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A Case of Fanconi Syndrome with Multiple Fractures and Height Loss as Main Symptoms Caused by Adefovir Dipivoxil

Yangzi Dan[1] and Yang Fan[2]

[1]Department of infectious disease, Wufeng Tujia Autonomous County People's Hospital, Yichang, China

[2]Department of Infectious Diseases, Renmin Hospital of Wuhan University, Wuhan, China

***Corresponding author:**

Yang Fan,
Department of Infectious Diseases, Renmin Hospital of Wuhan University, Wuhan, China

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1. Abstract

We present a case of a 57-year-old male who experienced extensive bone pain, difficulty in getting up, weakness in walking, and height loss. He had been taking adefovir dipivoxil tablets for the treatment of hepatitis B. Laboratory tests revealed impaired renal function, a significant decrease in blood phosphorus level, positive urine protein, positive urine glucose, and CT scan showed multiple fractures. After excluding other diseases, he was diagnosed with adefovir dipivoxil-induced Fanconi syndrome. Following the discontinuation of adefovir dipivoxil, and supplementation of disodium hydrogen phosphate, along with oral vitamin D3 and calcitriolthe, patient's symptoms and laboratory indicators improved significantly. In this case, we focus on bone pain, multiple fractures, height loss, as well as abnormal renal function and electrolyte imbalance, aiming to enhance the understanding of Fanconi syndrome.

2. Introduction

Fanconi syndrome (FS), is known as proximal convoluted tubule (PCT) alterations that lead to impairment of PCT reabsorption [1]. This impairment leads to defective reabsorption of various substances, including sodium, chloride, water, bicarbonate, phosphate, glucose, amino acids, lactate, citrate, low-molecular-weight (LMW) proteins, and several other substances [2-5]. In children, it is typically caused by inborn errors of metabolism, such as Lowe's syndrome, Dent's disease, cystinosis, hereditary fructose intolerance, galactosemia, tyrosinemia, Alport syndrome, and Wilson's disease [5]. In adults, FS is most frequently caused by drug-induced nephrotoxicity [6], as the proximal tubules are involved in the excretion of several drugs. It has been associated with antiretroviral medications such as tenofovir, didanosine, lamivudine, and stavudine, especially in HIV + patients undergoing multidrug therapy [7-9].Other causes are anticancer agents such as ifosfamide [10], immune checkpoint inhibitors nivolumab/ipilimumab [11], and tyrosine kinase inhibitors [12]. In addition to mitochondrial damage caused by drugs, which induces nephrotoxicity and thus leads to FS, chronic heavy metal exposure had been associated with FRTS [3,13].There have been numerous reports indicating that nucleoside (nucleotide) analogues may cause PCT injury, which in turn induces FS. Here, we report a case of FS caused by long-term oral administration of adefovir dipivoxil (ADV), presenting with generalized bone pain, multiple fractures, and height loss as the main symptoms.

3. Case Presentation

Patient, male, 57 years old, was admitted to the hospital due to "bone pain for 4 years and height loss for 1 year". At admission, the patient had obvious pain in the chest, waist, bilateral hips, and lower limbs. He had difficulty getting up, weakness in walking, and was unable to climb stairs. He stated that his height had decreased by approximately 15 cm in the past 3 years. Past medical history: He had suffered from chronic hepatitis B for more than 20 years and started oral administration of ADV for antiviral treatment 13 years ago, without regular reexaminations. In the past 3 years, he had sought medical attention multiple times due to bone pain, and examinations revealed multiple fractures throughout the body. Specifically: In September 2022, thoracic

