Hypophosphatemic Osteomalacia Due to Drug-induced Fanconi's Syndrome Associated with Adefovir Dipivoxil Treatment for Hepatitis B

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Abstract

We herein present the case of a 58-year-old Japanese man with Fanconi's syndrome with a 13-month history of bone pain in his ribs, hips, knees and ankles. He had been receiving low-dose adefovir dipivoxil (ADV) for the treatment of lamivudine-resistant chronic hepatitis B virus infection for eight years and subsequently developed severe hypophosphatemia and proximal renal tubule dysfunction. Magnetic resonance imaging showed multiple insufficiency fractures in the ribs, ileum, tibia and calcaneus. Whole-body bone scintigraphy demonstrated increased uptake in those areas. Following dose reduction of ADV and the administration of treatment with calcitriol and phosphates, the patient's serum phosphate level increased and his clinical symptoms improved. Physicians prescribing ADV should carefully monitor the renal function and serum phosphate level.

Key words: hypophosphatemia, osteomalacia, Fanconi's syndrome, adefovir dipivoxil, hepatitis B virus

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Introduction

Adefovir dipivoxil (ADV) is a commonly used antiviral agent in the treatment of chronic hepatitis B virus (HBV) or human immunodeficiency virus (HIV) infection. Although high-dose ADV therapy (60-120 mg/day) is nephrotoxic (1), low-dose ADV therapy (10 mg/day) has been reported to be safe (2-7). However, there is an increasing number of reports stating that the long-term use of low-dose ADV causes proximal renal tubular dysfunction, a feature of Fanconi's syndrome, especially in East Asian populations (8-24). We herein report a case of severe hypophosphatemic osteomalacia with Fanconi's syndrome caused by low-dose ADV for the treatment of chronic hepatitis B virus infection.

Case Report

A 58-year-old man was referred to our clinic in January

2011 with a 13-month history of progressive generalized bone pain involving the bilateral rib cage, hips, knees and heels. The patient had been diagnosed with chronic active hepatitis B in 1992. He was positive for both the HBs and HBe antigens but negative HBe for antibodies. The level of HBV-DNA (TMA) was 7.7 LGE/mL. Both the serum alanine aminotransferase (ALT) (106 U/L; normal range <30 U/L) and alpha-fetoprotein (651 ng/mL; normal range <8.7 ng/mL) levels were elevated. The patient was started on lamivudine (100 mg daily) therapy in February 2001. In September 2003, he developed lamivudine resistance; therefore, the lamivudine therapy was switched to ADV (10 mg daily) therapy. From September 2006 to November 2010, lamivudine was added to the ADV regimen. In December 2009, the patient developed pain in his heels and ankles. In January 2011, he came to our clinic with progressive generalized bone pain involving the bilateral rib cage, hips, knees, ankles and heels. He had a family history of HBV carriers (all brothers and sisters), HBV-related cirrhosis (mother) and

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Figure 1. Whole-body ^{99m}Tc -methylene diphosphonate bone scintigraphy and magnetic resonance imaging (MRI). (A) The initial bone scan showed significant abnormal isotope uptake (arrows) in multiple ribs and the right ileum, left ankle and left heel. (B) A follow-up scan obtained six months after the reduction of adefovir, showed partial resolution of the abnormal isotope uptake. (C) MRI revealed insufficiency fractures (arrows) in the left distal tibia and left calcaneus. T1-weighted image shows low-intensity insufficiency fractures. (D) Short TI inversion recovery image shows high-intensity bone edema.

hepatocellular carcinoma (older sister).

The patient was 56.0 kg in weight and 161.6 cm in height and had a body mass index of 21.4 kg/m². His heart rate was 78 bpm and his blood pressure was 128/74 mmHg. On a physical examination, he had generalized bone tenderness, especially in the regions mentioned above. No strumas were palpable. There were no specific signs in the respiratory, digestive or circulatory systems. There was no edema in the patient's legs. The laboratory data revealed hypophosphatemia (1.39 mg/dL; normal range 2.5-4.5 mg/dL), hypouricemia (2.82 mg/dL; normal range 3.60-7.00 mg/dL) and increased levels of alkaline phosphatase (ALP, 921 U/L; normal range 115-359 U/L) and bone alkaline phosphatase (BAP, 76.1 U/L; normal range 3.7-20.9 $\mu\text{g/L}$). The serum creatinine level was normal (1.06 mg/dL; normal range 0.6-1.10 mg/dL). However, it gradually increased up to 1.23 mg/dL. The serum calcium (9.62 mg/dL), intact parathyroid hormone (PTH, 26 pg/mL; normal range 10-65 mg/dL) and 1,25 dihydroxyvitamin D (46.4 pg/mL; normal range 20.0-60.0 pg/mL; 1,25-hydroxyvitamin D RIA kit 'TFB'; Immunodiagnostic Systems Ltd., Boldon, UK) levels were all within the normal range. The serum fibroblast growth factor 23 level was low (3.8 pg/mL; normal range 10-50 pg/mL; FGF23 ELISA kit; Kainos Laboratories, Inc., Tokyo, Japan) (25). The serum FT₃ level was 3.0 pg/mL (1.9-3.5 pg/mL) and the FT₄ level was 0.90 (0.88-1.56 ng/dL), both within the normal range; however, the TSH (5.67 $\mu\text{U/mL}$; normal range 0.210-3.850 $\mu\text{U/mL}$) level was slightly ele-

