Case Report

Fanconi syndrome caused by low-dose adefovir dipivoxil

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ABSTRACT

منذ عام 2008م، التقارير اقترضت أن اديفوفير ديبيفوكسيل بالجرعة المنخفضة لا يسبب سمية للكلى، ولكن هناك تقرير يوضح أنه يسبب متلازمة الفانكوني. قام مستشفانا بتشخيص 3 مرضى صينيين في عمر 64, 45 و63 عاماً. كان جميع المرضى يعانون من آلام العظام و / أو ضعف في العضلات وهذا أثناء عملية العلاج بتناول اديفوفير ديبيفوكسيل وقد شخصوا بمتلازمة الفانكوني الناجمة عن اديفوفير ديبيفوكسيل بالجرعة المنخفضة. نسبة الفوسفات للمريض الأول و الثاني أصبحت طبيعية أو في المعدل الطبيعي تقريباً وهذا بعد تناول انتاكافير بدلا عن اديفوفير ديبيفوكسيل و مع أو بدون تناول مكملات الفوسفات. ولكن المريض الثالث لم يتحسن بشكل ملحوظ بعد تناول تينوفوفير بدلاً عن اديفوفير ديبيفوكسيل بالرغم من أنه تناول كمية كبيرة من مكملات الفوسفات، ونسبة الفوسفات لم تتحسن بشكل ملحوظ. أن أعراض متلازمة الفانكوني الناجمة عن اديفوفير ديبيفوكسيل بالجرعة المنخفضة ليست نادرة في سكان آسيا. المراقبة المنتظمة للبول ونسبة الفوسفات في الدم ضرورية أثناء عملية العلاج باديفوفير ديبيفوكسيل. كانت النتائج مرضية ولكن تينوفوفير ليس مناسباً بدلاً عن اديفوفير ديبيفوكسيل.

Adefovir dipivoxil (ADV) at a low-dose (10 mg daily), which was previously considered not nephrotoxic, was reported to have induced acquired Fanconi syndrome (FS). We report one 64-year-old Chinese woman and 2 Chinese men (ages 45 and 63 years) with bone pain, and/or muscle weakness on ADV therapy that were diagnosed with low-dose ADV-induced FS. The serum phosphate normalized, or nearly normalized in the first and second patients after changing ADV to entecavir with, or without phosphate supplement, but did not improve significantly in the third patient after changing ADV to tenofovir, even though he was supplied with a higher dose of phosphate. Low-dose ADV-related FS is not rare in the Asian population. Regular monitoring of urine and serum phosphate is necessary during therapy with ADV. Prognosis was favorable, however, tenofovir is not a suitable replacement for ADV.

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Adefovir dipivoxil (ADV), a phosphonate nucleotide analogue, causes potent inhibition of both reverse transcriptase and hepatitis B virus (HBV) DNA polymerase in vitro against wild type and lamivudine-resistant chronic hepatitis B virus infection (CHB). Previously, ADV nephrotoxicity was thought to be dose dependent, which did not develop at a low-dose of 10 mg daily.[1] However, since 2008, evidence emerged that a low-dose of ADV could induce acquired Fanconi syndrome (FS), a generalized proximal renal tubular dysfunction. However, the mechanisms and optimal therapy for low-dose ADV-induced FS are not fully identified yet. Here, we describe 3 Chinese patients diagnosed with low-dose ADV-acquired FS within the last one and a half years to discuss the racial disparity, clinical features, management of low-dose ADV induced FS.

