Tenofovir Induced Fanconi Syndrome Complicated by Bilateral Neck of Femur Fractures

Sir,

Tenofovir disoproxil fumarate (TDF) is considered a first-line drug for the treatment of human immunodeficiency virus infection (HIV).[1] TDF is an acyclic nucleotide analog of adenosine monophosphate, which has emerged as a highly effective antiretroviral agent. Accelerated bone loss and higher rates of osteopenia and osteoporosis have been noted among HIV-infected individuals.[2,3] Rates of osteoporotic fractures have also been shown to be higher among HIV-infected patients than age-matched controls.[4,5] Tenofovir has been found to be associated with a greater decline in bone mineral density (BMD) than other antiretroviral agents.[6] Here, we report a case of Tenofovir- induced Fanconi syndrome which led to osteomalacia and osteoporosis.

This 56-year-old lady, who is a homemaker, with three children presented to the Orthopedics outpatient department with bilateral pathological fractures of the neck of the femur. Pelvis X-ray showed a compressive stress fracture of the medial cortex of both femoral necks (L>R) [Figure 1]. It also showed the evidence of osteoporosis. Her magnetic resonance imaging showed suspicious linear undisplaced fracture with minimal surrounding marrow edema in the proximal shaft of the left femur. She was then referred to the Endocrinology team for further evaluation of osteoporosis and bilateral pathological fractures of the neck of the femur. She had attained menopause 18 years ago but was not on calcium or 25- hydroxy vitamin D supplements since then. She had a past history of tuberculosis (tuberculoma) and was treated with a full course of category 2 anti-TB medication 7 years ago.

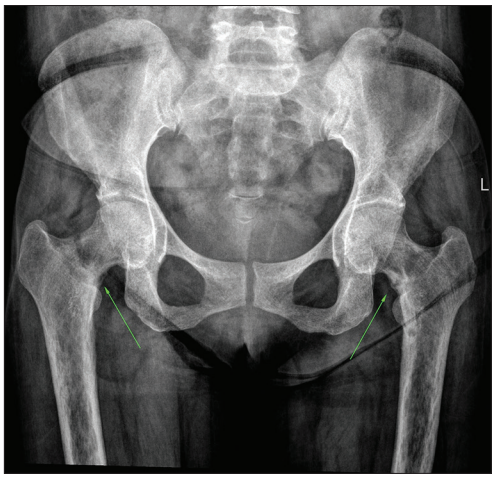

Figure 1: X-ray- hip and pelvis – Pre-treatment. Compressive stress fracture of the medial cortex of both femoral neck (L>R)

She was also diagnosed with HIV infection 8 years ago and has been on antiretroviral therapy (combination of Tenofovir, Lamivudine, Efavirenz) since then, with good adherence. She was diagnosed to have primary hypothyroidism 8 years ago, and she has been on T. Thyroxine 100 mcg a.m. once a day (OD) since then. She was also on Atorvastatin 20 mg OD for dyslipidemia. She was suspected to have Tenofovir-induced osteoporosis with multiple fractures. The presence of normal calcium (9.7 mg/dL (normal range: 8.70–10.70)) with low phosphorus (2.27 (normal range: 2.50–4.50)) and elevated alkaline phosphatase (375 (normal range: 30–120) suggested the presence of osteomalacia. The 25-hydroxy vitamin D level was 22.3 ng/mL (normal range: 30.0–100.0), and serum creatinine was 1.02 mg/dL (normal range: 0.50–1.20). A low parathyroid hormone (PTH) value of 12.5 pg/mL (normal range: 6.0–80.0) which is unusual in osteomalacia, suggested the presence of adynamic bone disease and a combination of osteoporosis and osteomalacia.

The bone mineral density as measured by the dual-energy X-ray absorptiometry (DXA) scan revealed marked osteoporosis in both femurs (T score - 3.2) and the left forearm (T score- - 3.7). The lumbar spine showed osteoporosis (T score- - 2.6) [Figure 2]. Proximal renal tubular acidosis was documented on venous blood gas which revealed hyperchloremic metabolic acidosis. Lowered Tmp/GFR confirmed the presence of phosphaturia. These findings along with aminoaciduria and glycosuria in this patient led to a diagnosis of Fanconi syndrome. As Tenofovir is known as an inciting agent for Fanconi syndrome, this medication was stopped, and she was switched over to zidovudine/Lamivudine and Efavirenz.

She was additionally treated with calcitriol, cholecalciferol, and calcium supplements with which she improved. Now she is doing well, and her bone pains are better. She is now able to independently walk around without a walker after 6 months of treatment. Her calcium, phosphorus, alkaline phosphatase, and PTH have also improved. Her repeat X-ray showed healed stress fractures with cortical thickening and endosteal sclerosis of both femoral necks [Figure 3].