vated. Anti-thyroid peroxidase (TPO) antibodies were positive (353.3 IU/mL; normal range <5.0 IU/mL). There was no metabolic acidosis. The patient's blood HCO₃⁻ was 22.7 mEq/L. A urinalysis showed proteinuria (100 mg/dL), glucosuria (250 mg/dL) and general aminoaciduria. These findings suggested that the patient had Fanconi's syndrome and chronic thyroiditis. Magnetic resonance imaging (MRI) revealed multiple insufficiency fractures in the bilateral ribs, ileum, right femur, left distal tibia and left calcaneus. ^{99m}Tc -hydroxymethylene diphosphonate (HMDP) scintigraphy demonstrated significant abnormal uptake in the ribs, left shoulder, pelvis, right knee and left ankle and heel (Fig. 1). We diagnosed the patient with osteomalacia due to Fanconi's syndrome secondary to ADV therapy for chronic hepatitis B and chronic thyroiditis. Following the reduction of the dose of ADV from 10 mg every day to every other day with supplementation with alfacalcidol (4 $\mu\text{g/day}$) and phosphate (1.5 g/day), the patient's serum phosphate and creatinine levels normalized, and both the glycosuria and proteinuria resolved (Fig. 2). Clinical symptoms, such as bone pain, also disappeared.

Discussion

ADV, a nucleotide analog widely used in the management of patients with chronic hepatitis B, can be nephrotoxic, even at low doses. ADV-induced nephrotoxicity is dose-dependent. The incidence of an increase in the level of cre-

Figure 2. Clinical course. LAV: lamivudine, ADV: adefovir, ALT: alanine aminotransferase, Cr: creatinine, P: phosphate, HBeAg: hepatitis B e antigen, FT₃: free triiodothyronine, FT₄: free thyroxine

atinine of greater than 0.5 mg/mL from baseline is 35% at 48 weeks and 50% at 72 weeks in patients receiving 120 mg/day of ADV (1). Hypophosphatemia occurs in 50% of patients after 48 weeks and 61% of patients after 72 weeks of ADV treatment (1). Among patients treated with 30 mg of ADV, 21% exhibit an increase in creatinine of more than 0.5 mg/dL from baseline by week 48, while 16% are hypophosphatemic (6). Conversely, a 10-mg/day dose of ADV is generally well tolerated, with no increases in adverse events or laboratory abnormalities compared with a placebo, as reported in two registered trials (2, 3). In subsequent studies, the incidence of an increase in serum creatinine of 0.5 mg/dL or more has been reported to occur in 2-8% of patients on long-term ADV therapy (4-7, 26-29). However, this is not the case in the Japanese population. Tamori et al. (10) reported that the serum creatinine levels increased in 14 (38%) of 37 patients, while the serum phosphate levels decreased to below 2.5 mg/mL in six (16%) of 37 patients during therapy. More recently, Tanaka et al. (20) reported that, among 292 patients, 28 (9.6%) developed renal impairment [defined as an estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73 m²] and 14 (5.2%) developed persistent hypophosphatemia, suggesting that the Japanese may be more susceptible to renal tubular toxicity. Further studies are required to clarify this issue.

There is an increasing number of case reports from East Asian countries that show that even patients on low-dose ADV exhibit nephrotoxicity (Table). The ages of these patients varied from 22 to 74 years, with a median of 56 years. The male/female ratio was 4.5. Symptoms became clinically evident after a median of 36 months (range 6-71

months). Muscle weakness and generalized bone pain were the major symptoms. Following discontinuation or reduction of the dose of ADV, the serum phosphate levels and clinical symptoms improved in almost all cases, suggesting that ADV-induced nephrotoxicity is reversible.

ADV-induced nephrotoxicity is characterized by a decrease in the level of phosphate and a slight increase in the level of creatinine, resulting in renal proximal tubular dysfunction, the features of Fanconi's syndrome (30). Although the mechanisms underlying the development of ADV-induced nephrotoxicity are not fully understood, ADV may cause apoptosis or mitochondrial toxicity of the renal tubular epithelium (31). The human organic anion transporter-1 (hOAT1), a basolateral membrane protein of the proximal tubule, mediates the active uptake of ADV from the blood into proximal tubular cells (32). ADV is secreted into the urine by multidrug resistance proteins (MRPs) 2, 4 and 5, which are located on the apical side of proximal tubular cells (33). The overexpression of hOAT1 or underexpression of MRPs, therefore, may result in the accumulation of ADV in the renal tubules and subsequent tubular toxicity. Genetic polymorphisms, which affect the expression of these proteins, may contribute to ADV-induced nephrotoxicity (34, 35).

