Drug-Induced Acute Interstitial Nephritis Mimicking Acute Tubular Necrosis after Initiation of Tenofovir-Containing Antiretroviral Therapy in Patient with HIV-1 Infection

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Abstract

We describe a case of 68-year-old Japanese man with HIV-1 infection who developed acute kidney injury with prominent tubular dysfunction immediately after starting tenofovir-containing antiretroviral therapy. Antiretroviral therapy was discontinued in two weeks but renal function, as well as tubular function, did not shown full recovery even at a 3-year follow-up examination. Acute tubular necrosis, a rare but well-known side effect of tenofovir, was suspected, but kidney biopsy confirmed interstitial nephritis. It is important to distinguish drug-induced interstitial nephritis from acute tubular necrosis, because early steroid administration can improve renal dysfunction caused by acute interstitial nephritis.

Key words: tenofovir, acute interstitial nephritis, acute tubular necrosis, acute kidney injury, HIV infection, kidney biopsy

(Intern Med 51: 2469-2471, 2012)
(DOI: 10.2169/internalmedicine.51.7766)

Introduction

Renal proximal tubular dysfunction is a well-known side effect of tenofovir (1, 2). Although rare, it sometimes leads to acute tubular necrosis (ATN) and results in acute kidney injury (AKI) (1, 3). Drug-induced acute interstitial nephritis has a similar clinical presentation to ATN, but has different etiology and management (4, 5). Here we report a case of tenofovir-induced acute interstitial nephritis (AIN) which mimicked ATN after initiation of tenofovir-containing antiretroviral therapy (ART).

Case Report

A 68-year-old Japanese man with history of hypertension and diabetes mellitus was diagnosed with HIV infection and pneumocystis pneumonia (PCP). The latter was treated with sulfamethoxazole/trimethoprim plus prednisolone for three weeks, and the patient was referred to our hospital. Reactivation of PCP occurred and he was again treated with sulfamethoxazole/trimethoprim for three weeks. After completion of PCP treatment, sulfamethoxazole/trimethoprim was replaced with atovaquone for secondary prophylaxis, and one month later ART was started with tenofovir/emtricitabine plus lopinavir/ritonavir (baseline CD4 count 39/μL, HIV viral load 990,000 copies/mL). Baseline renal function tests were within the normal range (serum creatinine 0.53 mg/dL, blood urea nitrogen 8.7 mg/dL) with urine β2 microglobulin (β2MG) of 2,327 μg/L. The concurrent drugs were atovaquone (which was switched to prophylactic dose of sulfamethoxazole/trimethoprim on ART day 2), azithro-
mycin 1,200 mg/week, and olmesartan. No concurrent non-steroidal anti-inflammatory drug was used.

Serum creatinine started to rise and on ART day 14, it reached 2.66 mg/dL, with β2MG of 321,400 μg/L. No fever or rashes were observed, but prominent eosinophilia was noted (18.6% of leukocytes, 4,400/μL). Urine dipstick test showed proteinuria +3, occult blood +2, and glycosuria +1, together with renal tubular epithelial cells and granular casts in urine. Serum potassium, sodium, and phosphate levels were within the normal ranges. Serum IgE was high (1,040 IU/mL), and serum antinuclear antibodies, antineutrophil cytoplasm antibody, and cryoglobulin were negative. Renal ultrasonography was also negative for specific findings.

ART and the other concurrent medications, with the exception of azithromycin, were discontinued on that day. Hydration with central venous catheter was started. At 21 days after commencement of ART, serum creatinine reached a peak level of 5.39 mg/dL, though renal function started subsequently to improve slowly. At 32 days after discontinuation of ART, ART with darunavir/ritonavir plus raltegravir was provided (serum creatinine 2.59 mg/dL). The patient was discharged 44 days after re-commencement of ART without any complications. To our knowledge, this is the fourth reported case of tenofovir-induced AIN, in addition to the three cases reported by Schmid et al. (6). Nevertheless, it is difficult to entirely rule out the involvement of sulfamethoxazole/trimethoprim, the other drug which was used just before the occurrence of AIN, had been intermittently used for more than two months before the introduction of ART without any complications. In this case, we performed renal biopsy 5 months after the episode, renal biopsy was performed (serum creatinine 1.76 mg/dL, β2MG 15,677 μg/L). Examination of the specimen showed interstitial infiltration of lymphocytes, plasma cells, and a few eosinophils. There was no vacuolation in tubular cells and the brush border was intact. The glomeruli were histologically normal (Fig. 1a, b).

Immunofluorescence study was negative for IgG, IgM, IgA, C1q, C3, C4, or fibrinogen. Electron microscopic examination demonstrated no abnormalities in the mitochondria of tubular cells (Fig. 1c). The final diagnosis was drug-induced AIN. Serum creatinine and β2MG were still elevated three years later at 1.47 mg/dL and 25,718 μg/L, respectively.

Discussion

We described a case of tenofovir-induced AIN, which clinically mimicked ATN, after commencement of tenofovir-containing ART. Although the causative drugs were discontinued in two weeks, renal function did not show full recovery and the patient developed chronic kidney disease (Fig. 2). Tenofovir was highly likely the causative drug, because sulfamethoxazole/trimethoprim, the other drug which was used just before the occurrence of AIN, had been intermittently used for more than two months before the introduction of ART without any complications. In this case, we performed renal biopsy 5 months after the episode, renal biopsy was performed (serum creatinine 1.76 mg/dL, β2MG 15,677 μg/L). Examination of the specimen showed interstitial infiltration of lymphocytes, plasma cells, and a few eosinophils. There was no vacuolation in tubular cells and the brush border was intact. The glomeruli were histologically normal (Fig. 1a, b).
induced AIN may have been misdiagnosed. Although a prominent eosinophilia and hyper-IgE (1,040 IU/mL) was noted for this case, these laboratory findings are commonly observed in patients with HIV-1 infection (7, 8). It is therefore difficult to diagnose AIN solely based on these laboratory findings in patients with HIV infection.

The pathomechanism of tenofovir-induced ATN is considered to be mitochondrial toxicity in proximal tubular cells (9, 10). In contrast, interstitial nephritis occurs as an allergic response triggered by exposure to a drug (4, 5). It is important to distinguish AIN from ATN, because early steroid administration can improve the recovery of renal function in AIN (4, 5).

AIN should always be included in the differential diagnosis in a patient with AKI and prominent renal tubular damage following the introduction of tenofovir. In addition to prompt discontinuation of tenofovir, renal biopsy followed subsequently with steroid therapy at an early stage could produce a favorable renal outcome.

Author’s disclosure of potential Conflicts of Interest (COI).


Acknowledgement

The authors thank Makoto Mochizuki for the histopathological examination, and all the clinical staff at the AIDS Clinical Center for their excellent work.

All authors contributed to the concept, design, and writing of this submission.

References