Case Report. *Case 1.* A 64-year-old female was hospitalized in the endocrinology ward in November 2011. She developed muscle weakness in the lower extremities, and generalized bone pain of one month duration. The pain, predominately in the lumbosacral portion and ankles was dull, persistent, and aggravated by walking. She had type 2 diabetes mellitus for 10 years, and CHB over 8 years. She had been taking lamivudine (LAM, 100 mg daily) and ADV (10 mg daily) as an anti-HBV therapy for 3 years. Family history was unremarkable. Laboratory data on admission showed

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hypophosphatemia, aminoaciduria, normoglycemic glucosuria, and increased urinary fractional excretion of phosphate (FE_{PO4}). Laboratory results are shown in **Table 1**. Dual energy x-ray absorptiometry (DEXA) showed low bone mineral density (BMD) with L1-L4 vertebral bodies T score of -2.6 (normal values -1 - +1) standard deviations (SD). The aminoaciduria, glucosuria without hyperglycemia, and increased FE_{PO4} were consistent with FS. She refused renal biopsy. According to the temporal relationship between ADV therapy and occurrence of FS, we postulated that FS was induced by ADV. The ADV was replaced by entecavir (ETV, 0.5 mg daily). Meanwhile, LAM was ceased, and oral caltrate with vitamin D tablets (elemental calcium 0.6 g daily, vitamin D3 125 IU daily) were commenced. Bone pain and muscle weakness were alleviated, urinalysis, and serum phosphate (1.35 mmol/L) normalized 4 months after discharge. The subsequent improvement of clinical symptoms and laboratory results after ADV cessation confirmed the diagnosis.

Case 2. A 45-year-old male presented to the Neurology Department in December 2012 with proximal muscle weakness in the lower extremities, and generalized bone pain of one year duration. He had received LAM (100 mg daily) since year 2000 for CHB treatment. He was maintained on ADV (10 mg daily) monotherapy since LAM resistance developed in 2004. The bone pain, predominant in the thorax and lower limbs was persistent, and dull. In several local hospitals, he was diagnosed with spondyloarthropathy (SpA). Methotrexate and analgesics were administered. However, the bone pain and muscular weakness worsened. He could not stand up from squatting position, or walk without assistance. Family history was unremarkable and no herbal remedy was taken. Physical examination revealed tenderness on the thoracic wall, and grade IV lower extremity proximal muscle strength. Cerebrospinal fluid pressure and tests were normal. No abnormality was revealed in brain and spine MRI. But preliminary investigations showed hypophosphatemia, aminoaciduria, normoglycemic glucosuria, and increased urinary FE_{PO4}, which were suggestive of FS. Laboratory data are summarized in **Table 1**. Thereafter, he was transferred to the Nephrology Department.

Table 1 - Laboratory data of the 3 patients included in this study on admission.

Laboratory test	Normal range	Case 1	Case 2	Case 3
Serum				
Phosphate (mmol/L)	0.97-1.62	0.73	0.50	0.36
Calcium (mmol/L)	2.05-2.60	2.11	2.31	2.18
ALP (U/L)	30-140	145	290	342
Potassium (mmol/L)	3.5-5.5	3.97	3.13	3.64
FBG (mmol/L)	3.9-6.1	5.84	4.77	4.80
HbA1c	4.3-6.3	5.3	5.0	5.3
Creatinine (μmol/L)	53-133	59	111	128
Uric acid (μmol/L)	150-420	49	110	94
iPTH (pg/ml)	15-65	NA	27.36	29.71
25(OH) D3 (μg/L)	20-50	NA	15.1	9.2
Albumin (g/L)	35-50	37.5	43	42.4
Hepatitis B e-antigen	negative	negative	negative	negative
Alanine transaminase (U/L)	0-50	9	31	12
Hepatitis B virus-DNA	<1.0*10^3	<1.0*10^3	<1.0*10^3	<1.0*10^3
eGFR (ml/min/1.73m^2)		93.2	67.1	51.0
Arterial blood gas				
pH	7.35-7.45	7.324	7.314	7.264
AB	22-26	21	18.3	15.7
Urine				
Protein	negative	2+	2+	2+
Glucose	negative	1+	3+	4+
Amino acids	negative	positive	positive	positive
α1 microglobulin(mg/g creatinine)	0-15	500	230.16	328.26
Protein (mg/24 h)	22-132	588.6	1563	1023
FE_{PO4}(%)	5-20	82	118	80.3

ALP - alkaline phosphatase, FBG - fasting blood-glucose, HbA1c - glycosylated hemoglobin, iPTH - intact parathyroid hormone, 25(OH)D3 - 25 hydroxycholecalciferol, eGFR - estimated glomerular filtration rate, AB - actual bicarbonate, FE_{PO4} - fractional excretion of phosphate.

