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Case Report

Bilateral femoral head necrosis and pathological fractures resulted from Fanconi syndrome due to adefovir dipivoxil treatment: a case report and systematic analysis of 7 cases

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Abstract: We presented a case of a patient underwent bilateral total hip arthroplasty for femoral head necrosis and pathological femoral neck fracture resulted from adefovir dipivoxil related Fanconi syndrome. Then, we ran a systematic analysis of seven similar cases. Surgical treatment was used in three cases, while no surgical treatment was conducted in the other four. Satisfactory clinic outcome was achieved in all 7 cases. As conclusion, hypophosphatemic osteomalacia is a potential risk for any patients who undergo adefovir dipivoxil treatment. And early intervention could improve the symptoms and prevent pathological fractures or bone necrosis.

Keywords: Osteomalacia, necrosis, pathological fracture, adefovir dipivoxil, Fanconi's syndrome

Introduction

Fanconi syndrome is defined as dysfunction of proximal renal tubule that results in impaired reabsorption of amino acids, glucose, urate and phosphate [1]. Chronic hypophosphatemia would cause osteomalacia that would influence the metabolism of bone, which would produce a series of symptoms, such as mild muscle weakness, bone and joint pain, and bone fractures [2].

Hepatitis B virus (HBV) infection is one of the most common infectious diseases and causes worldwide liver-related deaths [3]. Adefovir dipivoxil (ADV) is a nucleoside reverse transcriptase inhibitor used to suppress HBV replication and remit liver disease [4]. Although safety of low-dose ADV therapy (10 mg/day) has already been proved by large clinical trials [5, 6], several cases of pathological fractures due to osteomalacia associated with low-dose ADV therapy for hepatitis B have been reported recently [7-11].

Initially, we presented a case of a male patient underwent bilateral total hip arthroplasty for femoral head necrosis and pathological femoral neck fracture induced by low-dose ADV treatment. And in addition, using the methodology of evidence-based medicine, we ran an online database search. A total of 7 cases were included in our analysis.

Case report

Patients and methods

A fifty-one-year-old man complained of pain and limited motion of both hip joints and was admitted to our hospital in August 2014. He had continually experienced increasing pain and motion limitation of both hip joints for 3 years. The patient had a medical history of hepatitis B with treatment of adefovir 10 mg per day for 5 years. He didn't have history of trauma or other medical situation and was not taking any other drugs.

The patient showed a limited range of motion (ROM) and tenderness of both hip joints, but there was no abnormality in other routine physical examination.

