Effects of Bilateral Distal Femoral Stress in a Patient on Long-Term Pamidronate

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Abstract

Recent studies have shown an association between long-term bisphosphonate therapy and low-energy subtrochanteric femoral fractures. These fractures have the unusual characteristics of occurring after a period of prodromal symptoms such as local pain, stress reaction, and low-energy transverse or oblique fractures in the subtrochanteric area of the femur.

In this article, we present the case of a 62-year-old patient who was on pamidronate when she fell and sustained a femoral fracture resulting from bilateral stress phenomena in the distal third of the femoral shaft. Before the fracture, she had osteoporosis (confirmed with dual-energy x-ray absorptiometry) and prodromal symptoms in the right thigh. She also had left thigh pain radiating to the left knee, which was attributed to lower thigh pain from a prior diagnosis of osteoarthritis (OA) in the left knee. The femoral fracture healed with retrograde nail fixation, the left thigh pain resolved with prophylactic nail fixation, and pamidronate therapy was continued.

Management options for femoral stress phenomena in patients on long-term bisphosphonates include discontinuation of the medication and prophylactic stabilization of the femur. Associated ipsilateral knee OA, present in our patient's case, may be a *red herring* in distal femoral stress phenomena.

Bisphosphonates are an integral part of osteoporosis management. They reduce bone resorption and thereby reduce overall bone loss and improve bone density.[1,2] However, recent studies have shown an association between long-term alendronate use and stress fractures in the femoral shaft.[3-6] These fractures have a characteristic presentation. Often, prodromal progressive midthigh pain occurs with no history of trauma and, if unrecognized, a low-energy subtrochanteric femoral shaft fracture may follow.

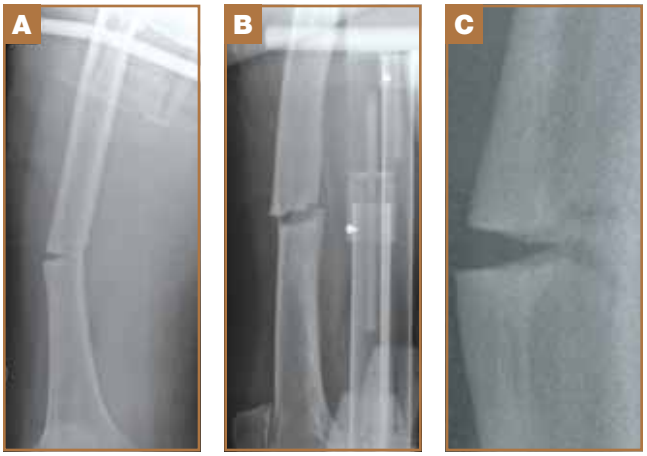

Figure 1. Anteroposterior (A) and lateral (B) radiographs of right femur show transverse distal femoral shaft fracture through stress riser over lateral cortex. Magnified view of right femoral fracture (C) shows thickened lateral cortex, both periosteal and endosteal.

In this article, we present a case of bilateral distal femoral shaft stress phenomena in association with long-term pamidronate therapy. Given the unusual site, prodromal pain could be attributed to preexisting osteoarthritis (OA) of the knee.

The patient provided written informed consent for print and electronic publication of this case report.

Case Report

A 62-year-old woman presented with pain and deformity in the right thigh after falling during a walk. Medical history included hypertension, OA of the left knee, and osteoporosis confirmed with dual-energy x-ray absorptiometry. Her T-score improved from -3.8 (before osteoporosis treatment) to -3.0 (after 3 years of treatment). As she could not tolerate the persistent gastroesophageal reflux and vomiting brought on by alendronate, she was started on intravenous pamidronate 60 mg every 3 months. She had been on that regimen 5 years before presentation. There were no previous osteoporosis-related fractures.

Radiographs showed a transverse fracture of the distal femoral shaft with lateral cortical thickening (**Figures 1A-C**).