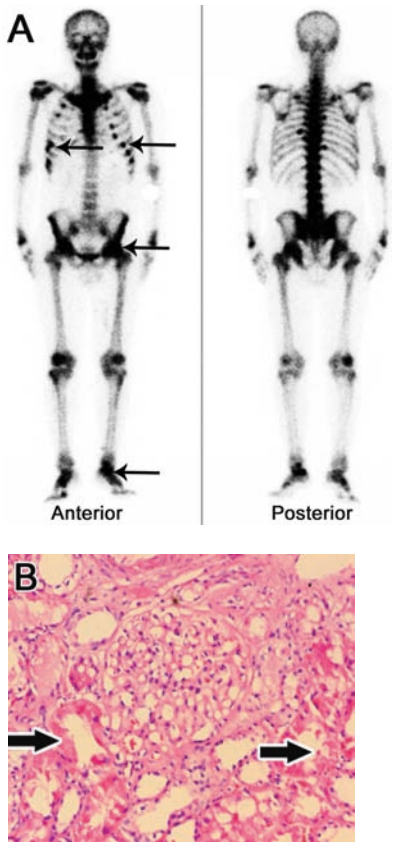

Figure 1 - An image showing: **A**) bone scintigraphy showing significant abnormal uptake in bilateral ribs, left caput femoris, and left ankle; and **B**) tissue section from renal biopsy demonstrating normal glomeruli and remarkable proximal tubular epithelial cells degeneration (arrows) (Hematoxylin & Eosin ×400).

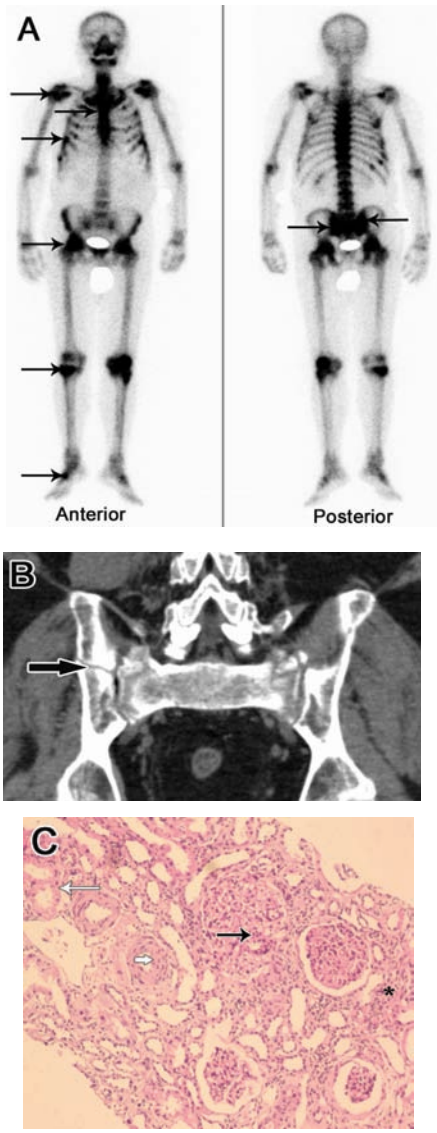

Figure 2 - An image showing: **A**) bone scintigraphy with diffused increased uptake in bilateral shoulder joints, sternum, multiple ribs, seventh to eighth thoracic vertebras, bilateral hip joints, bilateral sacroiliac joints, left knee joint, upper part of right tibia, and right acrotarsium (arrows); **B**) sacroiliac joints CT scan showed blurred articular surface, right ilium fracture (arrow); and **C**) tissue section from renal biopsy demonstrating glomerular mesangial proliferation (black arrow), tubular epithelial cells with granular degeneration (white arrow), interstitium with lymphocyte infiltration (asterisk), and small artery with thick wall (arrow head) (Hematoxylin & Eosin ×100)

The x-rays of flat bones were normal, and DEXA showed low BMD with a mean femoral neck T score of -4 SD. The ^{99}mTc-methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy revealed increased uptake in bilateral ribs, left femoral head, and left ankle (**Figure 1A**). Renal biopsy showed normal glomerulus and remarkable granular-vacuolar degeneration in proximal tubular epithelial cells on light microscopy (LM) (**Figure 1B**). Immunostaining was negative for immunoglobulins, complements, and surface antigen of the hepatitis B virus (HbsAg).

