Case Report / Olgu Sunumu

Bilateral Incomplete Atypical Femoral Fracture due to Long-Term Bisphosphonate Use: A Case Report

Uzun Süreli Bifosfonat Kullanımına Bağlı Olarak Gelişen Bilateral İnkomplet Atipik Femur Fraktürü: Bir Olgu Sunumu

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Abstract

Although the overall safety profile of bisphosphonates (BP) is favorable, adverse effects associated with long-term use have came up during recent years. In this report, a case of bilateral incomplete atypical femoral fracture (AFF) due to prolonged BP use was presented. A 69-year-old patient, who has been in surgical menopause for 20 years and was started on BP following vertebral fracture almost 10 years ago, was admitted with thigh pain, which was increased two weeks ago. On physical examination, she had antalgic gait, increased thoracic kyphosis and tenderness to percussion over the thoracolumbar region. Lateral cortical thickness in the subtrochanteric region of both femurs and cortical radiolucency on the left femur were observed on plain radiography. Loss of height in L3 and L4 vertebrae was detected on vertebral radiography. Serum 25-hydroxy vitamin D [25(OH) D], parathyroid hormone, alkaline phosphatase and calcium levels, along with osteoporosis markers were all within the normal ranges. As the patient was diagnosed with AFF, BP therapy was terminated and vitamin D-calcium supplementation was continued. Since she did not have severe pain, conservative management (limited weight bearing, using a walking stick) was recommended for 3 months. Teriparatide therapy was started and she was discharged with recommendations. AFF, which is a rare disorder, should be kept in mind in patients on long-term BP treatment who are admitted with thigh pain and, necessary interventions should be tailored before the occurrence of complete fracture.

Keywords
Atypical femoral fracture, bisphosphonate, osteoporosis, teriparatide

Öz

Bifosfonatların (BP) güvenlik profili genel olarak iyi olmakla birlikte son zamanlarda uzun süreli kullanımları ile ilişkilendirilebilen yan etkiler gündeme gelmeye başlamıştır. Bu olgu raporunda uzun süre BP kullanımına bağlı olarak gelişen bilateral inkomplet atipik femur fraktürü (AFF) olgusu sunulmuştur. Yirmi yıldır cerrahi menapozda olup, 10 yıl kadar önce vertebra kırığı sonrasında BP tedavisi başlanan 69 yaşındaki hasta, 6 ay önce başlayan ve 2 haftadır artış gösteren uyluk ağrısı nedeniyle başvurdu. Fizik muayenesinde antaljik yürüyüşü mevcuttu. Torakal kifozu artmıştı. Künt perküsyonla torakolomber vertebral hassasiyeti mevcuttu. Direkt grafilerinde her iki femurda subtrokanterik bölgede lateral kortekste kalınlaşma ve solda kortekste radyolusen görünüm tespit edildi. Vertebra grafilerinde ise L3 ve L4 vertebralarda yükseklik kaybı mevcuttu. Serum 25-hidroksi vitamin D [25(OH)D], parathormon, alkalen fosfataz ve kalsiyum düzeyleri ile osteoporoz markerları normal sınırlardaydı. AFF olarak değerlendirilen hastanın BP tedavisi kesilerek kalsiyum ve vitamin D takviyesine

Anahtar Kelimeler
Atipik femur fraktürü, bifosfonat, osteoporoz, teriparatid

Received/Geliş Tarihi : 23.12.2014
Accepted/Kabul Tarihi : 12.02.2015

doi:10.4274/meandros.2033

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devam edildi. Ağrısı çok şiddetli olmadığından 3 ay süre ile konservatif tedavi (sınırlı yük verme, baston kullanımı) önerildi. Teriparatid tedavisi başlanarak önerilerle taburcu edildi. Uzun süredir BP tedavisi altında olan ve uyluk ağrısı ile başvuran hastalarda nadir görülen bir durum olan AFF akılda tutulmalı ve komplet kırık aşamasından önce gerekli yaklaşımlarda bulunulmalıdır.