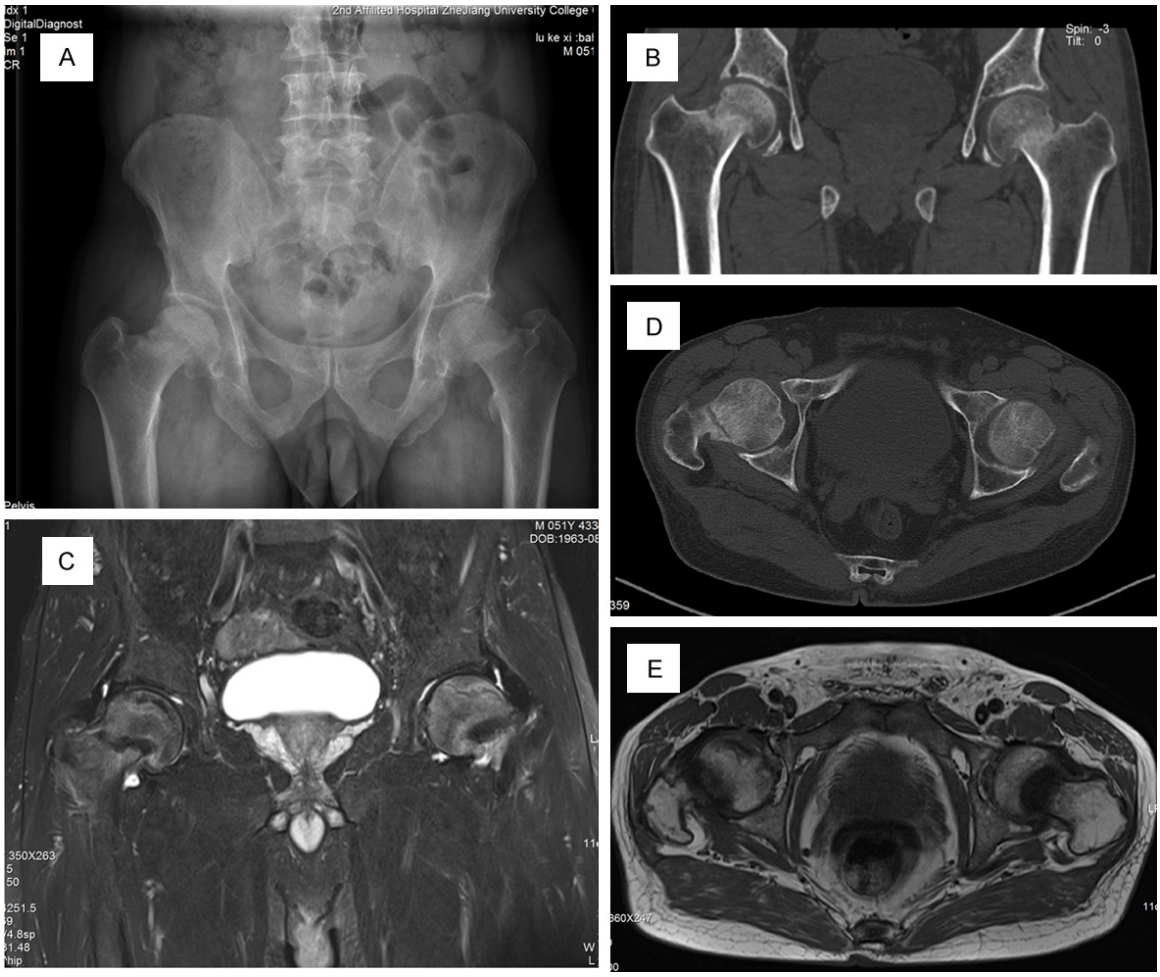

Figure 1. Radiological examinations at admission. A: Plain radiograph of the pelvis and both femoral heads showed bilateral femoral neck fractures. B, C: Computer tomography (CT) scan also showed bilateral femoral neck fractures. D, E: Magnetic resonance imaging revealed bilateral femoral head necrosis and neck fractures.

Radiological examinations at admission showed femoral head osteonecrosis and femoral neck fracture of both hips (**Figure 1**). Whole body bone scintigraphy showed increased uptake in both shoulder joints, both knees, both ankle joints, both shaft of femur and junction zone of rib and rib cartilage of both sides (**Figure 2**).

Laboratory tests showed hypophosphatemia (0.34 mmol/L, normal: 0.81-1.45 mmol/L) and hypocalcemia (2.06 mmol/L, normal: 2.20-2.65 mmol/L). He had dysfunction of coagulation (prothrombin time 18.2 s; prothrombin time activity 55%; activated partial thromboplastin time 51.7 s). He showed hypoalbuminemia (32.1 g/L, normal: 35.0-52.0 g/L). Immunologic tests and tumor markers tests all came to normal results. B mode ultrasound image showed liver cirrhosis and splenomegaly. Furthermore, we ran a 24 h urinalysis which showed increased urinary excretion of phosphate (775 mg/day, normal: 20-220 mg/day). And blood test showed a low level of parathyroid hormone (7.10 pg/ml, normal 15.00-65.00 pg/ml), the excretion of calcium was normal (116 mg/day, normal 100-300 mg/day). These findings demonstrated hypophosphatemia and hyperphosphaturia. However, given the patient had low level of parathyroid hormone, we considered that the phosphate reabsorption was caused by dysfunction of the proximal renal tubule dysfunction.

Based on these results and history, we made a diagnosis of pathologic fracture resulted from hypophosphatemic osteomalacia due to Fanconi syndrome secondary to adefovir treat-

