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Case Report

Hypophosphatemic osteomalacia with pathological fractures during tenofovir therapy in a chronic hepatitis B patient: a case report and literature review

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Abstract: Tenofovir is widely used in treatment regimens for human immunodeficiency virus (HIV) and chronic hepatitis B virus infection. Its use has been associated with Fanconi syndrome and hypophosphatemic osteomalacia in patients with HIV infection. However, renal and bone toxicity in patients with chronic hepatitis B (CHB) are not as prominent as in HIV infection. We report a case of osteomalacia and fractures induced by tenofovir for CHB treatment. A 31-year-old man was admitted to our hospital because of severe chest pain and hypophosphatemia. He had CHB and had been treated with adefovir at a daily dose of 10 mg for 10 years. He was switched to tenofovir because of proteinuria 6 months ago. Laboratory and radiological findings suggested a diagnosis of Fanconi syndrome with osteomalacia and multiple fractures. His bone pain and hypophosphatemia were improved after the cessation of tenofovir. Patients taking tenofovir should receive routine monitoring of serum creatinine and phosphate levels, especially in patients with pre-existing renal disease, thus preventing osteomalacia or fractures.

Keywords: Hypophosphatemic osteomalacia, fracture, tenofovir, Fanconi syndrome, chronic hepatitis B

Introduction

The current preferred approach to the therapy of chronic hepatitis B (CHB) is long-term use of antiviral medications. Prolonged therapy with the nucleotide analogues adefovir and tenofovir, however, is associated with renal toxicity [1]. This renal injury resembles Fanconi syndrome and presents with variable degrees of proximal renal tubular dysfunction, including hypophosphatemia, hypouricemia, aminoaciduria and glucosuria, resulting in bone mineralization defects, osteomalacia, and fractures [2]. Nephrotoxicity appears to be less common with tenofovir than adefovir treatment, despite their similar molecular structure. Proximal renal tubule abnormalities and osteomalacia can occur during long-term tenofovir treatment in patients with HIV [3, 4]. However, in ongoing registration studies of tenofovir for chronic hepatitis B, renal toxicity has been rare [5]. Tenofovir-related bone fractures have never been reported in patients with HBV monoinfection [6]. Here, we reported a case of Fanconi syndrome, hypophosphatemia osteomalacia and pathological fractures induced by tenofovir therapy in a patient with CHB monoinfection. All cases previously reported in the literature and possible mechanisms of nephrotoxicity were also reviewed.

Case report

A 31-year-old man visited the hospital for evaluation of severe chest pain. He had been well until 3 months ago when he developed right-side chest pain after sneezing and physical activity. He denied any fever, cough, chest distress or shortness of breath at that time. He went to the local hospital and the examinations were unremarkable except “trace proteinuria”. Approximately 1 week before this admission, chest pain exacerbated and involved bilateral chest wall. He also complained of severe back pain as well as the hip joint and heel pain. The pain was initially dull and tingling but worsened during physical activity, and it had gotten worse to the point that he could not stand and walk as

Table 1. Laboratory data

Variables	Reference Range, Adults	At admission	At discharge (1 week after admission)	Follow up (3 months after admission)
Potassium (mmol/L)	3.50-5.50	3.39	3.92	Normal (data NA)
Phosphate (mmol/L)	0.81-1.45	0.30	0.54	0.77
Calcium (mmol/L)	2.20-2.65	2.13	2.14	Normal (data NA)
ALP (U/L)	30-120	473	328	NA
25-OH-VITD (ug/L)	20.0-50.0	20.3	NA	NA
PTH (pg/mL)	15.00-65.00	12.32	13.47	NA
Creatinine (μmol/L)	40-106	104.4	89.0	Normal (data NA)
eGFR (ml/min)		69.95	111.24	NA
Urea acid	208-428	158	NA	NA
FPG (mmol/L)	3.89-6.11	5.07	NA	NA
HbA1c (%)	4.3-6.3	5.1	NA	NA
ABG PH	7.350-7.450	7.337	NA	NA
ABG HCO3+ (mmol/L)	22.0-26.0	21.6	NA	NA
Urine Protein	Negative	1+	Negative	NA
Urine Glucose	Negative	4+	2+	NA
24-hour urine potassium (mmol)		78.7	NA	NA
24-hour urine phosphate (mmol)		41.6	NA	NA
HBV-DNA (copies/ml)	<1000	<1000	NA	NA
ALT (U/L)	<45	42	35	Normal (data NA)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; 25-OH-VITD = 25-OH vitamin D; PTH = parathyroid hormone; ABG = Arterial blood gas; FPG = Fasting plasma glucose; NA = not available.

