CASE REPORT

Development of osteomalacia in a post-liver transplant patient receiving adefovir dipivoxil

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Abstract

We report the case of a patient treated with living donor-related liver transplantation who suffered from osteomalacia during adefovir dipivoxil (ADV)-containing antiviral therapy for lamivudine-resistant hepatitis B virus infection. The patient had generalized bone pain, with severe hypophosphatemia after 20 mo of ADV therapy. Radiographic studies demonstrated the presence of osteomalacia. The peak plasma ADV level was 38 ng/mL after administration of ADV at 10mg/day. It was also found that ADV affected the metabolism of tacrolimus, a calcineurin-inhibitor, and caused an increase in the plasma levels of tacrolimus. The disability was reversed with the withdrawal of ADV and with mineral supplementation. ADV can cause an elevation of plasma tacrolimus levels, which may be associated with renal dysfunction. High levels of ADV and tacrolimus can cause nephrotoxicity and osteomalacia. This case highlights the importance of considering a diagnosis of osteomalacia in liver transplantation recipients treated with both ADV and tacrolimus.

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INTRODUCTION

In hepatitis B virus (HBV) DNA-positive patients, the rate of HBV recurrence after liver transplantation (LT) remains high without prophylaxis using hepatitis B immunoglobulins (HBIG) and lamivudine (LAM)[1-3]. Resistance to LAM is characterized by the substitution of methionine with valine or isoleucine at residue 204 within the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the viral DNA polymerase[4-5]. Adefovir dipivoxil (ADV) is a potent nucleotide analogue against both the wild-type and LAM-resistant HBV[6-7], and it has been reported that ADV can prevent and treat recurrences of HBV infection following LT[8-10].

Hypophosphatemic osteomalacia results from a ge-

Table 1 Laboratory data on admission

Blood chemistry		Arterial blood gas		Urinary chemistry	
Total protein	6.3 g/dL	pH	7.375	Urinary Na	0.78 g/d
Albumin	3.9 g/dL	PaO2	86.8 mmHg	Urinary K	0.20 g/d
AST	39 IU/L	PaCO2	37.1 mmHg	Urinary Cl	0.67 g/d
ALT	22 IU/L	HCO3-	21.2 mmol/L	Urinary Ca	0.14 g/d
ALP	3410 IU/L	Anion gap	11.3 mmol/L	Uurinary phosphate	0.43 g/d
γ-GTP	116 IU/L	Base excess	- 3.0 mmol/L	% TRP	53.7 %
Total bilirubin	0.6 mg/dL			Urinary creatinine	0.45 g/d
Direct bilirubin	0.2 mg/dL			Ccreatinine clearance	37.9 mL/min
Urea nitrogen	36 mg/dL			Uurinary glucose	2.57 g/d
Creatinine	1.1 mg/dL			Urinary protein	1.44 g/d
Uric acid	1.7 mg/dL			Urinary NAG	49.0 U/L
Plasma glucose	90 mg/dL			Urinary BMG	129, 220 μg/L
Na	142 mEq/L			Generalized aminoaciduria	(+)
K	3.5 mEq/L				
Cl	113 mEq/L				
Ca	8.0 mg/dL				
P	1.4 mg/dL				
Mg	2.1 mg/dL				
Prothrombin time (INR)	0.96				
Serum BMG	3.5 mg/L				
Bone-type ALP	551 μg/L				
Intact-PTH	85 pg/mL				
1, 25-dihydroxy vitamin D3	21.3 pg/mL				

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; γ-GTP: γ-glutamyl transferase; P: phosphate; BMG: β2-microglobulin; %TRP: % tublar reabsorption of phosphate; NAG: N-acetyl-β-D-glucosaminidase; Intact-PTH: intact parathyroid hormone.

neralized dysfunction of the proximal renal tubule, leading to impaired reabsorption of amino acids, glucose, urate, and phosphate[11]. The chronic loss of phosphate and the adequate synthesis of 1, 25-dihydroxy vitamin D3 together produce phosphate depletion and failure to properly mineralize bone. Recently, patients with acquired osteomalacia have been reported during treatment of human immunodeficiency virus (HIV) infection using nucleotide analogues such as tenofovir and ADV[12-16]. We report herein a case of osteomalacia that developed during ADV therapy after living donor-related liver transplantation (LDLT).