Introduction

Bisphosphonates (BPs) are potent inhibitors of osteoclast-mediated bone resorption. Although the overall safety profile of BPs is favorable, adverse effects associated with long-term use have came up during recent years. One of them is atypical femoral fractures (AFF) (1-6). The absolute risk of AFF is 3.2-50/100.000 patient-years. The risk increases with prolonged therapy. AFF incidence in patients receiving BPs increased from 1.78/100.000 patient-year for 2 years of use to 113.1/100.000 patient-year for 10 years of use (7,8). When BPs are stopped, the risk of AFF declines (8). There have been reports of AFF with denosumab which is another antiresorptive agent (8,9). The pathogenesis of AFF can be related to long-term suppression of bone turnover. The recent evidence suggests that AFF is a "stress or insufficiency fracture" (8). Generalized suppression of remodeling as a consequence of BP therapy does not negatively affect periosteal and endosteal callus formation. BPs localize in areas developing stress fractures and, suppression of intracortical remodeling at the site of an AFF could impair the process by which stress fractures normally heal (8,10). The risk difference between ethnical groups suggests that the lower limb geometry contributes to AFF formation. The lateral cortex of the femur sustains increased tensile stress due to bending. People with lower limb geometry that could exacerbate this effect, such as bowed femur, as well as Asian race may precipitate the damage in the lateral cortex of the femur (8). AFFs occur in the subtrochanteric region or diaphysis of the femur. These fractures are associated with no or minimal trauma. AFF should be suspected in patients with thigh pain and findings of stress fracture of the femur. The prevalence of bilateral AFFs is high and, therefore, contralateral femur should also be examined. Periosteal thickening of the lateral cortex together with a transverse cortical lucency can be detected on plain radiographs in the early stages. Further options for imaging include magnetic resonance imaging, computed tomography and bone scintigraphy. It is accepted as "incomplete AFF" when cortical lucency accompanies. Incomplete AFFs involve only the lateral cortex. Complete AFFs have some common features; fracture line originates at the lateral cortex, transverse or short oblique configuration, extending through both cortices and the fracture may have a medial spike; noncomminuted fractures or minimal comminution can be seen (7,8). Focal periosteal reaction accompanied by endosteal thickening of the lateral femoral cortex is described as focal lateral thickening. Medial spike, typically arising from the distal but possibly also from the proximal femoral fragment, is defined as medial cortical projection of the fracture (11). Since the medial cortex is more intact, it terminates with a protrusion (spike) when the fracture advances to the medial cortex. According to the American Society of Bone and Mineral Research (ASBMR) revised definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five major features must be present. None of the minor features is required, but have sometimes been associated with these fractures. The major and minor criteria according to the revised ASBMR diagnostic criteria of AFF are as follows (8).

Major Features

1) The fracture is associated with minimal or no trauma,

2) The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur,

3) Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex,

4) The fracture is noncomminuted or minimally comminuted,

5) Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site.

Minor Features

1) Generalized increase in cortical thickness of the femoral diaphysis,

2) Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh,

3) Bilateral incomplete or complete femoral diaphysis fractures,

4) Delayed fracture healing.

AFF is associated with certain medications (e.g. BPs, glucocorticoids, proton pump inhibitors) and comorbid conditions (e.g. diabetes, rheumatoid arthritis, vitamin D deficiency). These conditions, which were formerly listed within minor criteria according to the 2010 ASBMR diagnostic criteria, were removed from the revised diagnostic criteria. Fractures with features similar to AFF have been reported in patients with other bone diseases (e.g. hypophosphatasia, pycnodysostosis and osteopetrosis) and these conditions should be kept in mind in the differential diagnosis. However, their bilaterality as well as prodromal pain are the distinguishing clinical features of AFF (8,10).

In the treatment of AFF, it is suggested to discontinue the antiresorptive agent and prescribe adequate supplementation of vitamin D and calcium. Prophylactic nail fixation is recommended for incomplete fractures (with cortical lucency) accompanied by pain. If the patient has minimal pain, conservative therapy with limited weight-bearing through the use of crutches or a walker may be considered (8,10).

