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Proximal Femur Fracture (31-A3.2) Associated with the Use of Tenofovir by an HIV-positive Patient: Case Report

Fractura de fémur proximal (31-A3.2) asociada al uso de tenofovir en paciente VIH + : Reporte de caso

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Abstract

We present the first case report of a human immunodeficiency virus (HIV)-positive adult patient with a fragility fracture of the proximal femur associated with antiretroviral therapy (ART) with tenofovir disoproxil fumarate (TDF) in Chile. Currently, patients diagnosed with HIV start ART early, resulting in more years of exposure to these drugs. The accumulated exposure time to TDF has been associated with a decreased bone mineral density and progressive renal failure, potentially leading to acquired Fanconi syndrome, osteomalacia, and an increased risk of fracture. We present a case of a 44-year-old, HIV-positive man assessed at the emergency room after a fall from standing height which resulted in a proximal femoral pathological fracture. Laboratory findings at admission revealed hypokalemia, hypocalcemia, hypophosphatemia, and hypovitaminosis D. Multidisciplinary management was performed, with TDF discontinuation, ART change, and supplementation with calcium and vitamin D. Closed reduction and fixation with a long cephalomedullary nail was successful, with early motor rehabilitation, functional recovery, and bone consolidation at 12 weeks. Musculoskeletal pain in HIV-positive patients on ART must raise the clinical suspicion of an adverse drug effect; the follow-up of these subjects must include serial monitoring of renal function and serum calcium and phosphorus levels. Screening and suspicion of such complications would enable an early intervention, improving the patients' condition and preventing pathological fractures.

Keywords

- proximal femur fracture
- antiretroviral agents
- tenofovir
- case report

Resumen

Presentamos el primer reporte de caso en paciente adulto con virus de la inmunodeficiencia humana (VIH +) con fractura por fragilidad en fémur proximal asociada al uso de terapia antirretroviral (TARV) con fumarato de disoproxilo de tenofovir (FDT) en Chile. Actualmente, los pacientes diagnosticados con VIH inician tratamiento precoz

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con TARV, lo que implica mayor cantidad de años de exposición a los fármacos de la terapia. El tiempo de exposición acumulado al FDT se ha asociado a disminución de la densidad mineral ósea y falla renal progresiva, pudiendo el paciente desarrollar síndrome de Fanconi adquirido y osteomalacia, con riesgo aumentado de fractura. Presentamos el caso de un hombre de 44 años, VIH +, evaluado en urgencia tras caída a nivel que resultó en fractura patológica del fémur proximal. Los exámenes de ingreso destacaron hipocalemia, hipocalcemia, hipofosfatemia e hipovitaminosis D. Se realizó manejo multidisciplinario, con suspensión del FDT, un cambio en la TARV, y suplementación con calcio y carga de vitamina D. Se realizó reducción cerrada y fijación con clavo cefalomedular largo, que evolucionó favorablemente con rehabilitación motora precoz; el paciente recuperó su funcionalidad previa, y se observó consolidación ósea a las 12 semanas. La aparición de dolor osteomuscular en pacientes VIH+ en TARV debe levantar alta sospecha clínica de efecto adverso a medicamiento; el seguimiento de estos pacientes debe incluir el control seriado de la función renal y de los niveles séricos de calcio y fósforo. La búsqueda y sospecha de estas complicaciones permitiría una intervención precoz, mejorando la condición de los pacientes y previniendo fracturas patológicas.

Palabras clave
- fractura de fémur proximal
- terapia antirretroviral
- tenofovir
- reporte de caso

Introduction

Patients infected with the human immunodeficiency virus (HIV) can present multiple complications, some immunological, based on the level of CD4 cells, and others associated with the treatment. It has been shown that HIV-positive patients have higher osteoporosis rates[1] and a higher frequency of osteoporotic fractures[2] compared to the general population; the etiology of the fractures is multifactorial.

Several studies[3] have reported the association of tenofovir disoproxil fumarate (TDF) with a greater reduction in bone mineral density compared to other antiretroviral agents. In addition, progressive renal failure has been associated to the excretion of TDF by the kidneys, particularly at the proximal tubule (Fanconi syndrome); this increases the urinary excretion of phosphorus and inhibits vitamin D hydroxylation in the kidneys,[4] inhibiting calcitriol synthesis and resulting in osteomalacia.[5]

According to Bedimo et al.,[6] HIV-positive patients treated with TDF present a 12% increase in the risk of osteoporotic fracture by year of exposure compared to HIV-positive patients not treated with TDF.

