cell and white blood cell counts, probably due to a transient urinary tract infection. He was switched to 3TC, Tenofovir (TDF)
The patient’s serum creatinine concentration (s-Cr) was 0.9 mg/dL, and he had hallucinations as a side effect of the original therapy. The patient’s s-Cr was 1.6 mg/dL in November 2008, and a urinalysis by dipstick showed (2+) protein. His medication regimen was changed from TDF to abacavir (ABC) because the renal insufficiency was thought to be TDF nephrotoxicity. Nevertheless, his renal insufficiency continued to progress, and his urinalysis showed microscopic hematuria. His HIV viral load was undetectable (<50 HIV RNA copies/mL) and CD4 T-cell count was 200-300/μL during the course of these treatments. The patient’s s-Cr reached 2.0 mg/dL in June 2010, and he was admitted to the hospital for evaluation in August 2010. The patient was on the HAART including 3TC (150 mg a day), ATV/r (300 mg/100mg a day), and ABC (300 mg twice a day).

The patient’s height and weight were 170 cm and 52.0 kg, respectively. The patient had lost approximately 16 kg over the previous two years. A physical examination revealed a blood pressure of 138/92 mmHg, a heart rate of 68/min, and a body temperature of 36.6°C. He had articular disorders and left hemiplegia as a sequelae of brain toxoplasmosis.

Laboratory data showed a total leukocyte count of 5,300/μL with an absolute lymphocyte count of 2,100/μL, eosinophil count 0.0/μL, hemoglobin 13.5 g/dL, platelet count 230,000/μL, serum total protein 7.8 g/dL, serum albumin 4.1 g/dL, sodium 140 mEq/L, potassium 4.5 mEq/L, chloride 107 mEq/L, blood urea nitrogen (BUN) 25 mg/dL, s-Cr 2.18 mg/dL, calcium 9.1 mg/dL, HbA1C 4.9%, C-reactive protein 0.06 mg/dL. The level of serum immunoglobulins were: IgG 1.571 mg/dL, IgA 299 mg/dL, and IgM 54 mg/dL. The level of serum complement factors were; C3 117 mg/dL, C4 22 mg/dL and CH 50 48.7 U/mL. ACE 5.6 U/L; rheumatoid factor (RF) and anti-nuclear antibody (ANA) were negative; myeloperoxidase and proteinase 3 anti-neutrophil cytoplasmic antibody (ANCA) were not noted; surface antigen of hepatitis B virus (HBV), and antibody against hepatitis C virus (HCV) were negative. His viral load was <50 HIV RNA copies/mL and CD4 T-cell counts were 371/μL.

Urinalysis showed pH 5.5, negative nitrite, ± proteinuria, ± occult blood, and negative sugar. Urinary sediment showed 0-1 red blood cells/high power field (HPF, ≥400), 5-9 white blood cells/HPF, hyaline casts 0-1 counts/HPF. The patient’s urinary sediments contained crystals that appeared as rod-like forms (Fig. 2). The urinary excretion of N-acetyl-beta-D-glucosaminidase (NAG) and beta 2-microglobulin (β2MG) concentration increased to 8.1 U/L (normal range; <7.0 U/L) and 25.295 μg/L (normal range; <230 μg/L), respectively. The 24 hours creatinine clearance was 48 mL/min/1.73m² and a urinary protein excretion was 384 mg/24hr. The urine and blood culture findings remained negative.

Gallium-67 scintigraphy showed no kidney uptake. Renal ultrasound showed increased renal parenchymal echogenicity and hyperechoic stones in the bilateral renal pelvis causing dark shadowing without a dilation of renal pelvis (Fig. 3).

