Urinary β-2 Microglobulin Levels Sensitively Altered in an Osteomalacia Patient Receiving Add-on Adefovir Dipivoxil Therapy for Hepatitis B Virus Infection

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Abstract

Adefovir dipivoxil (ADV) is effective for hepatitis B virus (HBV) infection; however, ADV may provoke renal injury resulting in osteomalacia, and this side effect is seldom recognized until bone fractures emerge. We herein present a 66-year-old woman with HBV infection who received ADV for 6 years. Although she exhibited no sign of bone fractures, her urinary β-2 microglobulin (β2MG) level increased to 83,837 μg/L and scintigraphy revealed minimal fractures of the third rib. ADV was subsequently reduced and her urinary β2MG rapidly fell to 3,637 μg/L. Conversely, her urinary N-acetyl-β-D-glucosaminidase, and serum phosphate, alkaline phosphatase levels did not respond.

Key words: adefovir dipivoxil, hepatitis B, renal injury, osteomalacia, β-2 microglobulin

(Intern Med 55: 1599-1603, 2016)
(DOI: 10.2169/internalmedicine.55.6301)

Introduction

Adefovir dipivoxil (ADV), 9-[2-(bis-pivaloyloxyethyl)-phosphonylmethoxyethyl] adenine, is an analogue of adenosine monophosphate. Because ADV serves as a substrate for reverse transcriptase (1), this compound is clinically used as an antiviral agent for human immunodeficiency virus and hepatitis B virus infections. Dose-related nephrotoxicity of ADV has been reported (2, 3), which may ultimately induce serious complications including Fanconi’s syndrome, hypophosphatemic osteomalacia, and pathologic bone fractures (3). A daily administration of ADV at 10 mg is referred to as ADV therapy for hepatitis B virus (HBV) infection and was considered to be non-nephrotoxic in randomized control trials and cohort studies in Western countries (4-6). However, reports from East Asia clearly indicate that prolonged ADV therapy induces renal injury (7-9). Therefore, a sensitive and simple marker is required for long-term ADV administration to predict the early stage of renal injury and prevent serious complications, such as osteomalacia and bone fractures.

We herein report a case of hypophosphatemic osteomalacia developed during add-on ADV therapy and in this case, the patient’s elevated levels of urinary β-2 macroglobulin (β2MG) dramatically decreased during the resolution of the clinical manifestations.

Case Report

A 66-year-old woman was referred to our hospital for an evaluation of hypophosphatemia and a slightly elevated serum alkaline phosphatase (ALP) level. On physical examination, she was normally built, appeared neither acutely nor chronically ill, and had normal muscle strength. She was previously diagnosed with chronic hepatitis B infection and had received lamivudine (100 mg/day) for 13 years.

Because the virus had developed resistance to lamivudine, ADV (10 mg/day) had been added to lamivudine therapy 6 years previously. At the time she started taking ADV, her
laboratory data were as follows: aspartate aminotransferase (AST), 54 IU/L; alanine aminotransferase (ALT), 57 IU/L; ALP, 392 IU/L; serum creatinine, 0.48 mg/dL; serum phosphate, 4.2 mg/dL; hepatitis B virus surface (HBs) antigen, 5,290 IU/mL; HBe antigen, 0.1; HBe antibody, 96% inhibition; and HBV DNA, 7.6 LGE/mL. Her laboratory data on her first visit to our hospital are summarized in Table 1. Hypophosphatemia, increased fractional excretion of phosphate, remarkably elevated urinary β2MG and N-acetyl-β-D-glucosaminidase (NAG) levels, and slightly elevated serum creatinine and ALP levels were noted. Given the above history and the presence of abnormal laboratory data, a diagnosis of Fanconi’s syndrome induced by add-on ADV therapy was made. One month later, the patient complained of temporary pain in her right ankle that had emerged after walking, and she was referred to an orthopedist in our hospital. Although plain radiographs demonstrated no remarkable findings, further radiological examinations were performed because accelerated bone remodeling was anticipated due to an elevated serum alkaline phosphatase isozyme 3 level, a bone-specific alkaline phosphatase isozyme, of 272 U/L (normal: 45-151 U/L) (Table 1). Magnetic resonance imaging of the ankle showed a pseudofracture of the talus (Fig. 1). Furthermore, whole-body ⁹⁹m-technetium-methylene diphosphonate bone scintigraphy showed a spotty isotope uptake in the third right rib (Fig. 2), and dual-energy X-ray absorptiometry showed a decreased lumbar spine bone mineral density of 0.61 g/cm³ (T-score, -3.4), indicating a state of hypophosphatemic osteomalacia. According to these clinical courses and features, ADV was decreased from 10 mg every day to 10 mg every other day. Several laboratory parameters subsequently improved (Fig. 3). Of particular interest, her urinary β2MG levels rapidly and constantly fell over the patient’s course after ADV dose reduction (Fig. 3). In contrast, urinary NAG levels showed paradoxical changes, and serum creatinine and phosphate levels and fractional excretion of phosphate only modestly improved after ADV dose reduction. The patient has continued to receive add-on ADV therapy every other day, and to date there has been no increase in the serum AST, ALT, or ALP levels, and HBV-DNA also remains undetected.