usual. The patient went to our clinic and the laboratory test revealed severe hypophosphatemia with phosphate 0.30 mmol/L. Multiple ribs and vertebral fractures were confirmed by computed tomography.

Past medical history was significant for CHB of 10 years' duration with normal liver function test results prior to and at admission. He had been treated with adefovir at a daily dose of 10 mg for 10 years. He was switched to tenofovir (300 mg per day) because of proteinuria 6 months ago. Other medications received included spironolactone, irbesartan, and pentoxifylline for proteinuria. The social history and family history was unremarkable.

On examination, the blood pressure was 94/58 mmHg, the pulse was 70 beats per minute, the weight was 50 kg and the height was 170 cm. He had tenderness over the chest wall, lumbar spine area, hip, bilateral knee and heel joints. The patient denied any paresthesias, muscle cramps, or weakness. The remainder of the examination was normal.

He demonstrated persistent hypophosphatemia with a phosphate level in the 0.30-0.54 mmol/L range. In addition, he had a significantly elevated level of alkaline phosphatase (ALP) activity of 473 U/liter, low potassium, normal calcium, low vitamin D, and low parathyroid hormone (PTH). Arterial blood gas (ABG) analysis showed a low PH and low bicarbonate, suggestive of metabolic acidosis. He had a baseline creatinine level of 104.4 μmol/L and an estimated GFR of 70.0 ml/min by the MDRD formula. Urinalysis and 24-h urine collections confirmed normoglycemic glucosuria, proteinuria, phosphate and potassium wasting. Serum HBV DNA level was undetectable (<1000 copies/mL) and HBeAg was negative at admission. Laboratory values at presentation and during follow up were summarized in **Table 1**.

Whole body 99mTc-methylene diphosphonate (99mTc-MDP) bone scintigraphy showed an increased uptake in the bilateral upper extremities, bilateral ribs, lumbar and thoracic spine, right sacroiliac region, left knee, and bilateral heel joints, consistent with metabolic osteopathy and stress fractures (**Figure 1**). Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DEXA) revealed severe decreases at the lumbar spine and hip (T score

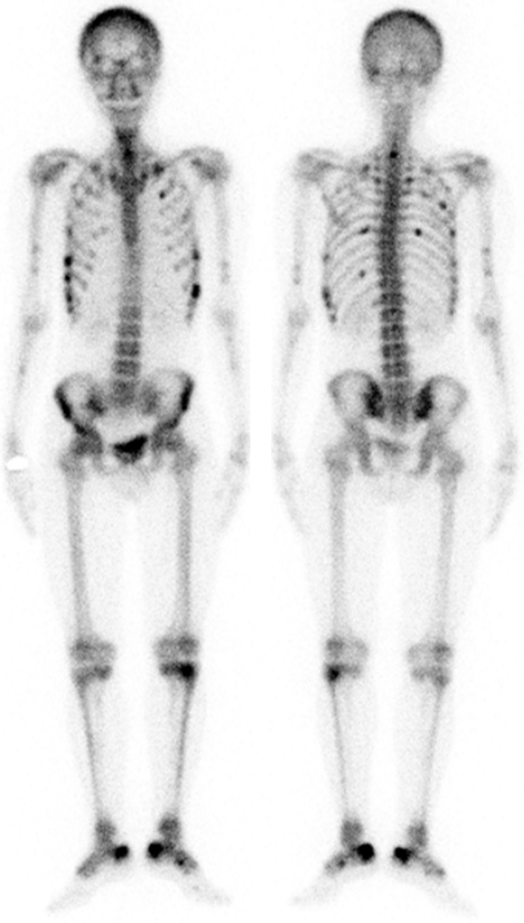

Figure 1. Bone scintigraphy shows increased uptake in the bilateral upper extremities, bilateral ribs, lumbar and thoracic spine, right sacroiliac region, left knee and bilateral heel joints, consistent with metabolic osteopathy and stress fractures.

