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Case Report

Tenofovir nephropathy in a patient with human immunodeficiency virus

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ABSTRACT

Tenofovir is an effective and widely used antiretroviral drug for the treatment of both human immunodeficiency virus (HIV) and hepatitis B virus infection. Although large clinical studies and post-marketing data support a benign renal profile for tenofovir, numerous cases of kidney injury have raised concerns about its nephrotoxic potential. Here, we describe the case of a 33-year-old man with HIV who was treated with tenofovir, following which he developed acute renal failure with proteinuria, glucosuria, hypouricemia, hypophosphatemia, and normal anion gap metabolic acidosis, which are suggestive of acute kidney injury with Fanconi's syndrome. A renal biopsy revealed acute tubular necrosis with eosinophilic intracytoplasmic inclusions within the proximal tubular cells. Electron microscopic images demonstrate giant mitochondria and display prominent clumping, loss, and disorientation of cristae. After the discontinuation of tenofovir treatment, the patient's renal function improved and the serum uric acid and phosphorous levels returned to normal. Tenofovir-induced Fanconi's syndrome is an adverse effect that should be considered when prescribing antiretroviral therapy.
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1. Introduction

Tenofovir is an acyclic nucleotide analog reverse transcriptase inhibitor approved for the treatment of human immunodeficiency virus (HIV) and hepatitis B virus infections [1]. Tenofovir is eliminated unchanged in the urine by a combination of glomerular filtration and proximal tubular secretion. Approximately 20–30% of the drug is actively transported into the renal proximal tubule cells by organic anion transporters-1 (OAT-1) and to a lesser extent by OAT-3 in the basolateral membrane. Subsequently, the drug is secreted into the tubular lumen by multidrug-resistance protein-4 (MRP-4) and MRP-2, which are apical membrane transporters [2]. However, it is believed that tenofovir may cause renal impairment by inhibiting the activity of DNA polymerase γ, which is essential for mitochondrial replication [3]. We herein present the case of an HIV-infected patient who developed acute kidney injury with Fanconi's syndrome after treatment with tenofovir.

2. Case report

A 33-year-old businessman with a known diagnosis of HIV infection for 7 years presented to our infectious disease clinic with the chief complaint of foamy urine for 2 months. His current medications were a regimen of tenofovir, lopinavir, and raltegravir, which he has been taking for 15 months.

Physical examination revealed only pale conjunctiva. The initial laboratory blood test results are shown in Table 1. The complete blood count results during his hospitalization revealed anemia and lymphopenia. His serum biochemical test results also showed abnormal renal function with hypouricemia and hypophosphatemia. His blood glucose level was normal and blood arterial gas analysis confirmed normal anion gap metabolic acidosis. Urinalysis showed evidence of glycosuria (3+) and proteinuria (1+). His 24-hour urine total protein was 3.67 g/day. The

Conflict of interest: none.

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Table 1
Laboratory data of our patient on December 6, 2012, 7 days before stopping tenofovir.

Item	Parameter		Parameter	
Biochemical data	White blood cell	9590/μL	Lymphocyte	18.8%
	Lymphocyte CD4%	16%	Lymphocyte CD8%	45%
	Neutrophil cells	71.7%	Monocytes	7.1%
	Platelet	391,000/μL	Hemoglobin	10.9 g/dL
	Blood urea nitrogen	42 mg/dL	Creatinine	3.8 mg/dL
	Albumin	2.7 g/dL	Globulin	5.2 g/dL
	Potassium	3.6 mEq/L	Sodium	134 mEq/L
	Magnesium	2.2 mEq/L	Ionized calcium	1.16 mmol/L
	Phosphorous	2.1 mg/dL	Uric acid	3.4 mg/dL
	Chloride	105 mmol/L	Fasting glucose	107 mg/dL
Urine biochemical data	Uric acid	36.2 mg/dL	Phosphorous	17.9 mg/dL
	Creatinine	53.9 mg/dL	24 h total proteinuria	3.67 g/day
	β2-microglobulin	33,571 ng/mL		
Urine dipstick	pH	5.5	Protein	1+
	Glucose	3+	White blood cell	3–5/HPF
	Red blood cell	0–2/HPF		
Arterial blood gas	pH	7.272	HCO_3^-	17.2 mmol/L
	pO_2	91.6 mmHg	pCO_2	38 mmHg
	O_2 saturation	95.3%		