A renal biopsy was performed to evaluate the cause of the
renal insufficiency. The renal biopsy specimens contained 43 glomeruli, 15 of which (35%) were globally sclerotic. The remaining glomeruli appeared histologically unremarkable, without evidence of collapsing sclerosis or podocyte hyperplasia as those found in HIVAN. None of the following was noted: thickening of the glomerular capillary walls, increased mesangial matrix, occlusion of glomerular capillaries, and swelling of endothelial cells (Fig. 4A). Approximately 70% of the cortex and medulla displayed widespread and severe interstitial fibrosis accompanied by diffuse inflammatory infiltrates consisting mainly of mononuclear cells and plasma cells, without neutrophils or eosinophils. The tubules were atrophic with focally thickened basement membranes (Fig. 4B). There were needle-shaped crystals surrounded by multinuclear giant cells in the tubulointerstitial compartment. In addition, there was a considerable number of granuloma-like lesions that mimicked the crystal-related ones throughout the biopsy specimens (Fig. 4C, D). The crystals were negative for staining with hematoxylin and eosin, and periodic acid-Schiff. These crystals were also negative for von Kossa stains, indicating that the crystals did not involve calcium. SV40 staining in the tubular epithelial cells was negative. The vessels displayed mild arteriolar hyalinosis without vasculitis and peritubular capillaritis. Immunohistochemistry showed weak nonspecific segmental granular mesangial staining for IgM and C3 in the areas. Electron microscopy showed no electron-dense deposits in the glomerulus. There was no evidence of HIV-related immune complex disease (HIVIC). The patient was histopathologically diagnosed to have diffuse TIN accompanied with granuloma reacting to crystal formation.

Discussion

Here we describe a case of slowly progressive renal insufficiency in an HIV-infected patient on HAART. In HIV-infected patients, four etiologically different groups of nephropathy should be considered. (I) HIV related nephropathies; (II) renal disease related to the immune deficiency; (III) nephropathies related to drug toxicity; (IV) nephropathies unrelated to the HIV infection (5). In the present case, the HIV activity was well-controlled. The patient had no findings of viral, bacterial, or parasite infection. There were no histological findings suggestive HIVAN, HIVIC, or other glomerulonephropathies. Rather, the main cause of renal insufficiency was thought to be diffuse TIN. Studies have shown that 5-25% of HIV-infected patients with renal insufficiency had a histological diagnosis of TIN (6, 7). TIN in HIV-infected patients can be triggered by various causes, including drugs, myoglobinuria, nephrocalcinosis, direct renal infection of HIV, hemodynamic factors including ischemia and dehydration. Among these factors, drugs are assumed to be the cause of TIN in the vast majority of the HIV-infected cases (8). It is conceivable that drug-induced TIN was the main cause of acute kidney injury in the current patient. The following are drugs that might cause TIN in HIV-infected
patients: antibiotics, antiretroviral medications, proton pump inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), furosemide, foscarnet and allopurinol (9). The current patient had not been given any drugs other than antiretroviral agents. Therefore, the antiretroviral agents were thought to be the causative agents of the renal insufficiency in this case.

HAART typically includes the combination of two reverse transcriptase inhibitors (RTIs) plus a protease inhibitor (PI). Several case reports and small case series demonstrated a potential risk of TDF nephrotoxicity (10). It has been reported that TDF nephrotoxicity usually presents acute tubular necrosis with or without Fanconi syndrome (11). A recent study showed that a characteristic feature of TDF nephrotoxicity in renal biopsy is eosinophilic intracytoplasmic inclusions within proximal tubular epithelial cells, corresponding to the giant mitochondria seen ultrastructurally. However, the exact mechanism of tubular injury remains unclear (12, 13). We did not detect these characteristic histological findings in the present case. Therefore it is difficult to prove that the renal insufficiency was due to TDF nephrotoxicity. However, there were some supportive findings that the renal injury could be distinctively attributed to TDF nephrotoxicity in our case. First, there are some case reports of TDF nephrotoxicity that presented TIN in renal biopsies (13). Second, the withdrawal of TDF appeared to have attenuated the decline of renal function in our case. Importantly, TDF withdrawal was shown to be sufficient to repair the tubular injury (14). Third, other potential causes of renal insufficiency in the former period of the therapy, such as drug, infection, or glomerulonephropathy were not detected. Therefore, the renal injury was distinctively attributed to
TDF in this case at least in the former period of the therapy. However the renal insufficiency continued to progress and microscopic hematuria was persistent even after the withdrawal of TDF. In the other hospital our patient had not undergone an extensive hematuria workup. But he did not have the symptoms or the findings suspected of urolithiasis, urinary tract infection, or bladder tumor. This suggests that factors other than TDF might have contributed to the decline of renal function.