computed tomography scan (CT) showed fractures of the right 3rd, 5th-8th, 11th, 12th ribs and left 2nd-4th, 8th-11th ribs, with callus visible at the fracture ends. Lumbar CT indicated lumbar degenerative changes, L5 instability, and L5/S1 intervertebral disc herniation. One year ago, he underwent "metal internal fixation surgery" in another hospital due to "low back pain". Physical examination on ddmission: Tenderness (+) in bilateral costal regions, poor mobility of the thoracolumbar spine, Tenderness(+) in bilateral inguinal regions,Bilateral"4" sign (+). Auxiliary examinations: chest CT: Multiple old rib fractures on both sides with visible callus formation (Figure 1A, B, C), lumbar spine CT plain scan: postoperative changes of the lumbar spine and lumbar degenerative changes, hip joint CT plain scan: left femoral neck fracture (Figure 2A), old fracture of the left femoral neck and the bilateral inferior pubic rami. (Figure 2B), bilateral knee joint CT plain scan: no abnormalities found, renal color doppler ultrasound: small kidney stones and calcifications in both kidneys. Laboratory examinations: routine urine test: occult blood 3+, protein 4+, urine glucose 2+, blood biochemical test: alanine aminotransferase (ALT) 30.49 U/L, aspartate aminotransferase (AST) 29.48 U/L, alkaline phosphatase 607.4 U/L (↑), total bilirubin 10.43 μmol/L, direct bilirubin 4.92 μmol/L, total protein 73.3 g/L, albumin 45.9 g/L, urea (Ure) 12.41 mmol/L (↑), creatinine (Cr) 156.7 μmol/L (↑), cystatin C 2.07 mg/L (↑), β2-microglobulin 5.11 mg/L (↑), creatine kinase 73.5 U/L, Cl- 114.64 mmol/L (↑), Ca2+ 1.37 mmol/L (↑), P3+ 0.60 mmol/L (↓), total carbon dioxide 20.1 mmol/L (↓), anion gap 11.39 mmol/L, alpha-fetoprotein(AFP), parathyroid hormone(PTH), rheumatoid factor(RF), antinuclear antibody(ANA), extractable nuclear antigen(ENA) antibody profile, antistreptolysin O(ASO), human leukocyte antigen-B27(HLA-B27), erythrocyte sedimentation rate, and C-reactive protein were all within normal limits.

The patient had normal blood glucose levels but significantly elevated urine glucose, along with decreased blood phosphorus, and increased levels of urine protein, serum creatinine, and alkaline phosphatase. Additionally, CT scan indicated multiple fractures without trauma. Based on these findings, it was initially considered that long-term use of ADV had led to hypophosphatemic osteomalacia and FS. To rule out hereditary FS, the patient further underwent peripheral blood whole-exome sequencing. The results showed no pathogenic or suspected pathogenic variants related to the patient's clinical phenotype and consistent with the genetic pattern. After confirming that the patient's FS was induced by ADV, ADV was switched to entecavir. Phosphorus supplementation was administered via oral disodium hydrogen phosphate, along with oral vitamin D3 and calcitriol. Three months later, pain was improved. Re-examination results showed: alanine aminotransferase 30.49 U/L, aspartate aminotransferase 30.5 U/L, creatinine 130.4 μmol/L, urea 9.07 mmol/L, inorganic phosphorus 0.81 mmol/L, and ionized calcium 1.34 mmol/L. Four months later, liver function, renal function, and hypophosphatemia had all returned to normal levels, pain was significantly relieved, he could sit, lie down, and walk freely, and is also able to climb stairs.

Figure 1. Lumbar spine CT scan.

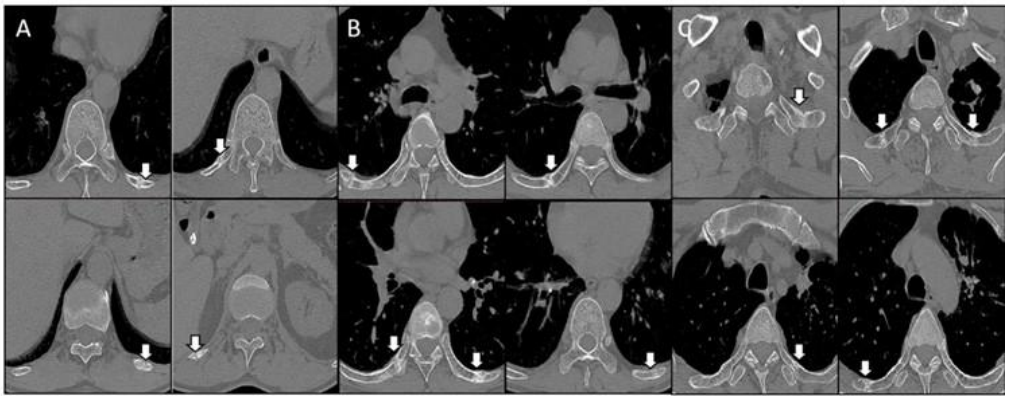

Figure 1 A/B/C show different rib sections. The location indicated by the white arrow is the fracture site.