The present case report discusses the management and warns about the potential adverse effects and increased risk of fractures in HIV-positive patients submitted to antiretroviral therapy (ART) with TDF.

Clinical Case

A 44-year-old male patient diagnosed as HIV-positive 11 years ago and with class-A chronic liver damage according to the Child-Pugh classification was transferred to an emergency service after a fall from standing height resulting in a left hip injury. The physical examination revealed left-sided muscle deformity, left hip functional impairment, and ecchymosis at the proximal third of the anterior muscle. The patient also referred generalized muscle and bone pain for 1 month.

The laboratory tests revealed mild chronic anemia, thrombocytopenia, hypokalemia, hypocalcemia, and hypophosphatemia, in addition to hypoalbuminemia, hypoproteinemia, severe vitamin D deficit, and preserved renal function. The patient reported treatment with TDF for 5 years, and had no history of previous fractures.

Anteroposterior (AP) hip radiographs and AP and lateral left femur radiographs showed a proximal femur fracture classified as 31-A3.2 in the AO Foundation/Orthopaedic Trauma Association (AO/OTA) classification (►**Figure 1**).

This fragility fracture in a HIV-positive patient treated with TDF was managed multidisciplinary with discontinuation of the TDF, a change in the ART, and calcium and vitamin D supplementation.

The left femur fracture was treated with closed reduction and osteosynthesis with a wide cephalomedullary nail, ensuring a complete segment and avoiding stress areas. The surgery was uneventful (►**Figure 2**). Rehabilitation with load as tolerated started at the first postoperative day.

The patient evolved favorably, with no complications. Serial follow-up evaluations were carried out at 3, 6 and 12 weeks. Twelve weeks after surgery, the radiographs showed signs of consolidation (►**Figure 3**), and the functional assessment revealed a Harris score of 92 points. The laboratory tests showed preserved renal function and normalization of bone metabolism, with the following findings: creatinine: 0.74 mg/dL (normal range: 0.70 mg/dL to 1.2 mg/dL); calcium: 8.7 mg/dL (normal range: 8.4 mg/dL to 10.4 mg/dL); phosphorus: 3.2 mg/dL (normal range: 2.7 mg/dL to 4.5 mg/dL); total protein: 7.1 mg/dL (normal range: 6.0 mg/dL to 8.0 mg/dL); potassium: 3.9 mg/dL (normal range: 3.5 mg/dL to 5.1 mg/dL); and vitamin D: 39.2 ng/mL (normal range: 20.0 ng/mL to 100.0 ng/mL).

