INSUFFICIENCY FRACTURES DUE TO HYPOPHOSPHETMIC OSTEOMALACIA CAUSED BY ADEFOVIR INDUCED FANCONI'S SYNDROME

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Abstract: In patients with chronic hepatitis B infection with high viral loads, Adefovir dipivoxil (ADV) is a commonly used antiviral drug (1). Though studies have shown 10 mg day dosage of ADV to be safe, very rarely, long term treatment can result in Fanconis syndrome, a generalized dysfunction of the renal proximal tubular cells (2). In Fanconis syndrome, there is impaired reabsorption of important metabolites with increased urinary loss of phosphate leading to generalized osteopenia and osteomalacia causing multiple insufficiency fractures (1). Here we report a case of multiple insufficiency fractures caused by hypophosphatemic osteomalacia due to Fanconis syndrome as a result of long term usage of ADV at the dose of 10mg/day. In the setting of chronic hepatitis B infection causing chronic liver disease, bony metastases from hepatocellular carcinoma could be a close differential to multiple insufficiency fractures and needs to be carefully ruled out. Through this case we would like to indicate that even a conventional dose of 10mg/day of ADV in patients with chronic hepatitis B infection can cause hypophosphatemic osteomalacia associated with Fanconis's syndrome. We recommend that patients treated with long-term ADV should be carefully monitored for the occurrence of ADV-induced Fanconi's syndrome.

Keyword: Fanconi syndrome, Adefovir dipivoxil, Chronic hepatitis B infection, hypophosphatemia, insufficiency fractures

INTRODUCTION

Adefovir dipivoxil (ADV) is a prodrug of Adefovir and is a structurally similar acyclic nucleoside analogue. At a high dosage of 60 to 120 mg / day it has been shown to cause nephrotoxicity leading to an increase in the serum creatinine levels and a decrease in serum phosphorus (2). However, ADV shows an adverse – event profile similar to that of a conventional dose of 10 mg / day (1). It was approved for the treatment of chronic hepatitis B at a dose of 10 mg / day (1). In 2002, it was approved for the treatment of chronic hepatitis B at a dose of 10 mg / day (3). Fanconis's syndrome predominantly affects the proximal renal tubule. It results in dysfunction of the proximal renal tubule causing impaired reabsorption of bicarbonate, amino acids, glucose, urate and phosphate and increased excretion of these solutes in urine (1). There is failure of bone mineralization as a result of impaired synthesis of 1, 25 – dihydroxy vitamin D3 and chronic loss of phosphate (4). The resulting electrolyte imbalance and osteomalacia cause symptoms of muscle weakness, fatigue, bone pain and fractures (1).

The Nephroxicity is usually reversible if therapy is stopped immediately. We report a case of Fanconi's syndrome in a patient with chronic hepatitis B infection on a long term treatment with ADV at a dose of 10 mg/day.

CASE REPORT

HISTORY AND CLINICAL EXAMINATION:

Our patient, a 43 year old gentleman, was found to be HBS Ag positive in 1999, during a pre-vaccination screening while being treated for duodenal ulcer, and has been on intermittent follow up in our institution since then. During a routine follow up in April 2005 he was found to have high viral load and was started on Tab Adefovir 10mg OD and has been on it since then. After initiation of ADV therapy there was significant reduction of viral load with no detectable levels thereafter. He was found to have chronic liver disease with multiple regenerative nodules on ultrasound in February 2009. He presented to the Department of Orthopedics in April 2011 with weakness and pain in the left lower limb and back for the past one and half years. He had exaggeration of pain, needing the assistance of walking aids for the past 2 months. Over the past week his pain worsened to an extent that he was unable to walk. On physical examination, he had normal strength with tenderness over the lumbar spine and anterior chest wall, with no neurologic symptoms.