CASE REPORT

A 48-year-old Japanese man was diagnosed with HBV-related decompensated liver cirrhosis in January 2000 and began undergoing LAM therapy at 100 mg/d. The serum HBs antigen (HBsAg) and HBe antigen (HBeAg) were positive, anti-HBe antibody was negative, and HBV-DNA was detected at 8.0 log genome equivalent (LGE)/mL by transcription-mediated amplification (TMA) before the treatment with LAM. Three months later, his serum HBV-DNA decreased to < 3.7 LGE/mL with a favorable initial response. The response persisted up to February 2001, at which time LAM-resistant mutants (YIDD) emerged with elevated transaminases [alanine aminotransferase (ALT) 374 IU/L (normal; 7-47 IU/L) and aspartate aminotransferase (AST) 444 IU/L (normal; 12-31 IU/L)]. In March 2002, the patient was started on ADV therapy at 10 mg/d combined with LAM, and the antiviral response was progressive, but slow. Although the HBV-DNA was decreased to 4.0 LGE/mL after 2 mo, liver function was not favorably improved. In accordance with our hospital policy, the patient could then be accepted as a liver transplant recipient. His wife volunteered to undergo right hepatectomy for living donation, and he underwent LDLT in May 2002. Serum HBsAg and HBV-DNA were negative, but anti-HBc antibody was positive in the donor. The anti-HBV prophylactic regimen consisted of an intravenous injection of HBIG and peroral administration of LAM (100 mg/d) plus ADV (10 mg/d). Intravenous HBIG was given at a dose of 10 000 IU during the anhepatic phase, and then daily for 6 d. Repeated doses were given to maintain anti-HBs titers above 500 IU/L for the initial 6 mo. The patient remained well with a combination of LAM, ADV, and periodic doses of HBIG injection to maintain anti-HBs greater than 200 IU/L. Anti-HBsAb was always positive, and HBsAg and HBV-DNA were not detected in his serum during observation.

Postoperative immunosuppression consisted of tacrolimus (target trough level 10-15 ng/mL) and steroids (intravenous methylprednisolone 500 mg/d tapered to oral prednisolone 20 mg/d from day 7). The tacrolimus trough level was lowered to 5 to 10 ng/mL, and the dosage of prednisolone was reduced to 2.5 mg/d during the 6th mo after transplantation.

The patient began to complain of right ankle pain in November 2003. His bone pain gradually increased and involved his knees and shoulders. He also began to experience weakness in his leg muscles, with difficulty in walking in July 2004. A neurological evaluation, an electromyogram (EMG), and a muscle biopsy were performed in February 2005, which revealed almost normal

Ant   Post
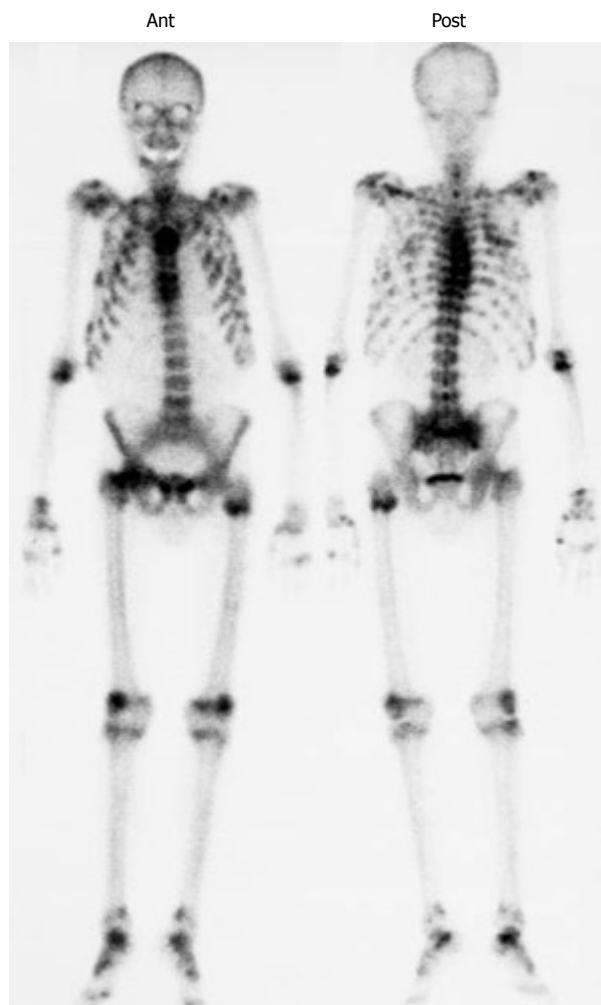
Figure 1 Whole body bone scintigraphy shows multiple foci of increased radiotracer uptake in the thoracic spine, the sacroiliac region, the rib cage, the shoulders, the knees, and the ankles.

