During the past decade, improvements in human immunodeficiency virus (HIV) treatment have provided an increase in the expected lifespan of HIV-infected patients. Therefore, side effects which are both related to disease and treatment are more common currently.

Musculoskeletal pain is usually seen in HIV-infected patients. Early differential diagnosis and treatment are important to prevent more challenging complications.[1] Osteoporosis, pathological fractures, and avascular necrosis are the most common musculoskeletal complications of HIV.[2-4]

Tenofovir is the first and still most commonly used agent in these patients.[5] Currently, it is mostly used in combination with other antiretrovirals. Tenofovir is a nucleoside reverse transcriptase inhibitor and the cumulative exposure of tenofovir treatment is an independent risk factor for osteoporotic fractures.[6] Therefore HIV-infected patients, particularly those who are on antiretroviral therapy, should be screened regularly for the loss of bone mineral density (BMD). Occult fractures should be kept in mind in these patients.

In this report, we present an HIV-infected patient presenting with right thigh pain and diagnosed with a femoral neck stress fracture.

CASE REPORT

A 54-year-old woman with anterior thigh pain was referred to our clinic from the neurosurgery department as radiculopathy. She complained pain for three months. She was admitted to our outpatient clinic twice; however, no pathology was detected. She was typically an exceptionally dynamic individual, yet disappointed with her constrained capacity to walk and she had no history of prior trauma. In her medical history, she had a three-year history of HIV. She was being treated with...
Femur fracture in a HIV-positive patient

Tenofovir 300 IU, elvitegravir 150 IU, emtricitabine 200 IU, and cobicistat 150 IU. She was also on ibandronic acid treatment for 16 months in terms of the risk of tenofovir-induced osteoporosis. On her physical examination, lumbar lordosis was normal. Lumbar flexion and extension were painless. The range of motion of the right hip was mildly limited and painful. Supine straight leg raising test was painful due to shortened hamstring muscles. The neurological examination included lower extremity strength, and sensory examination findings were normal. No atrophy of the lower extremity muscles was seen. Firstly, routine pelvic anteroposterior plain X-ray was done. Coxofemoral joint spaces were normal bilaterally (Figure 1). The patient underwent pelvic magnetic resonance imaging with a preliminary diagnosis of osteonecrosis. There was bone marrow edema in the inferomedial part of the femoral neck (Figure 2). To exclude other conditions such as metastases, whole-body bone scintigraphy was performed which showed an increased activity around femoral neck, suggesting a stress fracture.

In March 2016, BMD in the femoral neck region was found to be 0.785 g/cm². According to the Fracture Risk Assessment Tool (FRAX®) scoring system, 10-year probability of the hip fracture was found to be 0.7%. However, ibandronic acid treatment started to prevent the patient from tenofovir-related fractures (secondary osteoporosis). One year later, in March 2017, the BMD in the femoral neck region was found to increase as 0.823 g/cm². The patient continued the ibandronic acid treatment. The stress fracture occurred in an atypical region of the femoral neck at 16 months of the therapy. Blood test results showed a mild hypophosphatemia (2.3 mg/dL; reference range: 2.60 to 4.50 mg/dL). Serum calcium level was normal. Serum alkaline phosphatase level increased (160 U/L; reference range: 35 to 105 U/L). The level of parathyroid hormone and 25-hydroxyvitamin D levels were normal owing to regular follow-up at our osteoporosis outpatient clinic. Urinalysis showed an increased phosphaturia, while no calciuria was detected.

Based on the recommendation of the orthopedic surgeon, intramedullary nail stabilization was not applied at this stage. Instead, the patient was given a cane, and weight-bearing activities were limited. She started a physical therapy program. Also, ibandronic acid therapy was switched to risedronate therapy. The human leukocyte antigen-B5701 (HLA-B5701) allele test was performed to detect abacavir hypersensitivity and the result was found to be negative. The antiretroviral regimen was, then, switched to the abacavir 600 mg, dolutegravir 50 mg, and lamivudine 300 mg. The treatment was well tolerated. At eight weeks of the follow-up, she had no complaint during standing and walking. The range of motion of the right hip was normal and painless. A written informed consent was obtained from the patient.