In conclusion, we herein reported a case of severe hypophosphatemic osteomalacia with Fanconi's syndrome caused by the long-term use of low-dose ADV for the treatment of chronic hepatitis B. There is an increasing number of similar reports from East Asian countries, suggesting that ethnic factors or an increased number of patients with persistent HBV infection in these areas may influence the development

Table. Clinical Characteristics of the 22 Patients with Hypophosphatemic Osteomalacia Induced by Low-dose Adefovir Therapy for Chronic Hepatitis B

Reference	Ethnicity	Sex	Age (yr)	Duration of ADV use to		Baseline serum			Follow-up serum		Treatment strategies	Prognosis
				onset symptoms (months)	find hypo-phosphatemia (months)	phosphate (mg/dL)	creatinine (mg/dL)	ALP (IU/L) (normal range)	phosphate (mg/dL)	creatinine (mg/dL)		
8	Korean	M	42	6	18	1.2	1	1722 (80-270)	2.2	NA	ADV cessation, phosphate supplementation	improved
9	Unspecified	M	58	8	8	0.93	1.86	NA	NA	NA	ADV cessation	worsened creatinine clearance
10	Japanese	F	57	9	14	1.9	0.88	800 (30-397)	3.5	NA	ADV reduction, phosphate supplementation	improved
11	Japanese	M	48	20	50	1.4	1.1	3410 (116-280)	3	1.3	ADV reduction, phosphate supplementation	improved
12	Korean	M	66	36	36	1.7	1.2	157 (NA)	2	NA	Phosphate supplementation	improved
13	Korean	M	47	32	38	1.3	1.35	321 (38-126)	2.4	0.92	ADV cessation, phosphate supplementation	improved
14	Japanese	F	70	12	30	1.5	0.95	1977 (115-359)	Normal (data NA)	NA	Switched with entecavir, alphacalcidol	improved
14	Japanese	M	60	36	18	1.7	1.34	864 (115-359)	Normal (data NA)	NA	Phosphate supplementation, alphacalcidol	improved
15	Japanese	M	48	36	36	2	1.6	1314 (NA)	2.3	NA	ADV reduction (30mg/week), calcitriol	improved
16	Chinese Cambodian	M	40	22	27	2.0	NA	271 (NA)	2.98	NA	ADV cessation, phosphate, calcium, vitamin D3 supplementation	improved
16	Chinese Cambodian	F	53	58	64	1.53	NA	NA	2.98	NA	ADV cessation, phosphate, calcitriol	improved
17	Chinese	F	74	48	48	1.52	0.91	698 (43-141)	Normal (data NA)	NA	Switched with entecavir, calcitriol, phosphate supplementation	improved
18	Chinese	M	22	38	48	1.15	NA	492 (NA)	NA	NA	ADV cessation, phosphate supplementation	NA
19	Unspecified	M	68	20	38	2.23	1.5	443 (NA)	NA	NA	Switched with entecavir, phosphate, cholecalciferol	improved
20	Japanese	M	62	47	60	2	0.7	1594 (115-359)	Normal (data NA)	NA	Switched with entecavir, eldecalcitol	improved
21	Korean	M	62	36	60	2.2	1.49	328 (53-128)	1.8	NA	Phosphate, calcitriol	improved
21	Korean	M	54	41	59	1.0	1.12	432 (53-128)	NA	NA	Switched with entecavir	improved
22	Chinese	M	NA	>36	>36	1.98	0.98	420 (40-150)	3.53	NA	Switched with entecavir, calcitriol	improved
22	Chinese	M	NA	>36	>36	1.15	1.1	317 (40-150)	2.54	NA	Switched with entecavir, calcitriol	improved
23	Japanese	M	56	NA	48	NA	2.23	674 (104-338)	NA	1.5	ADV reduction	improved
24	Chinese	M	48	54	68	1.1	1.03	297 (40-150)	0.78	1.07	ADV cessation	improved
present case	Japanese	M	58	71	88	1.39	1.06	921 (115-359)	3.11	1.06	ADV reduction, phosphate, alfacalcidol	improved

M: male, F: female, NA: not available, ADV: adefovir, ALP: alkaline phosphatase

of this side effect. Following the cessation or dose reduction of ADV and the administration of treatment with alfacalcidol and phosphates, the serum phosphate level increased and the patient's clinical symptoms improved. Physicians prescribing ADV should be aware of the late onset of this complication and should carefully monitor the renal function and serum phosphate level.

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

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