In this report, a case of bilateral incomplete AFF due to prolonged BP use is presented.

Case Report

A 69-year-old patient, who has been in surgical menopause for 20 years, was started on BP therapy following a vertebral fracture almost 10 years ago. During this period, she used different BPs. She was admitted to our outpatient clinic with mild thigh pain lasting for 6 months and her complaints were increased in the past two weeks. Her medical history revealed no systemic diseases. Certain comorbid conditions and medications such as diabetes, rheumatoid arthritis, vitamin D deficiency, glucocorticoids, proton pump inhibitors, which can be related with AFF, were questioned. None of these conditions were present in our patient. Her systemic physical examination was normal. On musculoskeletal examination, it was observed that she had antalgic gait, increased thoracic kyphosis and tenderness to percussion over the thoracolumbar region. Lateral cortical thickness of the subtrochanteric region on both femur and cortical radiolucency on the left femur were found on anteroposterior and lateral femur radiography (Figure 1). Loss of height in L3 and L4 vertebrae was detected on vertebral radiography. Complete blood count, sedimentation rate, routine biochemical tests, protein electrophoresis, 25-hydroxy vitamin D [25(OH)D] and parathyroid hormone levels were within the normal ranges. C-terminal telopeptide of type 1 collagen (CTX), which is a bone resorption marker, was below the normal range. Bone mineral density was evaluated using dual-energy x-ray absorptiometry (Hologic

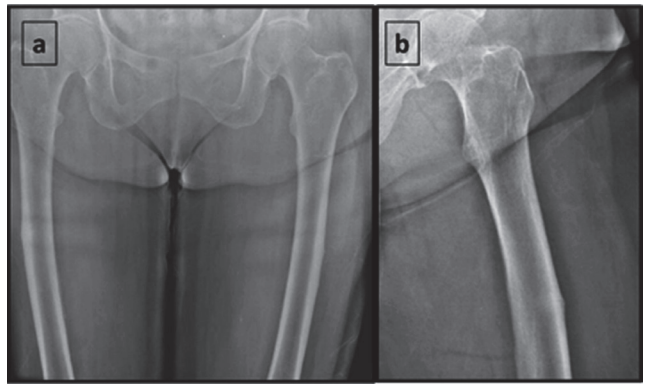

Figure 1. a) Focal lateral cortical thickening on anteroposterior radiograph of bilateral femur, b) Radiograph of left femur shows radiolucency of lateral cortex consistent with incomplete fracture

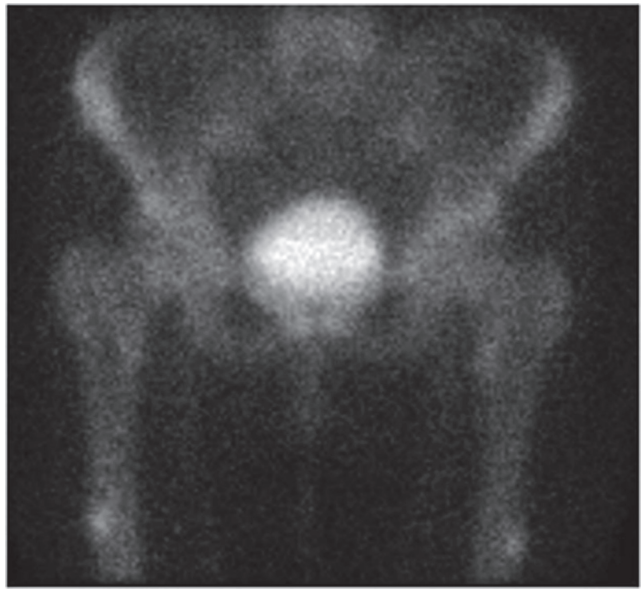

Figure 2. Bone scintigraphy shows increased uptake of radioisotope in the lateral cortex of bilateral femur

Explorer QDR, USA). The spine T-score was-2.0, total femoral T-score was -2.1, and femoral neck T-score was -2.3.