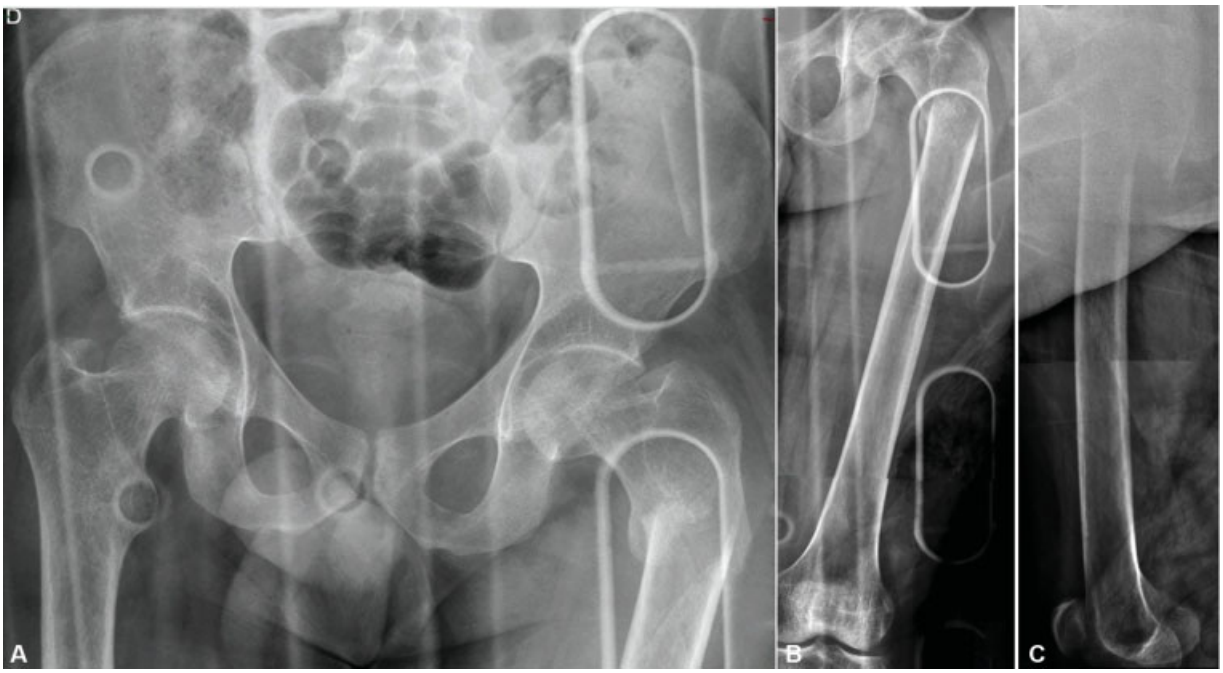

Fig. 1 Anteroposterior (AP) radiograph of the hip (**A**) and AP (**B**) and lateral (**C**) radiographs of the left femur on admission. Note the pathological subtrochanteric fracture.

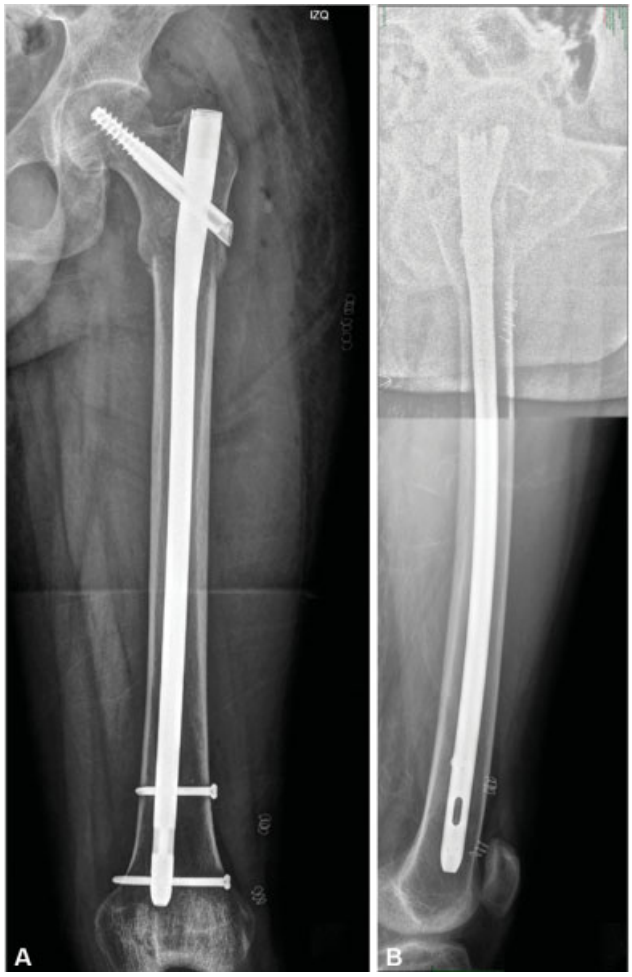

Fig. 2 Anteroposterior (**A**) and lateral (**B**) radiographs of the left femur during the immediate postoperative period.