**Discussion**

In this report, we presented a clinical picture of Fanconi’s syndrome observed in a 66-year-old Japanese woman with chronic hepatitis B infection who had received an add-on ADV therapy for 6 years. She exhibited no sign of bone

| Table 1. Laboratory Data of the Present Patient upon Referral to Our Hospital. |
|---------------------------------|-----------------|-----------------|
| Urinalysis                      | Biochemistry    | Immunology      |
| Protein (+)                     | Na 144 mEq/L    | CRP <0.1 mg/dL |
| Glucose (-)                     | K 3.7 mEq/L     | IgG 972 mg/dL   |
| Occult blood (+)                | Cl 114 mEq/L    | IgM 66.4 mg/dL  |
| β2MG 83,837 μg/L (Normal <230 μg/L) | TP 6.6 g/dL | IgA 106 mg/dL   |
| NAG 14.1 U/L (Normal 0.5-5.0 U/L) | Alb 4.0 g/dL  |                |
| Peripheral blood                |                 |                |
| WBC 4,800/mL                    | UA 1.9 mg/dL    | HbsAg >250     |
| RBC 4.49×10⁶/mL                 | Cr 0.88 mg/dL   | HbsAg N.D.     |
| Hb 15.2 g/dL                    | AST 18 IU/L     | HbcAb 12.7 S/CO|
| Plt 147×10³/mL                  | ALT 13 IU/L     | HbcAb 98.6 inhibition% |
| MCV 105.1                      | ALP 481 IU/L    | HBV-DNA <2.10  |
| MCHC 32.3                      | LD 197 IU/L     | Genotype C*    |
| FE (P)=46% (Normal range 10-20%) | T-cho 180 IU/dL | IU/L N.D.      |
| ALP isozymes                    |                 |                |
| ALP2 121 U/L (normal range 42-148 U/L) |          |
| ALP3 272 U/L (normal range 43-151 U/L) |          |
| ALP5 143 U/L (normal range 0-79 U/L) |          |

C*: hepatitis B virus genotype C, B2MG: β-2 microglobulin,
NAG: N-acetyl-β-D-glucosaminidase, FE (P): fractional excretion of phosphate
N.D.: not detectable, S/CO: sample/cut-off
Compared to other urinary and serum parameters related to renal injury and osteomalacia, the urinary β2MG levels were extremely high in this case. Furthermore, the urinary β2MG levels drastically fell after ADV dose reduction compared to other parameters. The urinary NAG level was paradoxically changed, and the serum creatine and phosphate levels and fractional excretion of phosphate were only modestly improved. According to these findings, measuring the urinary β2MG levels is suggested as one of the sensitive markers for monitoring the recovery of renal damage after reducing the ADV dose. It is of interest to confirm the usefulness of measuring urinary β2MG for monitoring renal damage during ADV treatment by large-scale prospective studies.

Drug-induced proximal tubular damage of the kidney may progress to Fanconi’s syndrome with decreased reabsorption of phosphate (10). This situation results in the development of hypophosphatemic osteomalacia (11). ADV is capable of provoking renal tubular damage (3) that might, in the end, result in serious complications such as multiple bone fractures. Therefore, sensitive and simple markers are required to predict the early stage of renal injury and prevent serious complications such as hypophosphatemia and bone fractures during ADV administration. β2MG is a 12 kDa protein produced throughout the body, filtered by the kidney glomerulus, and almost completely reabsorbed mainly in the renal proximal tubules (12). As a result, approximately only 0.3% of the filtered β2MG is found in the urine of healthy subjects (12). Therefore, the urinary levels of β2MG are recognized to be a damage index of the renal proximal tubules (12-14).

Although we suggest the use of urinary β2MG as a sensitive biomarker for monitoring the recovery of renal damage after reducing the ADV dose and that urinary β2MG could be a potential biomarker for ADV-induced nephrotoxicity, in a large majority of reports to date, urinary β2MG has only been measured at advanced stages of the disease. The major fractures when she was referred to our hospital, whereas in the majority of previous reports, an episode of bone fracture afforded the first clue for elucidating the adverse effects of ADV therapy (8). Notably, the patient already had osteomalacia associated with Fanconi’s syndrome, although she showed only moderate hypophosphatemia and slightly elevated serum levels of ALP and creatinine, which were not necessarily easy to attend to. In fact, ADV-induced osteomalacia is reported to be typically diagnosed by the incidence of bone fractures (8, 9); thus the present case is extremely rare in the sense that osteomalacia was found without any sign of bone fractures.

Figure 1. Magnetic resonance imaging (MRI) of the right ankle. (A) A T1-weighted image shows low-intensity areas in the talus (arrow) and calcaneus (arrowhead), indicating a pseudofracture. (B) A short T1 inverted recovery image reveals high-intensity areas in the talus (arrow) and calcaneus (arrowhead), indicating a pseudofracture or bone contusion.

Figure 2. Whole-body ⁹⁹ᵐTc-methylene diphosphonate bone scintigraphy showing an abnormal spotty uptake of the isotope in the 3rd right rib (arrow).
clinical manifestations and urinary β2MG levels of patients with Fanconi’s syndrome in previous reports are summarized in Table 2 (15-18). When we analyzed the patients described in Table 2, Fanconi’s syndrome was unfortunately diagnosed when the patients already complained of bone fracture-related symptoms and their urinary β2MG levels were extremely elevated. Jia et al. recently retrospectively analyzed Chinese patients with chronic hepatitis B infections and reported that urinary β2MG was elevated in the majority of the patients; however, they unfortunately did not perform a sub-analysis on the relationship between elevated urinary β2MG levels and potential renal injury (19).

In summary, we reported a case of ADV-induced osteomalacia in a patient with chronic HBV infection, which was shown prior to a clinical episode of bone fracture. In this case, the urinary β2MG levels sensitively and constantly fell after the reduction of the ADV dose, despite that finding that other parameters did not sensitively respond. According to these findings, we speculate that urinary β2MG is a potential candidate for sensitive clinical markers to monitor the recovery of renal damage after reduction of the ADV dose.

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

References
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