muscular fibers. He was admitted for further examination in May 2006. The laboratory data obtained on admission are shown in Table 1. He demonstrated persistent hypophosphatemia with a phosphate level of 1.4 mg/dL (normal range; 2.4-5.1 mg/dL). In addition, he showed significantly elevated levels (3410 IU/L) of alkaline phosphatase (ALP) (normal range; 116-280 IU/L). His serum creatinine level was 1.1 mg/dL and calculated creatinine clearance was 37.9 mL/min, indicating moderate renal insufficiency. Urinalysis and 24-h urine collection confirmed phosphate wasting, which can be caused by impairment of proximal renal tubular reabsorption of phosphate. Although his serum level of intact parathyroid hormone (intact-PTH) was slightly increased, his serum level of 1, 25-dihydroxy vitamin D3 was 21.3 pg/mL (normal range; 20-60 pg/mL). Indications were that the impairment of reabsorption of phosphate could be mainly brought about by the proximal renal tubular injury, and not by vitamin D deficiency, in this patient.

Radiographic studies including X-rays, MRI, and bone scans were performed. ^{99m}Tc-HMDP whole-body bone scintigraphy showed multiple foci of increased radiotracer uptake in the thoracic spine, the sacroiliac region, the

rib cage, the shoulders, the knees, and the ankles (Figure 1). X-rays and MRI findings showed pseudofractures (Looser's zones) in the right femoris, which could indicate osteomalacia.

The highest plasma level of ADV in the patient was 38 ng/mL, after administration of ADV at 10mg/day, which was approximately 3 times higher than that in patients with normal renal function. We also found that ADV contributed to the elevation of plasma tacrolimus levels in this patient, as the trough levels of tacrolimus with administration of ADV were 1.5 times higher than those without ADV. These results suggest that ADV could affect the metabolism of tacrolimus, and cause increases in the plasma levels of tacrolimus. In this context, high levels of both ADV and tacrolimus could contribute to nephrotoxicity and hypophosphatemia.

The patient was initially treated with phosphate supplementation and decreasing doses of ADV (10 mg/every other day → 5mg/every other day → 2.5mg/every day). After switching from ADV plus LAM to entecavir hydrate (ETV) at 1 mg/every other day, several laboratory parameters improved, including serum levels of phosphorus and ALP. He was maintained on phosphate replacement, and his bone pain also decreased dramatically (Figure 2).

DISCUSSION

We report herein a case with renal tubular injury, hypophosphatemia, and osteomalacia all of which developed during ADV therapy after LDLT. ADV is known to cause renal tubulopathy in patients with HIV or HBV infection[13-14], as is tenofovir, a major antiretroviral medication[15-16]. The pathophysiology of the proximal tubular dysfunction caused by ADV is thought to be due to the concentration of ADV in the mitochondria[17], and, consequently, mitochondrial toxicity and the inhibition of several ATP-dependent critical transporters in proximal tubular cells[18]. Although every-other-day administration of ADV (10 mg/2 d) is generally recommended when a patient has moderate levels of renal dysfunction, we recommend complete cessation of ADV treatment and a change to another antiviral reagent such as ETV[19-20], as the continued every-other-day administration of ADV may continue to injure the proximal tubular cells. It is unclear why, if all patients accumulate ADV in the proximal tubule, that only a small percentage of patients experience the renal complications seen in this case.

Tacrolimus is a calcineurin-inhibitor (CNI), which are immunosuppressive agents for liver transplantation[21]. Renal dysfunction is common after liver transplantation[22-25], and it has been reported to be associated with high levels of CNI[26]. ADV contributed to the elevation of plasma tacrolimus levels in this patient, and this elevation may have been associated with his renal dysfunction. In cases such as this one, tacrolimus levels should be reduced as far as possible and the interaction between tacrolimus and ADV should be given strong consideration in liver-transplant patients with HBV infection.