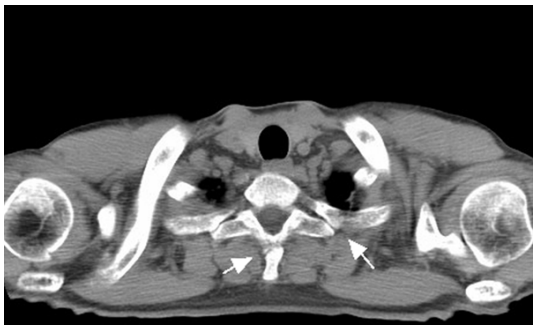

Figure 2. Chest computed tomography shows fracture deformities of T1 and the left rib (arrow).

-3.4 and -3.3 respectively). The chest computed tomography revealed fracture deformities of T1 and multiple ribs (**Figure 2**).

He was asked to discontinue tenofovir and was treated with neutral phosphate, potassium, calcium, and calcitriol supplementation. After discontinuation of tenofovir, several laboratory parameters improved, including phosphate, potassium, and creatinine. He was maintained on phosphate replacement after the discharge from the hospital. His bone pain and gait disturbances improved 3 months after cessation of tenofovir.

Discussion

Many published reports have shown that long-term therapy with adefovir or tenofovir for CHB infection can be associated with Fanconi syndrome resulting in hypophosphatemic osteomalacia [7-13]. Adefovir at a dose of more than 30 mg daily could be associated with renal dysfunction [5]. In contrast, tenofovir in a dose of 300 mg daily is rarely associated with this toxicity. Most reported cases of tenofovir-associated nephropathy were observed in HIV patients [4]. Tenofovir remains safe and well tolerated for CHB infection [5]. Literature review revealed only 6 other cases of Fanconi syndrome induced by tenofovir for CHB monoinfection (as showed in **Table 2**) [8, 14-16]. Renal dysfunction became clinically evident after a median 2.9 years (range 0.8-4.0 years) of tenofovir treatment. The reported serum phosphate at diagnosis ranged from 0.5 to 0.73 mmol/L. Two patients were diagnosed as having osteomalacia, however, no patient had pathological fractures. After discontinuation of tenofovir, serum phosphate level was increased and the features of proximal renal tubular dysfunction disappeared in all cases.

The risk factors for this complication and its frequency are only partially understood. A previous study of 51 CHB-infected patients who received either adefovir or tenofovir, revealed that risk factors of renal tubular dysfunction were age-dependent and pre-existing [8]. Five of seven patients with tenofovir-induced Fanconi syndrome, including our patient, had prior treatment with adefovir which may have predisposed to the development of renal tubular damage. Other risk factors include concomitant use of nephrotoxicity drugs, comorbidities such as diabetes and hypertension, and use of some protease inhibitors [17].

At least 3 mechanisms explain antiviral agent–induced renal injury: transporter defects, apoptosis, and mitochondrial injury [1]. Current evidence suggests that mitochondria damage play

Table 2. Clinical features of 7 patients with Fanconi syndrome induced by tenofovir for CHB monoinfection