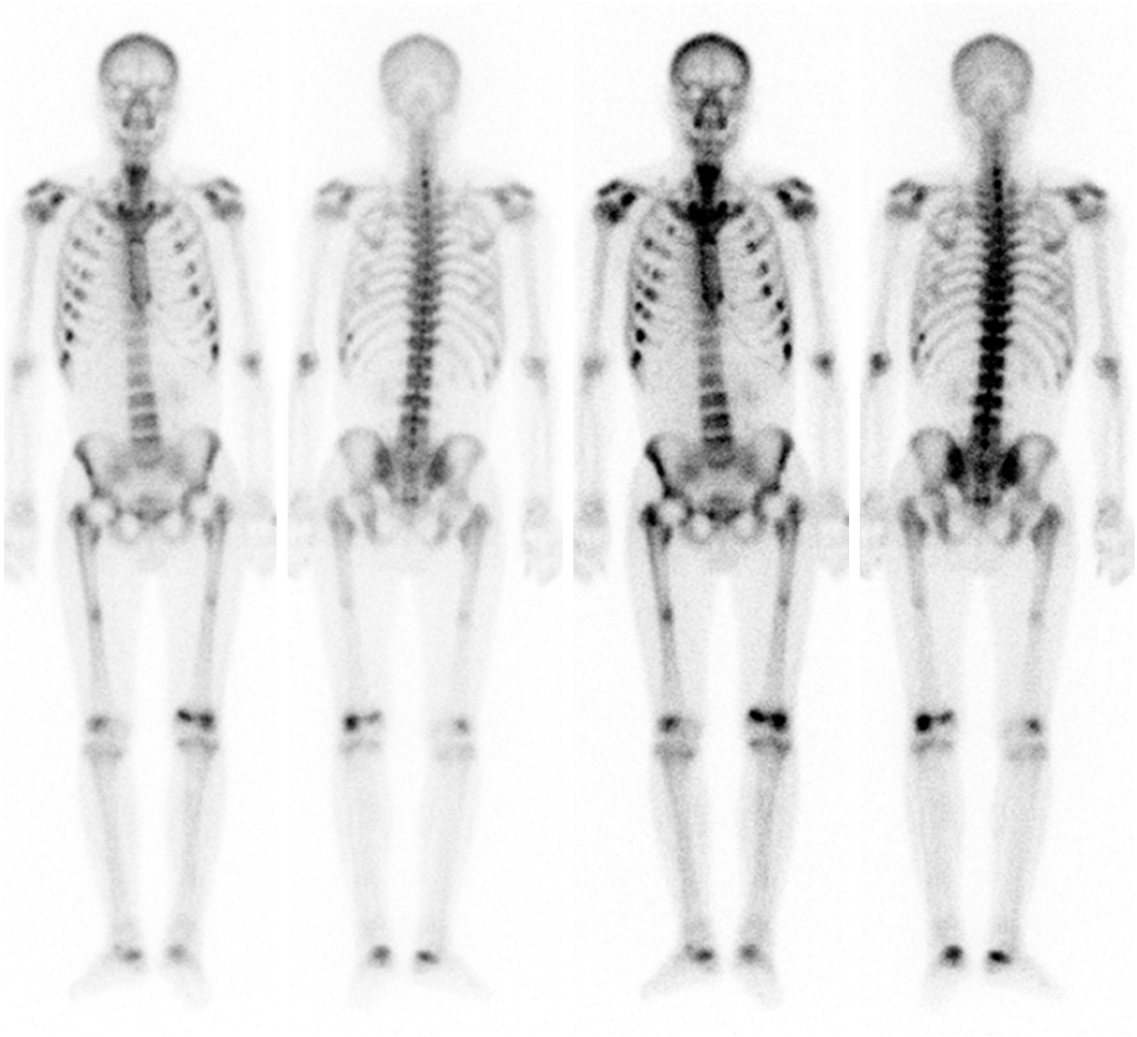

Figure 2. Whole body bone scintigraphy showed increased uptake in both shoulder joints, both knees, both ankle joints, both shaft of femur and junction zone of rib and rib cartilage of both side.

ment. Then we conducted a total hip arthroplasty for the left hip, using a Stryker implant (Secur-Fit-HA, **Figure 3**). Considering he had dysfunction of coagulation, 10 unite blood platelet was given post surgery. Adefovir 10 mg/day was replaced by entecavir 0.5 mg/day, and phosphate supplementation (1156 mg/day), calcium carbonate (600 mg/day) and calcitriol (0.5 μg/day) were given.

At 4 weeks after hospital, the patient reported improvement and release of symptoms. After 3 months, only slight pain existed in left hips. The patient came back to the hospital for total right hip arthroplasty and same implant was used (**Figure 4**). We suggested a monthly re-check of blood test. The patient reported significant improvement of all symptoms and he could walk more than 1 mile 3 months after the second surgery. Phosphate treatment was discontinued after normal results of re-check blood test.

Cases review

An online search was conducted, including Pubmed, Embase and Web of Science (before October 26, 2016). The search strategy was used as followed: ((fracture) OR (femoral head necrosis)) AND (Fanconi's syndrome) AND (low dose) AND (adefovir) without language limitation. Furthermore, we searched the Chinese databases, including CNKI and Wanfang data.