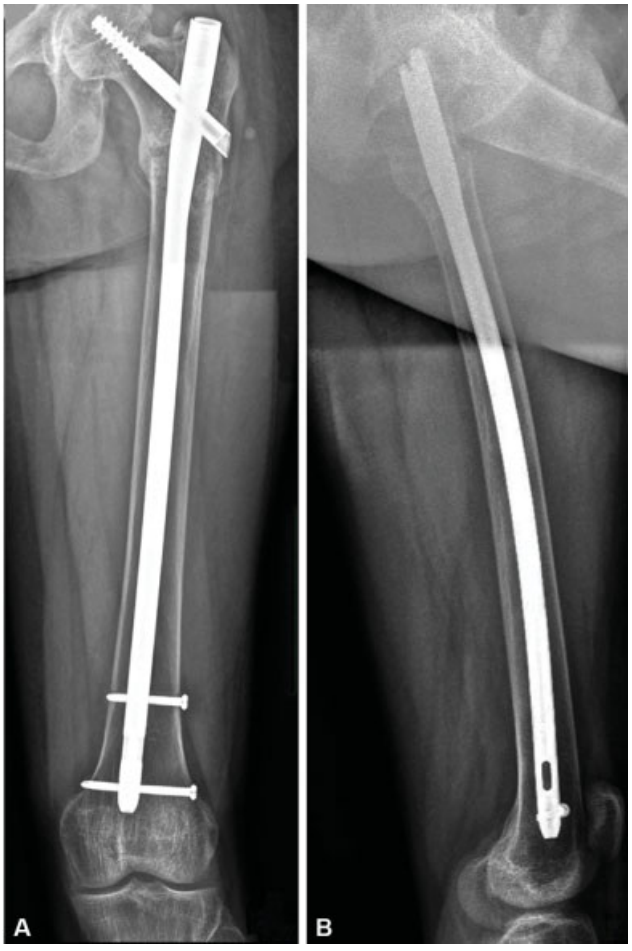

Fig. 3 Anteroposterior (**A**) and lateral (**B**) radiographs of the left femur 12 weeks after surgery. Note the signs of consolidation.

Discussion

Bone metabolism disorders are common in HIV-positive patients, and many subjects present premature osteoporosis and an increased risk of fracture.[7,8]

In an international cohort including 11,820 HIV-positive patients on ART, Borges et al.[9] noted that exposure to TDF was an independent risk factor for fracture.

Another side effect of TDF is renal proximal tubulopathy, but it is less frequently described.[8] Nephrotoxicity has been reported in 1% to 2% of HIV-positive patients treated with TDF.[10] It is known that high intracellular TDF levels interact with mitochondrial DNA;[11] renal proximal tubular injury is associated with this toxic effect on mitochondrial DNA.[12] Renal proximal tubular dysfunction due to TDF may result in increased urinary excretion of phosphorus and inhibition of the 1a-hydroxylation of vitamin D in the kidneys. The inhibition of 1a-hydroxylase in the kidney inhibits the synthesis of 1,25-dihydroxyvitamin D3, leading to osteoporosis secondary to osteomalacia.

The present clinical report describes the first case of a proximal femur fracture associated with the use of TDF in an HIV-positive adult patient in Chile. We have previously reported[13] a case of bilateral hip fracture associated with TDF treatment in a pediatric patient.

The international literature has limited case reports of fragility fractures in patients on ART. The first case was published by Rebolledo et al.[14] in 2011: that of a 54-year-old female patient with bilateral hip fracture who developed Fanconi syndrome after 5 years of TDF treatment.

In HIV-positive patients undergoing treatment with TDF, the presence of musculoskeletal symptoms, such as pain in the muscles or bones, must result in a high index of suspicion of changes in bone metabolism and adverse reactions to drugs. The usual follow-up laboratory tests must include bone metabolism, renal function, and hydric and electrolytic balance tests.

Bone density scan is a useful tool for the early detection of osteoporosis; currently, it is recommended for all HIV-positive patients older than 50 years of age.[8] We also recommend it in patients with bone and muscle symptoms or abnormal findings on bone metabolism laboratory tests, regardless of age.

With laboratory test results showing signs of renal proximal tubulopathy or bone metabolism alterations, as well as bone density scans revealing severe osteoporosis, physicians must consider the discontinuation of the TDF treatment and a change in the ART to manage the complications and reduce the risk of fracture.

Some publications have shown that bisphosphonates can be effective in preventing bone loss due to ART[15] or treating osteoporosis[16] in HIV-positive patients. However, there are no clear guidelines on their use.

The surgical management of these patients is not different from the usual treatment of fragility fractures; in addition, there are no reports of significant differences in terms of infectious complications or consolidation.[17]

In conclusion, the careful evaluation of the patients and the suspicion of drug-related complications are essential for the proper management and prevention of fractures in HIV-positive patients under ART.

It is important to treat these patients with a multidisciplinary team, to change the ART regimen in favor of drugs with milder effects on bone quality, to correct metabolic disturbances, and to provide a timely surgical treatment that enables early movement and rehabilitation to avoid further complications.

Conflict of Interests

The authors have no conflict of interests to declare.

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