CKD in a Patient Treated with Adefovir for Chronic Hepatitis B Virus Infection

Satoru Kudose, Ellen Lunenfeld, and Glen S. Markowitz

Clinical Images in Nephrology and Dialysis

Case Description

In 2017, a 33-year-old Black woman with cerebral palsy presented with chronic hepatitis B virus (HBV) infection and CKD with serum creatinine of 1.33 mg/dl (eGFR 61 mL/min per 1.73m²). She returned with serum creatinine of 1.43 mg/dl in 2020. The patient was diagnosed with HBV in 2008 and, since 2009, had been treated with entecavir 1 mg daily and adefovir 10 mg daily. The patient’s only other medication was norethindrone. Physical exam revealed blood pressure 110/74 mm Hg, body mass index 25.9 kg/m², and no edema. The patient had a urine protein-to-creatinine ratio of 1.4, serum potassium 3.2–3.9 mg/dl [reference range (RR): 3.6–5.2 mg/dl], serum phosphate 2.3 mg/dl (RR: 2.5–4.5 mg/dl), bland urine sediment, no glycosuria, serum albumin 3.9 g/dl, and negative HIV and hepatitis C virus serologies. Liver function panel showed mildly elevated aspartate transaminase (44 U/L, RR 10–40 U/L).

The kidney biopsy consisted of a single core of cortex and medulla containing 12 unremarkable glomeruli. Proximal tubules exhibited diffuse, mild to moderate degenerative changes characterized by luminal ectasia, cytoplasmic simplification, and prominent nuclei. Multiple interspersed proximal tubular epithelial cells contained enlarged, eosinophilic cytoplasmic inclusions that appeared red with the trichrome stain (Figure 1A & B). Mild tubular atrophy and interstitial fibrosis involved 5–10% of the cortex sampled. Interstitial infiltrates were sparse. Vessels appeared unremarkable. Immunofluorescence was unrevealing. Ultrastructural evaluation revealed tubular epithelial cells with markedly enlarged, dysmorphic mitochondria with clumping and loss of cristae. The largest mitochondria were similar in size to adjacent tubular nuclei (Figure 1C). The findings were diagnostic of an acute and chronic tubulointerstitial nephropathy, and the mitochondrial changes were characteristic of adefovir toxicity.

After the biopsy, treatment with adefovir was discontinued. Two months later, the patient’s creatinine remains elevated at 1.44 mg/dl.

HBV infection is a leading cause of morbidity and mortality worldwide (1). Chronic HBV infection is classified as inactive, immune-tolerant, or immune-active disease on the basis of a combination of serology, HBV viral load, and liver function tests. Current preferred initial therapy for immune-active chronic HBV infection includes pegylated-interferon and nucleotide analogs entecavir and tenofovir disoproxil/alafenamide (2). Less commonly, other antivirals such as lamivudine, telbivudine, and adefovir dipivoxil are used (2).

Adefovir nephrotoxicity is a rare cause of renal dysfunction in patients with chronic HBV infection, likely related to the lower dose used in this setting (4). Nonetheless, in rare instances, as seen in the case presented herein, adefovir nephrotoxicity can occur at the lower dose used in patients with HBV (4). Older patients and those with CKD may be at risk for nephrotoxicity (4).

The biopsy findings in patients with adefovir toxicity are strikingly similar to those described for another NRTI, tenofovir (5), and are characterized by proximal tubular injury with enlarged, dysmorphic mitochondria, likely related to inhibition of mitochondrial DNA synthesis (3,5). Tenofovir nephrotoxicity is often reversible upon drug discontinuation; less is known about the potential reversibility of adefovir toxicity.

Teaching Points

- Adefovir nephrotoxicity is a rare cause of renal dysfunction in patients with chronic HBV.
- Adefovir nephrotoxicity is characterized by acute and chronic tubular injury with enlarged, dysmorphic mitochondria that are often visible by light microscopy. Ultrastructural findings include proximal tubular injury and enlarged mitochondrial with clumping and loss of cristae.

1Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, New York
2Department of Nephrology, Summit Medical Group, Berkeley Heights, New Jersey

Correspondence: Satoru Kudose, Department of Pathology, Columbia University Irving Medical Center, Room VC14-238, 630 West 168th St., New York, NY 10032. Email: sk4521@cumc.columbia.edu

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The pathologic findings in adefovir nephrotoxicity are similar to the changes seen in the setting nephrotoxicity related to another NRTI, tenofovir disoproxil fumarate.

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Author Contributions
S. Kudose and G. Markowitz were responsible for conceptualization, visualization, and wrote the original draft; All authors were responsible for data curation and reviewing and editing the manuscript.

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Figure 1. | Histopathologic features of adefovir nephrotoxicity. (A) Proximal tubules display degenerative changes characterized by luminal ectasia, cytoplasmic simplification, and irregular luminal contours. Some of the tubules exhibit increased cytoplasmic eosinophilia (hematoxylin and eosin, ×200). (B) With the trichrome stain, giant mitochondria are visible as red cytoplasmic inclusions (arrows), ×600. (C) Ultrastructural evaluation demonstrates markedly enlarged mitochondria without discernable cristae, ×8000.