The cases that met the following criteria were included: (1) patient suffered pathological frac-

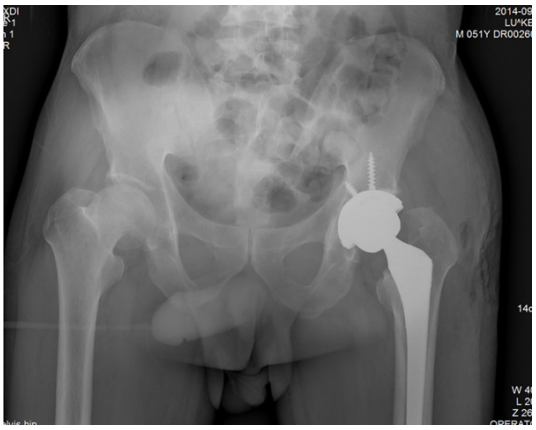

Figure 3. Plain radiograph after the first THA showed the implant in left hip.

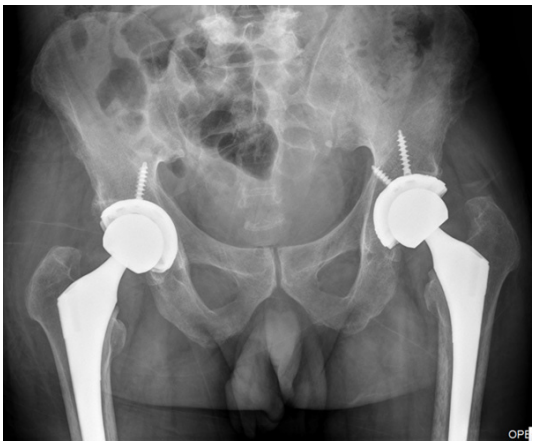

Figure 4. Plain radiograph after the second THA showed the implants in bilateral hips.

ture caused by osteomalacia due to Fanconi syndrome secondary to adefovir treatment; (2) the patient had no other disease that may influence the bone intensity such as osteoporosis; (3) the patient had not suffered any trauma that may cause the fracture.

The result of online search was reviewed according to the eligibility criteria, and data of included cases were extracted. The extracted information included the following items: region, gender, age, initial disease, dose of adefovir treatment, fracture site, surgical treatment, and drug treatment.

Results

After initial search with duplicated reports excluded, there remained 12 literatures. Four of them report no fracture happened. Other drugs could influence the bone quality were used in two of 11 reports. The patient had other disease that may cause femoral head necrosis in another report. Finally, five reports with six cases met eligibility criteria [7-11].

Including our case, 7 cases were summarized (**Table 1**). Two cases occurred in Japan, three in Korea, one in China and one in Italy. The mean age was 57 years old (from 43 to 70). Six cases were male, and one case was female. All of 7 cases applied low-dose adefovir for hepatitis B. Two cases used additional lamivudine. The mean duration of adefovir treatment was 5.3 years (from 4 to 7 years). Three of 7 suffered bilateral femoral neck fracture. One case suffered ulna fracture. One case had ribs IV to X fractures. One case had multiple insufficiency fractures in proximal tibia, proximal femur, sacrum and thoracolumbar spine. One case had sacrum fracture and multiple rib fractures. Our case presented bilateral femoral head necrosis. THA were used in two cases and internal fixation device was applied in another case, while no surgical treatment was conducted in the other four. Six of 7 cases used entecavir therapy to switch ADV treatment, the other one lower the dose of adefovir to 20 mg/week to achieve a normal level of phosphate in blood. Satisfactory clinic outcome was achieved in all 7 cases.

Discussion

Although it is well-known that high-dose ADV therapy (60 to 100 mg/day) could influence the kidney function and might result in Fanconi syndrome, low-dose ADV therapy (10 mg/day) is usually considered safe, which has been proved by large clinical trials [5, 6]. Low-dose ADV therapy has been a general treatment for HBV infection, especially for the patients with lamivudine resistance. Recently, there have been several case reports of hypophosphatemic osteomalacia induced by low-dose adefovir therapy [7-13]. And only a few papers reported fractures caused by hypophosphatemic osteomalacia induced by low-dose adefovir therapy [7-11]. What's more, only one Fanconi syndrome case report has reported left femoral head necrosis that might have possible connection with Fanconi syndrome because the patient had another situation of positive