Figure 1. An anteroposterior plain X-ray of pelvis.

Figure 2. A magnetic resonance imaging scan of pelvis showing bone marrow edema in inferomedial part of femur neck.
DISCUSSION

Human immunodeficiency virus is a worldwide pandemic disease. A normal life expectancy can be anticipated in HIV-infected patients with newly-developed medications. However, the increased life expectancy increases the rate of disease- and treatment-related complications. Avascular necrosis and osteoporosis are general musculoskeletal complications of HIV. It is reported that HIV-infected patients have a lower BMD than healthy individuals.[6]

The pathophysiology of osteoporosis in HIV is complicated. The HIV-associated factors such as viral effects, systemic inflammation, and side effects of antiretroviral regimen are thought to be main mechanisms.[7] Persistent systemic inflammation and elevated pro-inflammatory cytokines such as interleukin-1, interleukin-6 may lead to osteoclast activation.[8] Not only systemic inflammation, but also direct toxic effects of some viral proteins may disrupt the osteoblastic cell functions.[9]

In a meta-analysis, a prevalence of 6 to 16% of osteoporosis and 33 to 65% of osteopenia was found in HIV-infected patients.[10] Also, antiretroviral regimen was found to be associated with a higher risk of loss of BMD. Conventional risk factors for osteoporosis, such as hypogonadism, low body mass index, alcohol use, and smoking which can be frequently seen in HIV-infected patients, have been attributed as additional risk factors for osteoporosis.[11]

Antiretroviral drugs are known to increase osteoporosis through various mechanisms including induced osteoclastic functions, inhibited osteoblastic functions, and changes in calcium and phosphate balance.[12] Tenofovir has been reported, as it is most commonly associated drug with the decrease in BMD in antiretroviral drugs. There are remarkable studies available drawing attention to reduction in BMD with tenofovir.[13-15] A study investigating the fracture data in HIV-infected patients on antiretroviral therapy reported that vertebrae were the most frequent sites of fractures, followed by the lower extremities.[16] In particular, foot fractures were thought to be related to antiretroviral therapy in HIV-infected patients.[17-19] A recent meta-analysis including 12 studies showed that HIV-infected patients had a higher risk of vertebral fractures compared to controls.[20] Also, Llop et al.[21] reported the high prevalence of vertebral fractures in older HIV-infected patients and suggested using routine spinal plain graphs during follow-up. However, there is a limited number of data about femur fractures in HIV-infected patients in the literature.

Bisphosphonates are known to be the main drugs to prevent fragility fractures in HIV-infected patients. Natsag et al.[22] showed the positive effect of alendronate in HIV-infected patients, particularly in those with an increased serum C-telopeptide levels. Data on the efficacy of the other drugs such as denosumab or teriparatide are not sufficient in HIV-infected patients.[23] On the other hand, long-standing use of the bisphosphonates is related to an increased risk of the atypical femur fractures.[24-26] These fractures usually occur in patients who are on long-term bisphosphonate therapy and seen on the lateral aspect of the femur diaphysis. In our case, the stress fracture occurred in the femoral neck at 16 months of therapy. In these respects, it did not resemble a bisphosphonate-related atypical femur fracture. In addition, our patient was on ibandronic acid treatment, when the femoral stress fracture occurred. Ibandronic acid is known to be not as protective as other bisphosphonates in preventing hip fractures.[27] Therefore, ibandronic acid therapy was switched to risedronate therapy. Also, she continued calcium and vitamin D combination. At eight weeks, she was able to resume her daily living activities.

In conclusion, diagnosis before fracture displacement in these patients may increase the success of conservative treatment. Physiatrists and orthopedic surgeons should be aware of musculoskeletal pain in patients infected with HIV, particularly in those receiving antiretroviral therapy to prevent more severe emerging complications.

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