Taken together, the diagnosis of ADV-induced FS and hypophosphatemic osteomalacia (OM) secondary to FS was established. The ADV was replaced with ETV (0.5 mg daily). Oral caltrate with vitamin D tablets (elemental calcium 0.6 g daily, vitamin D3 125 IU daily), calcitriol (0.5 μg daily), potassium citrate, intravenous phosphate (elemental phosphate 186 mg daily), and skimmed milk rich in phosphorus were commenced. The bone pain resolved slightly, but muscle weakness was dramatically relieved. After 2 weeks when discharged, he walked unaided and his serum phosphate had increased to 0.76 mmol/L. Two months after discharge, serum phosphate increased

to 0.91 mmol/L, urinalysis was normal, and FE_{PO4} decreased to 41.7%.

Case 3. A 63-year-old man diagnosed with low-dose ADV-induced FS at a local hospital 2 months earlier, presented to the Rheumatology Department in May 2013 for developing bone pain and hypophosphatemia after ADV withdrawal, and phosphate supplement. He was commenced on LAM (100 mg daily) therapy in 2001 for CHB treatment. The LAM was replaced by ADV (10 mg daily) in 2007 due to LAM resistance. The bone pain, especially in the low back and knee joints was slightly improved by exercise. He had grade one hypertension for 3 years, and never took antihypertensive drugs. Before ADV-induced FS was diagnosed, hypophosphatemia lasted one year, and bone pain had lasted for 5 months.

The laboratory work-up at the local hospital showed positive Hbe-antigen, hypophosphatemia (0.61 mmol/L [normal range; 0.81-1.55 mmol/L]), aminoaciduria, and normoglycemic glucosuria. The epidermal growth factor receptor (eGFR) was 56.7 ml/min/1.73m^2. ADV-induced FS was diagnosed. The ADV was replaced with tenofovir (TDF, 300 mg daily). However, hypophosphatemia and bone pain worsened.

In our hospital, physical examination revealed tenderness over the thorax, spine, and knee joints. Serum phosphate was extremely low (0.36 mmol/L). Laboratory data on admission was consistent with FS (**Table 1**). Thereafter, he was transferred to the Nephrology Department. The DEXA scan revealed low BMD with L1-L4 vertebral bodies T score of -1.6 SD, and with femur T score of -2.7 SD. The ^{99m}Tc-MDP bone scintigraphy showed diffused increased uptake in bilateral shoulder joints, sternum, multiple ribs, seventh to eighth thoracic vertebras, bilateral hip joints, bilateral sacroiliac joints, left knee joint, right tibia, and right acrotarsium (**Figure 2A**). The CT scan of the sacroiliac joints showed blurring on bilateral articular surfaces and a right iliac fracture (**Figure 2B**). Renal biopsy showed mild glomerular mesangial proliferation, tubular epithelial cells with prominent granular degeneration, interstitium with lymphocyte infiltration, and small artery with thick wall on LM (**Figure 2C**). Immunostaining showed weak positive staining for immunoglobulin (Ig)A, IgM, and IgG, and negative staining for complements and HbsAg.

Given these results, an additional diagnosis of hypophosphatemic OM secondary to ADV-induced FS was established. Oral caltrate with vitamin D tablets (elemental calcium 0.6 g daily, vitamin D3 125 IU daily), alfacalcidol (0.25 μg daily), potassium citrate, oral and intravenous phosphate (elemental phosphate - 125 mg and 186 mg daily) were added. Loxoprofen sodium (60 mg daily) and salmon calcitonin (50 unit daily) were given. Bone pain was relieved but serum phosphate did not improve significantly. The dose of intravenous phosphate supplement was increased to 558 mg daily. After 2 weeks, he was discharged with hypophosphatemia (0.69 mmol/L).