Low bone mineral density is consistent with a diagnosis of osteopenia or osteoporosis, and it occurs in 40%–90% of HIV-infected individuals.[7] Although little is known regarding the pathogenesis of the changes in the body and bone composition in HIV-positive patients, it is likely that these changes are caused by the virus, antiretroviral therapies, or chronic inflammation.[8]

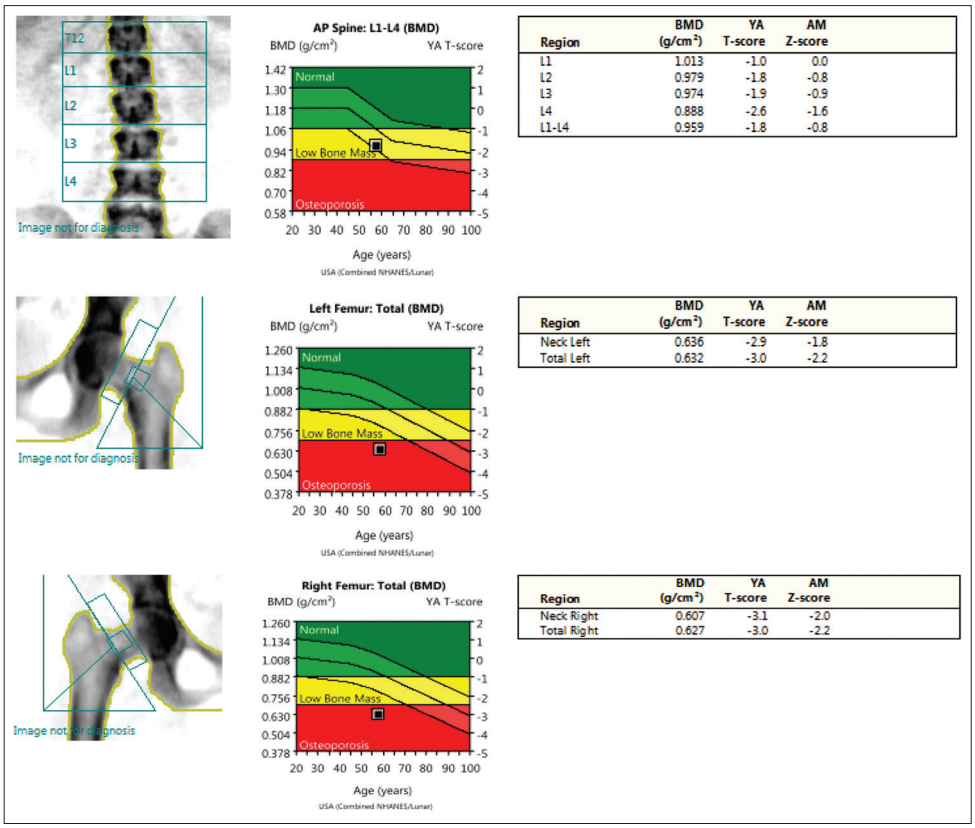

Figure 2: Bone mineral density

In adults, the decrease in bone mineral density has also been associated with prolonged treatment with Tenofovir,[9,10] indicating that medication effects may contribute to the initial increase in loss of bone mineral density after the start of treatment with antiretroviral therapy. An observational cohort study was done by Ayami *et al.* in an HIV infection–related drug survey of patients treated with TDF between April 2004 and March 2013. They found that treatment with TDF for≥5 years increases the risk of bone fractures in younger men, in addition to that seen in older postmenopausal women.[11]

Studies in rhesus monkeys and humans have indicated that bone fractures associated with antiretroviral therapy are due to losses in bone mineral density.[12-14] In particular, the antiretroviral drug TDF is associated with decreased bone mineral density and increased bone turnover markers, which leads to osteoporosis-related bone fractures.[13,15]

Another study showed that endocrine disruption [PTH - fibroblast growth factor 23 (FGF23)] is a primary contributor to TDF-associated bone mineral density decline in the age group of 15–22 years.[16]

Tenofovir is one of the highly utilized drugs among the antiretroviral therapies, and the physician should be made aware of Fanconi syndrome associated with its usage. Hence, patients on Tenofovir should be closely monitored for bone mineral density, calcium, albumin, and phosphorus.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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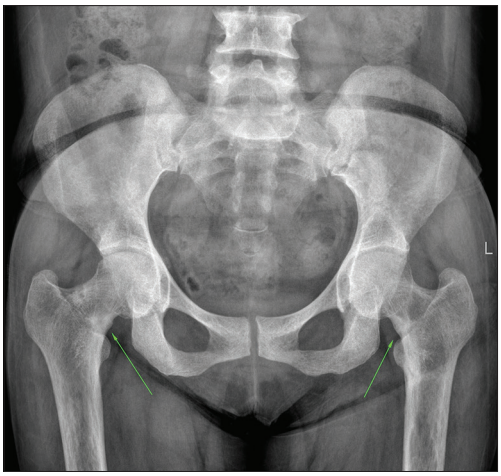

Figure 3: X-ray hip and pelvis 6 months after treatment. Healed stress fracture with cortical thickening and endosteal sclerosis of both femoral necks

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