

Insufficiency Fractures Related to Low-Dose Adefovir Dipivoxil Treatment for Chronic Hepatitis B

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SUMMARY

We present a case of a 53-year-old woman who developed multifocal insufficiency fractures associated with adefovir dipivoxil (ADV) induced osteomalacia, including recurring metatarsal insufficiency fractures and a subtrochanteric femoral insufficiency fracture requiring surgical fixation. She had received low-dose ADV treatment for 59 months for chronic hepatitis B viral infection at the time of presentation with subtrochanteric fracture. Imaging evidence of multifocal insufficiency fractures and metabolic disease on background of hypophosphatemia is attributed to hypophosphatemic osteomalacia from adefovir-induced renal proximal tubular dysfunction. Radiologists and clinicians should be aware of the possibility of insufficiency fractures in patients receiving ADV therapy to avoid delayed diagnosis and progression of high-risk proximal femoral fractures.

KEY WORDS:

Insufficiency fracture; stress fracture; femoral fracture; osteomalacia; Adefovir

INTRODUCTION

Adefovir dipivoxil (ADV) is an oral antiviral that has seen increased usage in the recent decade for treatment of chronic hepatitis B with improved outcomes, especially in lamivudine-resistant hepatitis B where switching to or adding on ADV was shown to be more effective in preventing a clinical breakthrough.¹ The recommended dose of 10 mg/day is generally well tolerated with no serious adverse outcomes apart from a low risk of nephrotoxicity.²

Since 2008, multiple case reports of hypophosphatemic osteomalacia related to Fanconi's syndrome induced by low-dose ADV therapy (10 mg/day) for hepatitis B have been published,³⁻⁶ mostly involving cases of East-Asian ethnicity. We believe that this is the first reported case of a pathological subtrochanteric femoral fracture requiring surgical fixation on background of multifocal insufficiency fractures related to low dose ADV in the radiology literature. In our literature review, there was only one other case of an ADV related pathological femoral neck fracture treated with total hip arthroplasty reported by Tanaka M *et al.*⁷

CASE REPORT

A 53-year-old woman with chronic hepatitis B infection on long-term medical treatment presented to our orthopaedics clinic with a 3-month history of mechanical pain in the left anterior thigh and groin exacerbated on weight bearing. There was no antecedent trauma and her symptoms progressively worsened with increasing ambulatory difficulty. At the time of presentation, she had been on lamivudine PO 100 mg OM for 88 months and ADV 10 mg OM for 59 months, which was started following a clinical breakthrough from lamivudine resistance.

Initial radiographs of the pelvis and left hip revealed no abnormality. Subsequent magnetic resonance imaging (MRI) of the pelvis showed a nondisplaced transverse subtrochanteric femoral fracture at the medial aspect of the lesser trochanter extending to the anterior cortex (Figure 1), as well as multiple insufficiency fractures at the right sacral ala (Figure 2a), right iliac bone (Figure 2b), anterior column of the left acetabulum (Figure 3a), bilateral pubic body (Figure 3b) and inferior rami (Figure 3c).

The patient underwent an uneventful proximal femoral nail anti rotation (PFNA) fixation and further biochemical and radiographic work-up was initiated on impression of ADV-induced osteomalacia resulting in pathological fracture.

A Tc-99m MDP whole body bone scan (Figure 4) done after surgery showed foci of increased radiotracer uptake at the anterolateral aspects of bilateral ribs and pubic bones compatible with stress fractures. In addition, diffuse mildly increased radiotracer uptake was also demonstrated in the calvarium, mandible, lower lumbar spine and sacrum suspicious for underlying metabolic disease.

A 24-hour urinalysis showed high-normal urine calcium (4.46; normal range, 0.65-6.24 mmol/L), high-normal urine phosphate (21.84; normal range 8.1-22.6 mmol/L), hypermicroalbuminemia (97.6; normal range 0.0-19.0 mg/L) and evidence of proteinuria with raised albumin:creatinine ratio. (432; normal range 0-30 mg/g). Serum alkaline phosphatase (ALP) was increased at 274 (normal range 32-103 U/L) and her serum inorganic phosphate was low at 0.64 (normal range 0.7-1.38 mmol/L). Serum creatinine, (57; normal range 50-90 umol/L), serum total calcium, (2.11; normal range 2.10-2.60 mmol/L), serum

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parathyroidhormone (PTH) (4.0; normal range 0.9-6.2 pmol/L) and 25 hydroxyvitamin D (23.5; normal range 10.1-40.3 ug/L) were within normal limits.

On the basis of the biochemical findings of hypophosphatemia and hyperphosphaturia with raised ALP and normal 25 hydroxyvitamin D, the impaired phosphate reabsorption was attributed to proximal renal tubular dysfunction secondary to ADV induced Fanconi's syndrome. The patient's clinical records were retrospectively reviewed and it was notable that the patient had previously presented on separate occasions with right and left foot pain at 32 and 47 months respectively after initiation of ADV and on both occasions, were demonstrated to have metatarsal stress fractures (Figures 5), which were missed clinically. A prior bone scan done 36 months before her current presentation for work-up of "persistently elevated ALP" also showed mild symmetrical radiotracer activity at bilateral femoral necks suspicious for stress-related changes, nonspecific at that point (Figure 6).