Normal range of urine β2-microglobulin: 609–2366 ng/mL; lymphocyte percentage: 20–45%; lymphocyte CD4 percentage: 29–55%; lymphocyte CD8 percentage: 19–37%.
HPF = high power field; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen.

urine β2-microglobulin level was 33,571 ng/mL. Fractional excretion of uric acid was 75.1% (normal range: 6–12%) and fractional excretion of phosphorus was 60.1% (normal range: 5–20%). Thus, the clinical picture suggested acute kidney injury with Fanconi's syndrome. A renal biopsy demonstrated that the glomeruli were normal; however, acute tubular necrosis and interstitial inflammation were noted (Fig. 1A) along with eosinophilic intracytoplasmic inclusions within the proximal tubular epithelial cells (Fig. 1B). Electron micrographic ultrastructural findings showed enlarged mitochondria (2–6 μm wide; normal mitochondria range is only 0.5–1 μm wide) with irregular shapes and dysmorphic mitochondria, which were largely devoid of cristae within the proximal tubular epithelial cells (Fig. 2). A review of his medications indicated that tenofovir was the most probable cause of his symptoms. After discontinuation of tenofovir, the patient's renal function improved and serum uric acid and phosphorous returned to the normal levels after 17 weeks of follow up (Fig. 3). His urine dipstick test, urine β2-microglobulin level, and 24-hour urine total protein were all in the normal range.

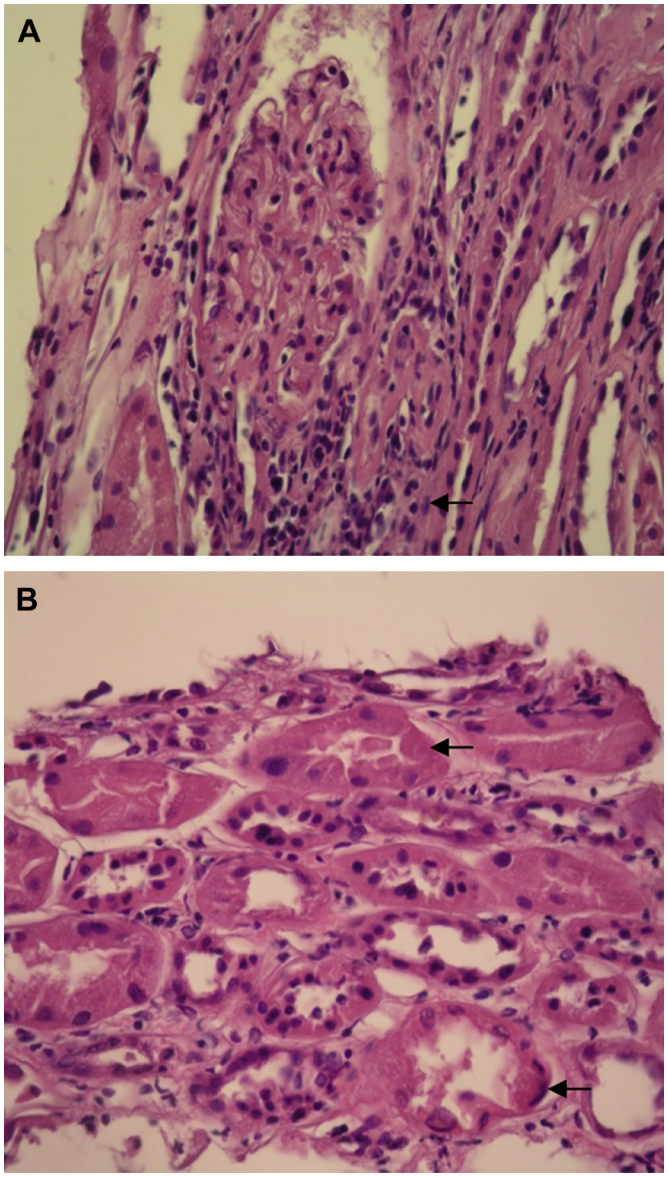

Fig. 1. (A). A renal biopsy specimen showing normal glomeruli. The arrow shows acute tubular necrosis and interstitial inflammation (hematoxylin and eosin stain at 400×). (B) Eosinophilic intracytoplasmic inclusions (arrow) are seen within the proximal tubular epithelial cells (hematoxylin and eosin stain 400×).