.**Figure 2**: Hip joint CT scan

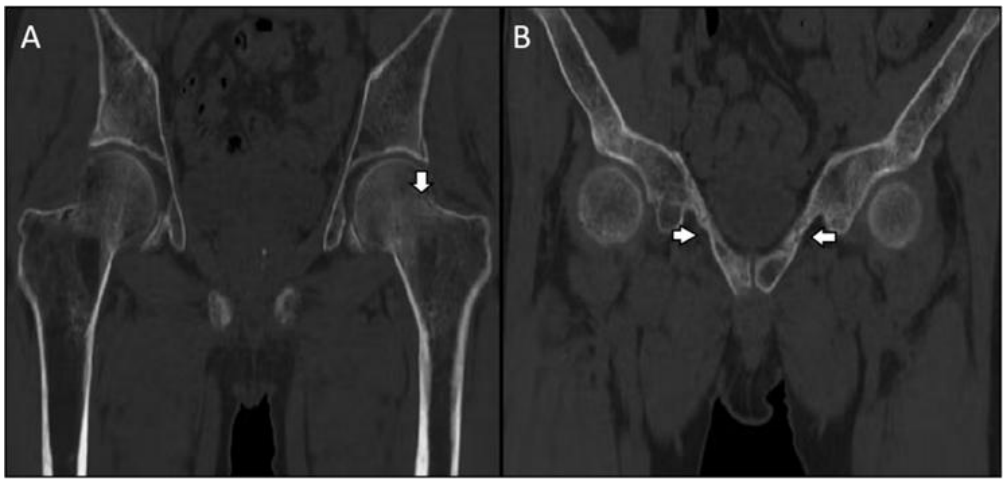

Figure 2A: old fracture of the left femoral neck; Figure 2B: old fractures of the bilateral inferior pubic rami. The location indicated by the white arrow is the fracture site.

Table 1. Key indicators before and after treatment.

Time/Indicators	ALT（U/L）	Cr（umol/L）	Ure（mmol/L）	P^{3+}（mmol/L）	Cl^-（mmol/L）
before treatment	30.41	156.70	12.41	0.71	114.64
4 weeks	14.59	147.00	11.90	0.60	113.41
7 weeks	16.70	134.80	9.94	0.88	110.10
10 weeks	19.51	137.30	9.07	0.84	109.60
12 weeks	21.20	132.70	8.27	0.89	108.35
16 weeks	20.13	131.90	8.20	1.01	107.22

Normal range: ALT:9-50U/L, Cr:45-133umol/L, Ure1.7-8.3, P3+ 0.87-1.45mmol/L, Cl- 98-110mmol/L