Patient	Age	Sex	Race	Therapy	Years on therapy	P (mmol/L)	Cr (μmol/L)	eGFR (ml/min)	OM	Management	FU P (mg/dL)	FU Cr (mg/dL)	FU eGFR (ml/min)
1 (our patient)	31	Male	Asian	A→T	10.0(A)+0.6(T)	0.30	104	70	Yes	T cessation	0.77	89*	111*
2 [8]	62	Male	NA	T	3.9	0.73	158	41	No	T→E	1.0	133	65
3 [8]	66	Male	NA	A→T	4.0(A)+3.7(T)	0.67	149	43	No	T→E	0.9	155	54
4 [14]	39	Male	Asian	A→T	1.0(A)+4.0(T)	0.60	127	59	No	T→E	1.2	117	64
5 [14]	54	Male	Western	T	2.0	0.68	135	51	No	T→E	1.0	108	66
6 [15]	49	Female	NA	A→T	5.0(A)+1.0(T)	0.55	NA	NA	Yes	T cessation	Normal (data NA)	NA	NA
7 [16]	40	Female	Asian	A→T	10.0(A)+0.8(T)	0.5	63.6	95	Yes	T→E	Normal (data NA)	NA	NA

* = measured at discharge; A = adefovir; T = tenofovir; E = entecavir; P = phosphate; Cr = creatinine; OM = Osteomalacia; FU = follow-up; NA = not available.

an important role in tenofovir cytotoxicity [4, 18]. Proximal tubule mitochondrial injury is partly attributed to decreasing mitochondrial DNA replication through inhibition of mitochondrial DNA polymerase. A previous study revealed that tenofovir was related to minimal mtDNA depletion and nonsignificant reductions in the mitochondrial protein cytochrome c oxidase [18]. Tenofovir has also been considered a weaker inhibitor of mitochondrial DNA polymerase γ than adefovir and cidofovir [19]. However, it remains unclear that only a small percentage of patients experience the renal complications with tenofovir exposure. One possibility is that patients with underlying mitochondrial DNA mutations or polymorphisms are more susceptible to tenofovir-induced mitochondrial toxicity. Secretory transporters, such as organic anion transporter (OAT) and multidrug resistance-associated protein (MRP), in the renal proximal tubule are suggested to contribute not only to high intratubular solute concentrations, but also to exposure of the tubular epithelium to high intracellular levels of potential cytotoxins [20]. More recent studies demonstrated increased drug-induced renal tubular cytotoxicity in cells expressing OAT1 versus cells lacking the transporter [21]. Tenofovir has been shown to be high affinity substrates of OAT1 [20]. In addition, previous studies showed that tenofovir-induced renal adverse effects might be associated with MRP2 polymorphisms or attributed to an interaction of the protease inhibitor with MRP2- or MRP4-mediated export [20]. However, the reason for the association of tenofovir-induced proximal tubular damage with these secretory transporters is currently unclear. Further studies are needed to reveal the mechanism and to identify the patients who have high risk for tenofovir-induced nephrotoxicity, thus preventing adverse effect.

We noted that although serum phosphate level increased in our patient after discontinuation of tenofovir, it remained outside the normal range after 3 months of tenofovir withdrawal. The rapid withdrawal of the drug usually reverses the renal damage, but proximal renal tubule dysfunction may persist to some extent in some patients [12]. Some patients need surgery to recover pathological fractures secondary to Fanconi syndrome [10, 11]. Early detection of nephrotoxicity and discontinuation of tenofovir are key points to avoid irreversible renal damage and bone complications. For this reason, routine monitoring of serum creatinine, phosphate, and urinalysis is prudent in patients with long-term tenofovir therapy, even for CHB monoinfection. Current HIV treatment guidelines recommend screening patients prior to starting tenofovir in order to record baseline renal function, and monitoring every 3-6 months during therapy using the calculated glomerular filtration rate measuring serum phosphate and checking urine for proteinuria [22]. If abnormalities arise, confirmation of the diagnosis should be done by laboratory and radiological tests. Cessation of tenofovir and switching to another agent, such as entecavir, should be considered.

To our knowledge, this is the first report of hypophosphatemic osteomalacia and pathological fractures associated with tenofovir therapy for CHB monoinfection. In light of our data, tenofovir should be used with caution in patients with evidence of pre-existing renal tubular dysfunction. Further studies on the pathogenesis of proximal renal tubular dysfunction due to tenofovir are needed to avoid these complications.

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Disclosure of conflict of interest

None.

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