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Case Report

Tenofovir nephropathy in a patient with human immunodeficiency virus

Wei-Shan Tsai^a, Lih-Shinn Wang^{a,b}, Yung-Hsiang Hsu^{a,c}, Yu-Li Lin^d, Te-Chao Fang^{a,d}, Bang-Gee Hsu^{a,d,*}^a School of Medicine, Tzu Chi University, Hualien, Taiwan^b Department of Infectious Disease, Buddhist Tzu Chi General Hospital, Hualien, Taiwan^c Department of Pathology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan^d Department of Nephrology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan

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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.

* Corresponding author. Department of Nephrology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan. Tel.: +886 3 8561825; fax: +886 3 8577161.

E-mail address: gee.lily@tzuchi.com.tw (B.-G. Hsu).

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

Item	Parameter	Parameter	Parameter
Biochemical data	White blood cell	9590/ μ L	Lymphocyte 18.8%
	Lymphocyte	16%	Lymphocyte CD8% 45%
	CD4%		Monocytes 7.1%
	Neutrophil cells	71.7%	
	Platelet	391,000/ μ L	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
Urine biochemical data	Chloride	105 mmol/L	Fasting glucose 107 mg/dL
	Uric acid	36.2 mg/dL	Phosphorous 17.9 mg/dL
	Creatinine	53.9 mg/dL	24 h total proteinuria 3.67 g/day
	β 2-microglobulin	33,571 ng/mL	
Urine dipstick	pH	5.5	Protein 1+
	Glucose	3+	White blood cell 3–5/HPF
Arterial blood gas	Red blood cell	0–2/HPF	
	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 β 2-microglobulin: 609–2366 ng/mL; lymphocyte percentage: 20–45%; lymphocyte CD4 percentage: 29–55%; lymphocyte CD8 percentage: 19–37%.

HPF = high power field; pCO₂ = partial pressure of carbon dioxide; pO₂ = partial pressure of oxygen.

urine β 2-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 μ m wide; normal mitochondria range is only 0.5–1 μ m 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 β 2-microglobulin level, and 24-hour urine total protein were all in the normal range.

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

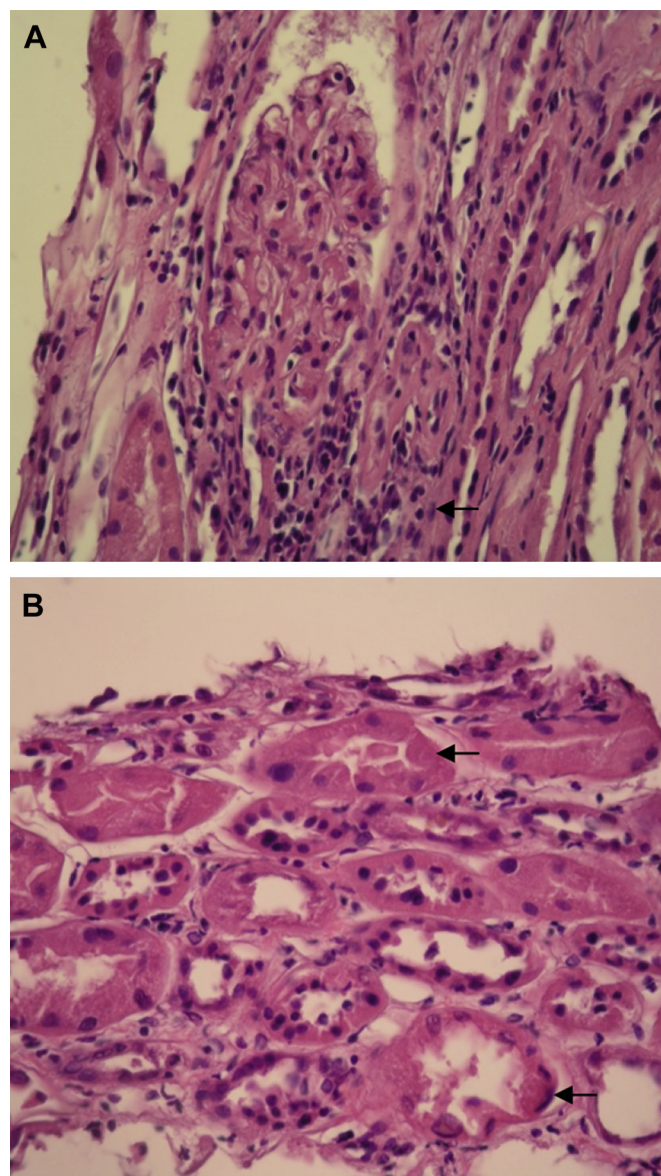


Fig. 1. (A). A renal biopsy specimen showing normal glomeruli. The arrow shows acute tubular necrosis and interstitial inflammation (hematoxylin and eosin stain at 400 \times). (B) Eosinophilic intracytoplasmic inclusions (arrow) are seen within the proximal tubular epithelial cells (hematoxylin and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

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

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