ATV has been reported to form crystals that result in obstructive kidney injury (15, 16). ATV may have played a role on the development of renal insufficiency in the current patient. The patient’s urinalysis showed persistent microscopic hematuria during the ATV therapy and rod-like crystals were detected in his urinary sediments. In addition, renal ultrasound showed hypeerechoic stones in the renal pelvis. Finally, the renal biopsy showed a large number of crystal-related granulomatous lesions in the tubulointerstitial area throughout the specimens. Unfortunately, ATV could not be identified in the crystals, because those obtained were too small in size to analyze the components. Nevertheless, all these findings are fully consistent with those found in the patients with ATV crystal nephropathy (17, 18).

The differential diagnosis of crystal nephropathy includes other drug-induced renal injuries accompanied with crystals, such as those caused by ampicillin, ceftriaxon, ciprofloxacin, sulfadiazine, triamterene, acyclovir, indinavir, and allopurinol (19, 20). However, the present patient was not given such drugs. He did not show a high concentration of uric acid in the serum and the urine, which eliminated the possibility of uric acid crystals. Importantly, it is generally accepted that ATV crystal nephropathy alone does not induce progressive renal impairment (18). It is possible that the pre-existing chronic renal injuries due to the previous administration of TDF may have rendered the patient more susceptible to the renal toxicity of ATV. The renal biopsy findings of the coexistence of acute and chronic tubulointerstitial injuries together with granuloma-like abnormalities were consistent with these hypotheses.

Another possible mechanism for the development of renal injury would be interactions between concomitant drugs. Some of the HAART drugs are known to interact with other HAART drugs. Such interactions may synergistically enhance renal insufficiency via the induction and/or inhibition of cytochrome P450 or renal tubule transporters (21). The nephrotoxic effects induced by TDF are often observed with concomitant use of Ritonavir (22). Therefore, there was a possibility that the TDF nephrotoxicity was enhanced by the use of Ritonavir in the current patient. A recent study has evaluated the renal injuries in kidney biopsies of 30 HIV patients undergoing ATV therapy (23). TIN was found in six patients and the combination of ATV and TDF was noted in three of them. These findings suggested a potential risk of TIN under the concomitant use of ATV and TDF. On the contrary, a recent report has shown the possibility that TDF discontinuation could predispose patients to urolithiasis in ATV-treated patients because TDF lowers the plasma level of ATV (24). Although the plasma level of ATV was not measured in the current patient, TDF discontinuation could have been a trigger for the enhancement of ATV crystal formation.

Additionally, some PIs or NRTIs have been shown to be associated with dyslipidemia, insulin resistance, diabetes mellitus or myocardial infarction (25). The present patient had hypertension and the vessels displayed mild arteriolar hyalinosis in the renal biopsy, therefore these vascular factors could additionally progress the mild glomerular sclerosis and slowly progressive renal insufficiency.

In summary, we described progressive renal insufficiency in an HIV-infected patient. HIVAN was not likely the cause of renal injury. Instead, the drugs used for HAART were thought to be the causative drugs of the renal insufficiency. The present case, therefore, suggests the possibility of HAART-induced nephrotoxicity even though the activity of HIV is controlled by such therapies.

The authors state that they have no Conflict of Interest (COI).

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References
13. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D’Agati VD, Markowitz GS. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnor-

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