3. Discussion

Tenofovir, the first nucleotidic inhibitor of HIV reverse transcription, became available in 2001. It has been extensively used worldwide and is now the most prescribed antiretroviral drug [4]. However, reports on its renal safety are still ambiguous. Two studies have demonstrated tubular dysfunction with tenofovir in 17–22% tenofovir-treated patients [5,6]. The incidence of acute kidney injury after initiation of tenofovir treatment has varied greatly, from 1.6/100 person-years to 1.5/1000 person-years [4], illustrating the inconsistency of reports. Risk factors for developing tenofovir-associated nephrotoxicity identified from studies have included increased age, low body weight, pre-existing decrease in kidney function, low CD4 count, and concomitant use of nephrotoxic drugs [1,7]. The proximal tubular cell is the main target of tenofovir toxicity because of its complement of cell membrane transporters that favor the accumulation of this drug. Unmodified tenofovir is excreted in the urine by both glomerular filtration and tubular secretion. To be secreted, tenofovir enters the epithelial cell at its basolateral pole using human OAT-1 and to a lesser extent using human OAT-3. It is then secreted in the tubular lumen through MRP-2 and MRP-4. When the plasma concentration increases or when apical secretion is inhibited, intracellular concentration of tenofovir increases. This results in partial inhibition of kidney mitochondrial DNA polymerase γ activity, which subsequently results in reduction in mitochondrial DNA (as mitochondrial replication is affected) and oxidative respiratory chain dysfunction [2,4]. Mitochondrial structural changes are induced in the proximal tubular epithelial cells. Because of a shortage of

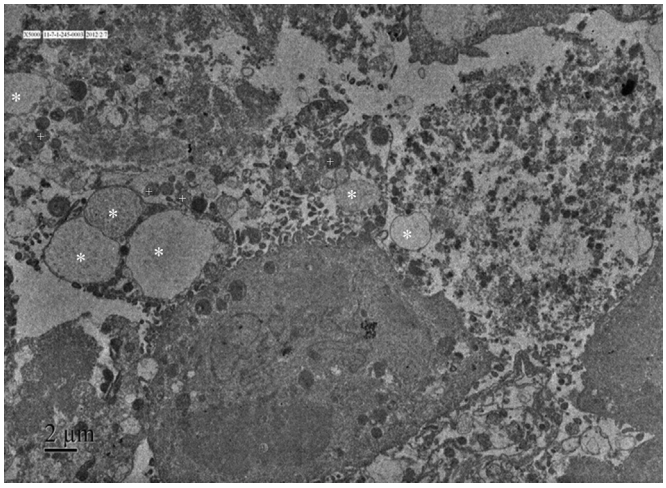

Fig. 2. Electron micrographic ultrastructural findings show tenofovir-induced epithelial cell dysfunction due to mitochondrial damage. Enlarged mitochondria (asterisks) are visible adjacent to normal-sized mitochondria (plus signs). Large mitochondria appear devoid of cristae, while other mitochondria show normal cristae content (original magnification 8000×).

adenosine triphosphate production, tubular cells cannot properly ensure reabsorption of ions and small molecules, such as potassium, glucose, phosphate, uric acid, amino acids, and β2-microglobulin. Therefore, these molecules are secreted in abnormal quantities in the urine, which is the definition of Fanconi's syndrome [4]. A histological examination mainly reveals acute tubular necrosis, primarily affecting the proximal tubules. Tubular ectasia, cytoplasmic simplification, prominent nucleoli, and loss of a brush border indicate a toxic origin. The only sign of tenofovir-specific toxicity is giant mitochondria visible as prominent eosinophilic inclusions in the cytoplasm of the proximal tubular epithelial cells. Some mitochondria are greatly enlarged, while others appear shrunken. Mitochondrial cristae could be absent or less abundant than normal, and sometimes grouped at one pole of the mitochondria [4,7].

Our patient appears to have developed proximal tubular dysfunction that was first evidenced by the presence of glucosuria with a normal blood glucose level. On further investigation, he was noted to have a low normal serum phosphate level with a high fractional excretion of phosphate, low normal serum uric acid with a high fractional excretion of uric acid, and normal anion gap metabolic acidosis with a urine pH of 5.5. Further urine studies showed evidence of significant proteinuria (3.67 g/day), with only 1+ albuminuria on a urine dipstick, which suggested a tubular source of the proteinuria. This was further supported by the high level of urinary β2-microglobulin (33,571 ng/mL). This constellation of blood and urinary derangements coupled with the proximal tubular epithelial cells in the urinary sediment is consistent with proximal tubular injury and Fanconi's syndrome. The patient had been taking tenofovir, raltegravir, and lopinavir for 15 months before admission. Raltegravir is a type of integrase inhibitor and was associated with rhabdomyolysis and renal dysfunction in three cases [8]. Lopinavir belongs to the family of protease inhibitors, and has been reported to cause renal dysfunction when boosted by ritonavir [9]. HIV-associated nephropathy is the most common cause of chronic kidney disease in HIV-infected persons who are not receiving highly active antiretroviral therapy. HIV mediates dysregulation of glomerular podocytes, the epithelial cells of which maintain the glomerular basement membrane, and apoptosis of renal tubular cells. The resulting lesions of HIV-associated nephropathy are a focal segmental glomerulosclerosis [10]. Renal