Although the patient had typical clinical features such as bone pain, hypophosphatemia, and elevated serum
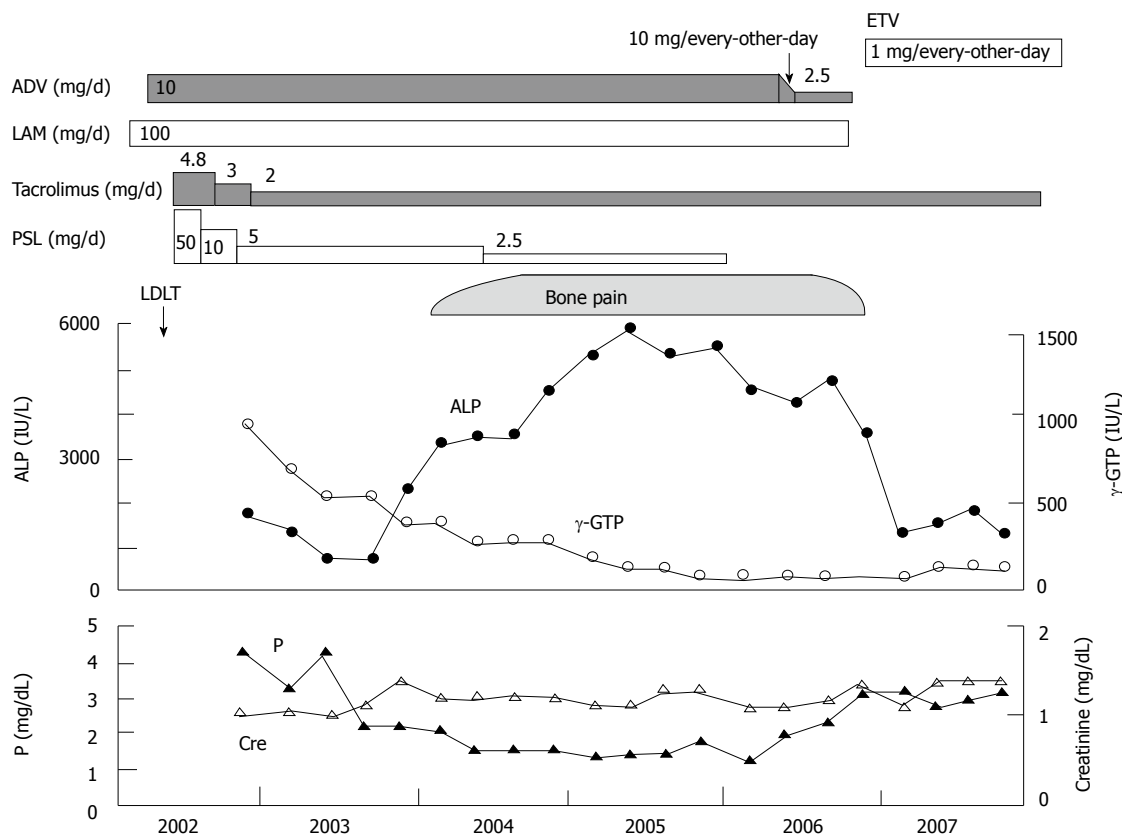
Figure 2 Clinical course of the present case. After switching from ADV plus LAM to ETV, serum levels of P and ALP improved, and the patient's bone pain also decreased dramatically. ADV: adefovir dipivoxil; LAM: lamivudine; ETV: entecavir hydrate; PSL: prednisolone; P: phosphate; APL: alkaline phosphatase; γ-GTP: γ-glutamyl transferase; LDLT: living donor-related liver transplantation.

APL levels for osteomalacia, the diagnosis of osteomalacia was delayed. It was initially difficult to distinguish bone-derived ALP and liver-derived ALP because the patient had persistently high levels of serum ALP and γ-glutamyl transferase (γ-GTP) associated with chronic rejection after LDLT.

Hypophosphatemic osteomalacia is a potential adverse effect of ADV[13], and patients treated with ADV should be monitored by measuring serum ALP and phosphorus levels. If patients develop bone pain or myopathy in response to ADV treatment, serum hypophosphatemia and phosphate wasting into urine should be confirmed. Initial treatment with phosphate supplementation and decreasing doses of ADV should be performed. Discontinuing administration of ADV and switching to ETV may be recommended for patients after LT, because these patients often have renal insufficiency associated with the use of CNI.

ACKNOWLEDGEMENTS

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