INVESTIGATIONS

Serological tests were performed showed Alkaline phosphatase of 260 μg/liter; ESR was 20; Vitamin D (25OH) was 6.78ng/mL (normal 20.0 – 32.0ng/mL). Serum calcium was 8.6mg/dL (normal 8.3 – 10.4mg/dL) and serum phosphorous was 0.6 mg/dL (normal range 2.5 – 4.6 mg/ dL). Ultrasound was done for the routine evaluation of chronic liver disease and showed features of chronic liver disease with multiple regenerative nodules. Extremities radiographs showed multiple fractures. MRI was done to further assessment of chronic liver disease, to rule out a hepatocellular carcinoma and also for further evaluation of the fractures.

IMAGING:

Figure 1a: Ultrasound images showing features of chronic liver disease with multiple hyperechoiec nodules suggestive of regenerative nodules. Figure 1b: T2W MRI abdomen shows features of chronic liver disease with multiple regenerative nodules.
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Hot spots on bone scan can be seen in many conditions such as trauma, arthritis, osteomyelitis, Paget’s disease, infarctions, metabolic problems like Cushings, osteomalacia induced fractures and also metastases (5). Our diagnosis of hypophosphatemic osteomalacia induced pathological fractures due to Fanconi’s syndrome secondary to adefovir therapy was made based on the following features:
- fractures in osteopenic and osteomalacic bone
- no soft tissue / marrow involvement
- insufficiency fractures involving the medial aspect of bilateral femur
- atypical site involvement such as ankle joint, not typical for metastases
- very low serum phosphorus, elevated alkaline phosphatase and normal serum calcium levels

Hence, adefovir was immediately stopped and phosphate was supplemented. Subsequently, the laboratory parameters improved, bone and joint pains decreased with significant reduction in analgesic requirements. The patient was asked to follow up on a regular basis for the evaluation of chronic liver disease and the development of hepatocellular carcinoma.

**DISCUSSION**

We have reported a case of multiple insufficiency fractures caused by hypophosphemic osteomalacia due to Fanconi’s syndrome in a patient of chronic hepatitis B on a long term treatment with adefovir at a dose of 10mg per day. The features of fanconi’s syndrome in our patient were long duration bone pain, pathologic fractures and renal tubular dysfunction. Fanconi’s syndrome leads to wasting of essential compounds such as amino acids, glucose, bicarbonate and phosphate in the urine which are normally reabsorbed in the proximal tubule. The diffuse osteopenia, osteomalacia with electrolyte abnormalities cause the bone pain with multiple insufficiency fractures (6). As in our case, it is characterised by normal calcium with a low phosphate and elevated ALP levels (1). The pathophysiology of proximal renal tubule dysfunction is thought to be due to an increase in the adefovir dipivoxil concentration in the mitochondria mediated by inhibition of several ATP – dependant transporters (4). Radiographs reveal diffuse osteopenia with multiple insufficiency fractures. Bone scan shows multiple sites of increased uptake. The various causes of fanconi’s syndrome include: multiple myeloma, amyloidosis, heavy metal poisoning, Vit D deficiency, post renal transplantation, paroxysmal nocturnal hemoglobinuria and drugs such as ifosfamide, Adefovir, Tenofovir, aminoglycosides, valproate, tetracycline and carbonic anhydrase inhibitors.

**CONCLUSION**

In this case, we found that Fanconi’s syndrome can be acquired even with conventional low dose of 10mg /day of adefovir in patients with chronic hepatitis B infection and clinicians should be aware of osteomalacia and insufficiency fractures caused by adefovir dipivoxil.

**RECOMMENDATIONS**

We propose that chronic hepatitis B patients who take adefovir over a long period of time should undergo regular monitoring of biochemical parameters, including tests for serum creatinine, phosphorus and calcium levels. If the laboratory tests indicate that Fanconi’s syndrome is possible, we suggest replacing adefovir with a different antiviral agent in order to prevent complications.

**BIBLIOGRAPHY**


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