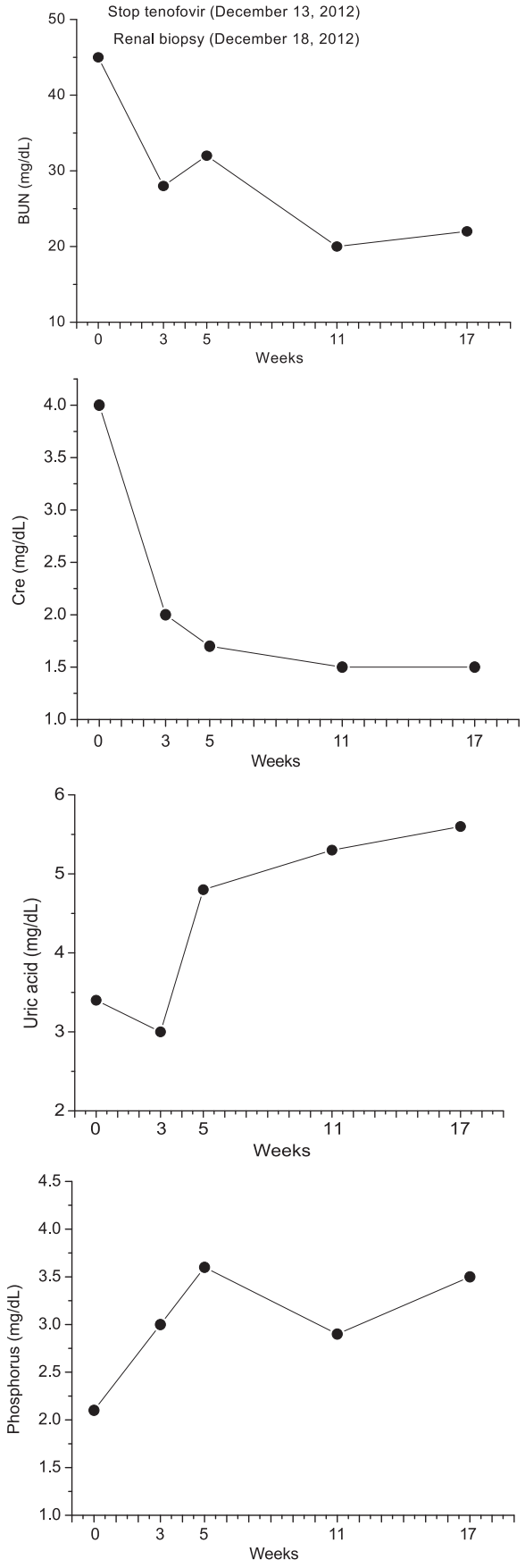

Fig. 3. Time course of serum BUN, creatinine, uric acid, and phosphorus levels after renal biopsy. BUN = blood urea nitrogen; Cre = creatinine.

biopsy in our patient revealed toxic acute tubular necrosis with eosinophilic intracytoplasmic inclusions within the proximal tubular cells. An electron microscopic examination demonstrated abnormal mitochondria with disruption of the normal cristae, consistent with tenofovir toxicity. All the data pointed to tenofovir-induced Fanconi's syndrome with acute renal failure. After discontinuation of tenofovir, the patient's renal function and Fanconi's syndrome improved after 17 weeks of follow up.

In summary, we reported a patient with tenofovir nephropathy who presented with acute renal failure with Fanconi's syndrome. A high index of suspicion may help prevent tenofovir nephropathy. It is possible to significantly reduce this risk by observing simple rules, such as measuring kidney function carefully, assessing kidney disease risk before prescription, and screening for abnormal proximal tubule function, which may be assessed by measuring tubular protein excretion and fractional urinary excretion of phosphate or uric acid, and using a dipstick to test for urinary glucose.

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