4. Discussion

Due to PCT damage, patients with FS experience excessive renal phosphate excretion, leading to increased phosphate in the urine and decreased phosphate in the blood. This impairs normal bone mineralization. In turn, hypophosphatemia triggers the release of more phosphate from bone tissue, further causing bone matrix mineralization disorders and the development of osteomalacia. Therefore, osteomalacia is usually the most common early complication of FS, whose main symptom is bone pain. In severe cases, it can result in multiple fractures or pseudofractures throughout the body [14,15]. The diagnosis of FS relies on identifying a characteristic pattern of proximal tubular dysfunction through both urine and blood testing. Urine tests of patients with FS show positive urine glucose, which is inconsistent with blood glucose levels and not caused by diabetes. In addition, urine protein is positive, and urinary calcium, potassium, phosphorus, uric acid, etc. are elevated, presenting with renal generalized aminoaciduria. Blood tests may reveal decreased blood calcium, phosphorus, potassium, and uric acid, increased blood chlorine, and elevated blood alkaline phosphatase [16-19]. In this case, the patient had suffered from bone pain for 4 years, which was unbearable. He experienced weakness in walking, difficulty in getting up from a sitting position, inability to climb stairs, and essentially lost labor capacity. He needed to take oral analgesics for daily pain management. Additionally, the patient noticed a gradual decrease in height, from 170 cm to 156 cm. Since the onset of symptoms, the patient had sought medical attention in the orthopedics department multiple times. Examinations revealed multiple rib fractured, left femoral neck fractured, the bilateral inferior pubic rami fractured, but these findings did not attract sufficient attention. Due to severe low back pain, he underwent “metal internal fixation surgery” half a year ago to relieve the pain. Upon admission to our hospital, examinations showed positive urine protein and urine glucose. Blood tests revealed a significant increase in alkaline phosphatase, low blood phosphorus, and elevated creatinine, CT scan confirmed multiple fractures. We ruled out alcoholic osteoporosis, vitamin D deficiency osteoporosis, traumatic fractures, and other conditions. After a comprehensive analysis of various examination, we determined that the patient’s condition did not match the characteristics of diseases such as primary osteoporosis, myeloma, metastatic carcinomatous bone lesions, and hereditary osteogenesis imperfecta. Given that the patient had been taking ADV for anti-hepatitis B virus treatment for 13 years, we considered a diag-

nosis of acquired FS, with a high suspicion that it was caused by ADV. Although it was impossible of heredity, we still performed whole-exome sequencing, and the results showed no pathogenic variants consistent with the patient's clinical symptoms, which supported the diagnosis of acquired FS. We immediately discontinued ADV and switched to entecavir for the treatment of chronic hepatitis B. Meanwhile, calcium and phosphorus supplements were administered. Approximately 3 months later, the patient's pain was significantly relieved, renal function was improved, blood phosphorus levels returned to normal, and urine protein, urine glucose, and other indicators returned to normal. ADV can effectively inhibit the replication of hepatitis B virus and is widely used in patients with hepatitis B. However, since the first case of ADV induced hypophosphatemic osteomalacia was reported in 2008 [20], its side effect of predisposing to renal damage has attracted widespread attention. Although the mechanism of ADV nephrotoxicity is still unclear, most studies have indicated that ADV-induced nephrotoxicity may be related to human proximal tubular drug transporters, mitochondrial toxicity and tubular epithelial damage [21]. ADV is absorbed from the blood by human organic anion transporter 1 (hOAT1) into the proximal convoluted tubules [22], and secreted into the lumen via apical multidrug resistance protein (MRP). Long-term administration of low-dose ADV may induce FS, possibly due to overexpression of hOAT1 and inhibition of MRP [23]. Additionally, its active metabolite, adefovir diphosphate, may impair energy metabolism by inhibiting mitochondrial DNA replication and inducing cytochrome oxidase deficiency [24]. These effects cause ATP depletion, disrupting Na-K-ATPase pump function and the transport of various substances, such as phosphate, amino acids, glucose. The clinical symptoms of ADV induced FS are insidious, with hypophosphatemic osteomalacia as the main manifestation. Patients often present with non-specific bone and joint pain, and may even develop pathological fractures, which makes it prone to missed diagnosis or misdiagnosis. FS induced by ADV at conventional doses mostly occurs 3 to 6 years after the initiation of medication, and is closely related to factors such as the patient's inherent renal status, age, and body weight. Once FS occurs, the suspected drug should be discontinued immediately. Additionally, phosphorus supplementation should be administered, and calcium supplementation may be required if necessary. Most patients' symptoms can be relieved in approximately 12 to 15 weeks.

5. Conclusion

Although large-scale clinical trials have demonstrated that ADV at the conventional dose is safe, long-term use still carries potential risks of renal and bone damage. Therefore, patients receiving ADV should undergo regular monitoring of liver function, renal function, blood phosphorus, and routine urine tests. If renal function impairment occurs, ADV should be replaced immediately. When patients receiving ADV present with bone pain or fractures, FS should be on high alert. The key principles for management of FS should focus on identifying and treating the underlying cause, then correcting fluid, electrolyte, and acid-base imbalances to mitigate symptoms and prevent complications.

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