Table 1. Characteristic of all seven cases

Author & Year	Region	Gender	Age (year)	Initial Disease	Drug	Duration of Drug	Fracture Site	Surgical Treatment[a]	Drug Treatment[b]
Tanaka 2012	Japan	Male	62	Hepatitis B	Adefovir (10 mg/day)	5 years	Femoral neck	THA	Entecavir, eldecalcitol and alendronate
Lee 2016	Korea	Male	43	Hepatitis B	Adefovir (10 mg/day)	7 years	Ulna	Internal fixation	Entecavir, elemental supplementation
Utsumi 2014	Japan	Female	70	Hepatitis B	Lamifvdine (100 mg/day); adefovir (10 mg/day)	5 years	Ribs IV to X	None	Lower-dose adefovir, elemental supplementation
Palermo 2014	Italy	Male	53	Hepatitis B	Lamivudine (unclear); adefovir (10 mg/day)	4 years	Sacral and ribs	None	Entecavir, elemental supplementation
Kim 2013	Korea	Male	62	Hepatitis B	Adefovir (10 mg/day)	6 years	Multiple insufficiency	None	Entecavir, elemental supplementation
	Korea	Male	54	Hepatitis B	Adefovir (10 mg/day)	5 years	Fractures	None	Entecavir
Our case	China	Male	55	Hepatitis B	Adefovir (10 mg/day)	5 years	Femoral neck	THA	Entecavir, elemental supplementation

[a]THA means total hip arthroplasty. [b]Entecavir means the antivirus drug therapy is replaced by entecavir treatment.

antimitochondrial antibody-M2 (anti-M2) which could cause bone necrosis [14]. To the best of our knowledge, this is the first study that reports a case with bilateral femoral head necrosis related to Fanconi syndrome caused by low-dose adefovir treatment.

It is interesting to speculate the mechanism of the bilateral femoral head necrosis in our case. As we do not have any clinical data such as MRI or X-ray before the admission, it's impossible to figure out whether the necrosis happened before the femoral neck fractures or not. As a result, we have several hypothesis of the mechanism of bilateral femoral head necrosis as following: 1) As it has been reported in a case report in 1979 that osteomalacia could cause bone necrosis [15], we firstly consider the bilateral femoral head necrosis was resulted from the osteomalacia due to long-time low-dose ADV treatment. 2) It is well-known that femoral head necrosis is one of the main complications of femoral neck fracture [16], so the necrosis could be secondary to the neck fracture due to ADV treatment. 3) Other unknown reasons.

Osteomalacia is a disorder of bone, defined as decreased mineralization of newly formed osteoid at sites of bone turnover [7]. Late diagnosis of osteomalacia may lead to pathological fractures and disabling symptoms such as severe muscle and joints pain, some fractures could be life-threaten. But early stagy of osteomalacia can only have some slight symptoms that may be misunderstood as age-relevant disease like arthritis or osteoporosis, and those symptoms alone rarely alert the physicians to the possibility of osteomalacia or hypophosphatemia. Classical diagnostic tests like dual X-ray absorptiometry may mislead the physicians. And 24 h urinalysis and blood phosphate test are usually not contained in the general tests at admission.

Dysfunction of the proximal renal tubule causes impaired reabsorption of amino acids, urate, bicarbonate and phosphate, resulting in Fanconi syndrome. The pathophysiology of ADV inducing Fanconi syndrome is reported to be related to an increase in the ADV concentration in the mitochondria mediated by inhibition of several ATP-dependent transporters [17, 18]. Entecavir is more effective than ADV with low incidence of resistance and favorable safety of drug [19]. Six of seven cases in this study switched ADV with entecavir and all of them came to effective improvements of blood-test results and clinic symptoms. Entecavir may be a better treatment choice than ADV and lamivudine.

According to our study, initial disease of all the cases is hepatitis B. It is well-known that ADV treatment is also used for the HIV infection, previous case report also reported osteomalacia caused by low-dose ADV treatment for HIV infection [12]. However, no one has ever reported any pathological fractures due to ADV-related Fanconi syndrome in AIDS population. We believe that this difference is caused by the epidemiological difference between hepatitis B and AIDS. Epidemiological data showed population of hepatitis B was far more than that of AIDS, especially in some Asian countries such as China and Korea [20-23].

Conclusion

In conclusion, hypophosphatemic osteomalacia is a potential risk for any patients who undergo adefovir dipivoxil treatment. If such patients complained of any muscle or bone discomfort, orthopaedic surgeons should be aware of the possibility of Fanconi syndrome, and additional radiological and laboratory examinations such as 24 h urinalysis, blood phosphate test, whole body bone scintigraphy, and MRI of affected area should be performed. And adefovir dipivoxil should be switched or dose-decreased once the diagnosis of ADV-related Fanconi syndrome is made. Early intervention could improve the symptoms of Fanconi syndrome and prevent pathological fractures or bone necrosis which might result in severe complications or burdensome operation.

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Disclosure of conflict of interest

None.

Abbreviations

THA, total hip arthroplasty; ADV, adefovir dipivoxil.

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