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On closer questioning, the patient confirmed that she had experienced some discomfort in the right knee and thigh for a few months. She attributed similar pain in the left knee and thigh to the knee OA she has had for a few years. Radiographs of the left femur showed similar lateral cortical thickening at the distal femoral shaft and advanced OA of the left knee (**Figure 2**).

The right femoral shaft fracture was managed with retrograde femoral nail fixation. The patient did not want to stop pamidronate as she was more concerned about her osteoporosis. The right femur healed (**Figure 3**). After recovery, the patient was offered prophylactic femoral nail fixation for the left femur to relieve the persistent left thigh pain radiating to the left knee. She initially refused surgery, but requested it 4 months after the index presentation. Based on significant OA in the left knee, her surgical options were either retrograde femoral nail stabilization or total knee arthroplasty with a stemmed femoral component to bypass the stress phenomena in the distal femur. Patient preferred and underwent nail fixation (**Figure 4**).

Figure 2. Anteroposterior radiograph of left distal femur and knee shows characteristic lateral cortical thickening and advanced osteoarthritis of left knee.

Figure 3. Anteroposterior and lateral radiographs of right femur show retrograde femoral nail and healed fracture.

Figure 4. Anteroposterior and lateral radiographs of left femur after prophylactic nail fixation.

The patient continued pamidronate under the care of her rheumatologist. As of this writing, she was still under orthopedic care. At 2-year follow-up, there was no thigh pain, but there were moderate osteoarthritic symptoms in the left knee for which she declined surgical intervention. She was independent, able to perform activities of daily living, and able to walk with a cane for distances up to a half-mile outdoors.

Discussion

As bisphosphonates have 2 phosphonate groups, they bind calcium, and thereby accumulate in high concentrations in bone. Alendronate and pamidronate are nitrogenous bisphosphonates with similar mechanisms of action. They block the enzyme farnesyl diphosphate synthase in the mevalonate pathway, which prevents formation of metabolites (farnesol, geranylgeraniol) essential for connecting small proteins to the cell membrane (prenylation). This leads to alterations in the ruffled border of the osteoclast, causing osteoclast inhibition, bone turnover, increased bone mass, and improved mineralization.

Long-term alendronate has been linked to specific types of proximal femoral shaft fractures.[3,4,6] Radiologic features include lateral cortex thickening (periosteal, endosteal) and transverse or oblique fractures in the subtrochanteric or midfemoral shaft regions. This type of fracture pattern and these radiologic features at a relatively younger age are character-

istic of patients taking alendronate.[4,7] The subtrochanteric area of the femur is exposed to high bending forces.[8] Because bisphosphonates have the effect of reducing bone resorption, they can interfere with bone remodeling and biomechanical properties in animal models.[9,10] Impaired bone remodeling in a high-stress area could be the cause of these stress fractures in the subtrochanteric region.

Studies have shown the beneficial effects of bisphosphonates persist after discontinuation of therapy. Five years after bisphosphonates were discontinued, bone mineral density was higher than its baseline, pretreatment levels,[11] and there were only slight increases in vertebral fracture.[12] Therefore, in the presence of stress phenomena and associated fractures in the femoral shaft, it seems logical to discontinue bisphosphonates and follow-up the femoral lesion, as discussed by Das De and colleagues.[13] In the event of a fracture, locking nail fixation, the standard treatment for femoral shaft fracture, is adequate.[13] If lesions are bilateral, there is a case for prophylactic stabilization of the femur to allow early full weight-bearing mobilization.

Our patient's lesions were in the distal femur, which is difficult to explain, as most of the bending stresses go through the subtrochanteric region. The femoral shaft radius of curvature appeared to be within normal limits, and there were no obvious deformities in either femoral shaft. These stress phenomena in the distal femur were identical to characteristics described in the reports on alendronate-associated stress fractures, except for the site of occurrence. The different site we identified and the fact that the patient was taking pamidronate are 2 distinguishing features when compared with previously reported stress fractures. We believe that patients on long-term therapy with any bisphosphonate should be closely monitored for stress phenomena throughout the femoral shaft. The presence of associated OA could well be a *red herring*.

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This paper will be judged for the Resident Writer's Award.