A computed tomography (CT) of the thorax, abdomen and pelvis was also performed to identify any malignant mass or metastases that may suggest oncogenic osteomalacia and this was negative.

The radiological findings of multi-focal insufficiency fractures and scintigraphic features of metabolic bone disease on background of hypophosphatemia lend support to the diagnosis of ADV-induced hypophosphatemic osteomalacia. Post-operative recovery was uneventful and the ADV dose was reduced with subsequent normalization of the phosphate levels.

DISCUSSION

Subtrochanteric femoral fractures are uncommon complications of osteomalacia that mostly necessitate surgical treatment. Pathological fractures of the proximal femoral diaphysis almost always manifest as a transverse fracture configuration through pre-existing Looser zones. The proposed mechanism for predisposition of the upper third of the femoral shaft to fracture is attributed to the concentration of high stresses during weight bearing, especially at the medial cortex, which in the setting of reduced compression strength in osteomalacia due to deficiency of mineralisation, results in zones of cortical bone injury (Looser zones), which precedes the development of a complete fracture.

In ADV-related hypophosphatemic osteomalacia, there is dose-dependent nephrotoxic proximal renal tubular dysfunction with resultant renal phosphate wasting, leading to osteomalacia. The diagnosis requires a high index of suspicion as the patients often present with nondescript, diffuse bone pain of significantly long duration which can be misconstrued as secondary to degenerative bone diseases or general decline. Radiographic examinations offer limited sensitivity and are often inconclusive, as early stress-related bony abnormalities are often not detected on plain radiographs.

Biochemical analysis in the form of 24-hour urinalysis, serum

ALP and serum phosphate often provide clues to the underlying metabolic dysfunction and aid in the differentiation from vitamin D-related osteomalacia. Further evaluation with bone scintigraphy and MRI may then be undertaken, as means of increased sensitivity for diagnosis of osteomalacia and related insufficiency stress injuries.⁸

MRI is highly sensitive for the detection of early insufficiency fractures that are radiographically occult, with demonstration of marrow oedema on fluid sensitive sequences. It is also highly specific for subacute or chronic fractures with the linear fracture line appreciated on both T1-weighted and fluid sensitive sequences.

Bone scintigraphy is a highly sensitive but less specific examination for detection of insufficiency stress injuries and Looser's zones as well as the demonstration of features related to underlying metabolic disorder. Multifocal uptake in the axial and appendicular skeleton are distinctive of stress fractures, the most common locations including the medial aspect of the proximal femurs, pubic bones, dorsal aspect of the proximal ulnae and distal scapulae and ribs. Increased uptake in the calvarium, mandible and anterior rib ends with beaded appearance (rachitic rosary sign) are also highly suggestive of underlying metabolic disorder. Although these metabolic features are not specific for osteomalacia and may be seen in other metabolic disorders, including renal osteodystrophy and primary hyperparathyroidism, the combination of lab findings and supportive metabolic features on bone scintigraphy are diagnostic of underlying hypophosphatemic osteomalacia.⁹

Our patient also developed bilateral recurring metatarsal stress fractures that preceded the subtrochanteric femoral fracture by 2 years. In retrospect, these are likely also related to ADV.

CONCLUSION

Radiologists should be aware of the risk of high-risk subtrochanteric femoral fractures and insufficiency fractures related to low-dose ADV treatment. The diagnosis of osteomalacia may rely on the combined findings, biochemical derangement and typical imaging findings. The recognition of a trend of multiple or recurring insufficiency fractures should prompt follow-up with periodic examinations to include blood calcium and serum inorganic phosphate to monitor for development of hypophosphatemic osteomalacia, shortening the time to diagnosis and preventing the development of subtrochanteric femoral fractures by reviewing the ADV treatment if necessary.

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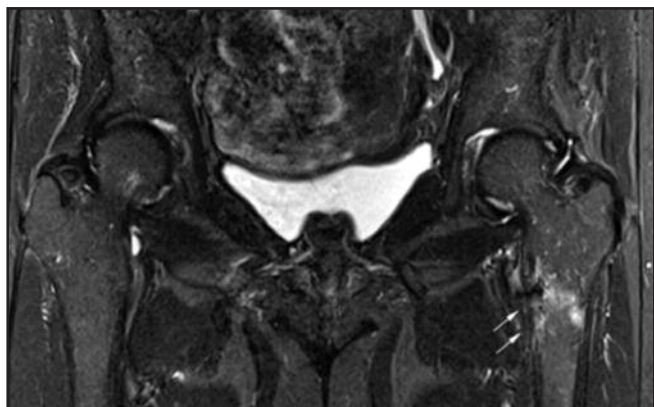


Fig. 1: Coronal T2W TIRM image demonstrating the nondisplaced subtrochanteric femoral fracture at the left proximal femur (white arrows), with associated marrow oedema.