Discussion. We diagnosed 3 Chinese CHB patients with FS induced by ADV at a dose of 10 mg daily within the last one and a half years. It is considered that overexpression of human organic anion transporter 1 (hOAT1) and/or underexpression of multi-drug resistant protein (MRP) 2 and 4 may result in accumulation of intracellular ADV, and subsequently lead to ADV nephrotoxicity.[2] The first case of low-dose ADV-induced FS was reported by Lee et al in 2008.[3] Since then, a total of 18 cases have been reported in PubMed. Except for a Caucasian,[4] and an African,[5] the other cases were Asian. It seems that Asians are more susceptible to this disease. Polymorphism of genes encoding MRP 2 and 4 may be implicated in racial disparity. In a study of CHB patients on long-term treatment with ADV+LMV, hypophosphatemia was associated with homozygosis for the C allele at position -24 of the ABCC2 gene encoding MRP2.[6] The G187W variant of ABCC4 gene encoding MRP4, with a significantly reduced excretion of ADV was present at quite different frequencies in various ethnic groups, 2.5% in Caucasian American, but 13% in Asian American.[7]

After reviewing the published cases, we found that bone pain and muscle weakness were the predominant initial symptoms of FS induced by low-dose ADV. Total body phosphate depletion, which resulted in hypophosphatemic OM and failure to form ATP, caused the above symptoms.[8] As regular serum phosphorus and urine monitoring during ADV therapy were ignored by many hepatologists, the disease was not revealed until severe symptoms had developed. But, bone pain and muscle weakness were not specific, therefore, patients would see doctors in different medical professions and may be misdiagnosed, or never diagnosed. Therefore, early and frequent monitoring of serum phosphorus, urine sugar, and urine amino acids should have been performed. Our patients all developed bone pain, and 2 of them suffered muscle weakness during the ADV therapy. They were not admitted to the nephrology department at first. For example, the second patient was admitted to the neurology section as a neurological disease was suspected for severe muscle weakness. In local hospitals, he was misdiagnosed as SpA. Fortunately, preliminary investigations of hypophosphatemia, aminoaciduria,

normoglycemic glucosuria raised the possibility of the diagnosis of FS as the consulted nephrologist had read relevant case reports. One of the ADV-related nephrotoxicity definitions was a serum phosphorus value of <1.5 mg/dL on 2 consecutive occasions.[9] Although our 3 patients had already developed FS and/or FS-related OM, serum phosphate levels were greater than 1.5 mg/dL. The same phenomenon was discovered in 7 published cases.[10-13] We are of the opinion, therefore, that a serum phosphate value of <1.5 mg/dL may not be a sensitive diagnostic criteria. Prognosis was favorable in most published cases. After several weeks to months, symptoms resolved gradually, urinalysis, and serum phosphate normalized, or partially improved after ADV dose reduction, cessation, or replacement with other antiviral drugs, phosphorus, calcium, and vitamin D3 or calcitriol supplements. But, the serum phosphate of our third patient kept decreasing after ADV withdrawal and oral phosphate supplement. It might be due to TDF, another nucleotide analogue. Cases of TDF-induced proximal tubulopathies have been reported, and some were confirmed by renal biopsy.[14] Renal tubular transporters hOAT1 and MRP4, which participated in tubular uptake and excretion of ADV, also interfere with TDF uptake and excretion.[9] Having the same tubular transporters might explain the poor therapeutic effect of TDF in our third patient. It was unfortunate that the patient refused to replace TDF with other anti-HBV drugs, although he was informed of its side effects.

In conclusion, a low-dose ADV-related FS is not rare in the Asian population. Bone pain or muscle weakness during low-dose ADV therapy should alert to the possibility of acquired FS. Regular monitoring of urine and serum phosphate is necessary during the therapy of ADV. Prognosis was favorable, the symptoms improved and investigations normalized in most patients after ADV dose reduction, cessation, or replacement with other antiviral drugs other than TDF.

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