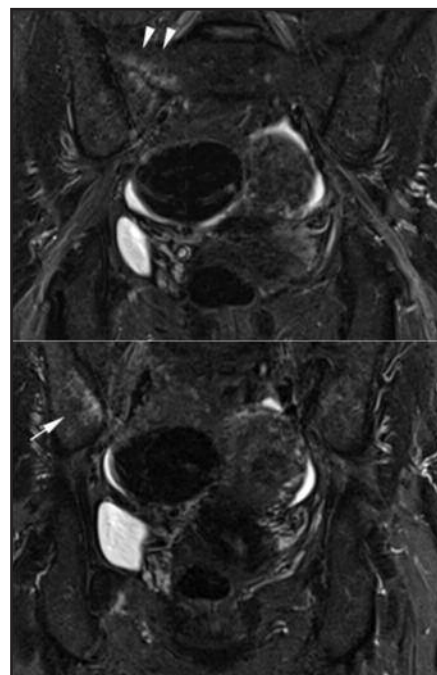


Fig. 2: Coronal T2W TIRM images demonstrating the nondisplaced fracture at the right sacral ala (arrow heads, figure 2a) and right ilium (white arrow, figure 2b) with marrow oedema.

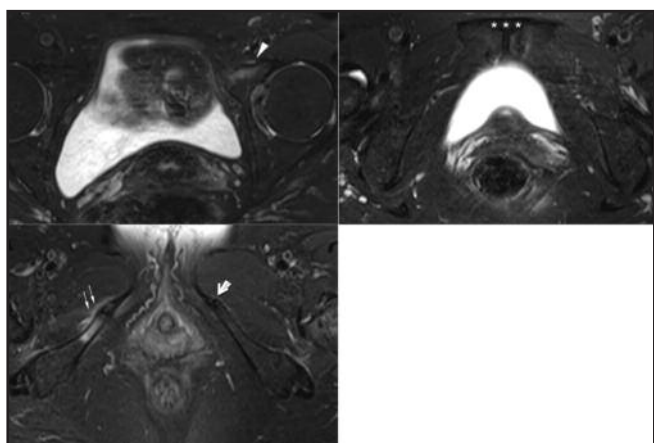


Fig. 3: Axial T2W TIRM images demonstrating marrow oedema associated with fractures of the left acetabular anterior column (arrow head, figure 3a), bilateral pubic bodies (asterisk, figure 3b, with T2W hypointense fracture cleft seen on the left) and bilateral inferior pubic rami (thin arrows on right, thick arrow on left, figure 3c).

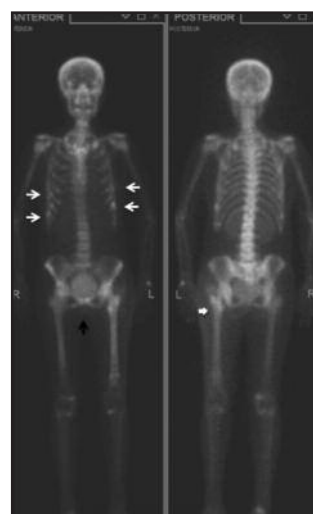


Fig. 4: Tc-99m MDP whole body bone scan post surgical fixation of the left hip subtrochanteric fracture showed foci of increased radiotracer uptake at the anterolateral aspects of bilateral ribs (white arrows) and pubic bones (black arrow) compatible with stress fractures. In addition, diffuse mildly increased radiotracer uptake was also demonstrated in the calvarium, mandible, lower lumbar spine and sacrum suspicious for underlying metabolic disease. Left hip fixation hardware noted with post-surgical radiotracer activity seen in the left femoral shaft (thick white arrow).



Fig. 5: Insufficiency fracture at the right 3rd metatarsal shaft with periosteal reaction 32 months after initiation of oral ADV (white arrow, Figure 5a) and at the left 4th distal metatarsal shaft with callus formation (black arrow, Figure 5b) 47 months after initiation of oral ADV.

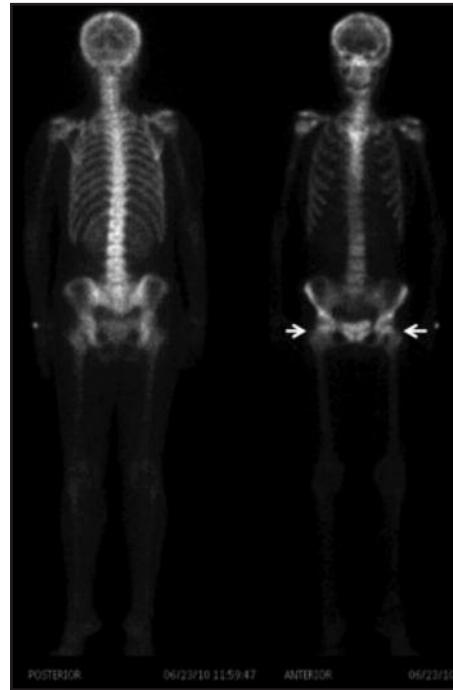


Fig. 6: Tc-99m MDP whole body bone scan performed 36 months after initiation of oral ADV showed mild symmetrical radiotracer activity at bilateral femoral necks suspicious for stress-related changes (white arrows), nonspecific at that point.

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