Radiographic findings of the patient were found to be consistent with AFF and she was admitted to the physical medicine and rehabilitation clinic. Her activity was limited and she was recommended to limit weight bearing by using a walking stick. Bone scintigraphy was performed and revealed increased focal uptake of radioactivity in the bilateral lateral cortex of the mid-diaphysis region of the femur and the vertebrae (Figure 2). BP therapy was terminated and vitamin D-calcium supplementation was continued. Since she did not have severe pain, conservative management was recommended for 3 months and teriparatide was prescribed. It was planned to continue the conservative therapy in case of evidence of radiographic healing at 3-month follow-up. Otherwise, orthopedic consultation should be planned for prophylactic fixation.

Discussion

AFF related with BPs usage is well defined in the literature and the risk of AFF increases with the prolonged therapy. Wang et al. (12) have shown that subtrochanteric/femoral shaft fractures are positively associated with higher adherence to long-term (≥3 years) oral BP therapy. In the early stages of AFF, periosteal and endosteal thickening as well as cortical lucency are seen at the fracture region. When there is cortical lucency, the AFF is classified as incomplete. Complete fractures have typical radiological features including both cortices of the femur whereas incomplete fractures include only the lateral cortex (8). In this case, the patient was on BP therapy for approximately 10 years and had thigh pain for a few months. Plain radiography findings suggested bilateral incomplete AFF. The evidence of increased focal uptake of radioactivity on bone scintigraphy at the same area confirmed the diagnosis. Hypophosphatasia that has radiological and clinical features similar to AFF should be considered in differential diagnosis of AFF. However, hypophosphatasia is associated with tooth losses in early ages, history of osteomalacia, recurrent metatarsal fractures, and delayed fracture healing (13). Hypophosphatasia was excluded due to the absence of these conditions in our patient's medical history and normal levels of parathyroid hormone, alkaline phosphatase and inorganic phosphate. In addition, high bilateral occurrence of AFF and accompanying prodromal thigh pain were discriminatory.

Low levels of bone resorption markers indicate suppression of bone turnover. As the assays were carried out after fracture, increased levels of bone turnover markers have been reported in AFF cases in the literature (14). In case of incomplete AFF, as the fracture has not occurred, the levels of bone resorption markers are not elevated (14,15). In our patient, CTX was also below the normal range.

In the literature, the treatment of AFF is based on post-fracture approaches and there are few studies on incomplete AFF treatment (16). Discontinuation of the antiresorptive agent and supplementation of vitamin D and calcium are general suggestions. In patients with cortical lucency accompanied by pain, prophylactic nail fixation is recommended. If the patient has minimal pain, conservative therapy, in which weight-bearing is limited through the use of crutches or a walker, may be considered (8,14). Prophylactic nail fixation is strongly considered to prevent complete fracture if there is no symptomatic and radiographic improvement after 3 months of conservative therapy. For patients with incomplete fractures and no pain, or those with periosteal thickening but no cortical lucency, limited weight-bearing may be continued and vigorous activity should be avoided (8).

In addition to discontinuation of BPs and calcium and vitamin D supplementation, an anabolic agent such as teriparatide may promote fracture healing. However, there is inconsistent evidence that teriparatide may advance healing of AFFs (8,14). Few publications report fracture healing with teriparatide when there is no recovery with conservative therapy (14,16). Saleh et al. (14) pointed out that the presence of a radiolucent line in an incomplete fracture poses a high risk of progression to a complete fracture. They conducted a retrospective study in order to define a management strategy for incomplete AFF and concluded that fractures without a radiolucent line appear to respond to conservative management and do not require surgical prophylaxis. They also stated that teriparatide treatment may promote healing of these fractures (14). In the current case, conservative therapy consisting of cessation of BP therapy, vitamin D-calcium supplementation, and limited weight bearing (using a walking stick) was recommended

for 3 months. Additionally, teriparatide, which is an anabolic agent, was started.

AFF are one of the adverse events associated with long-term use of BPs. In patients on long-term BP therapy presenting with groin or thigh pain, AFF, which is a rare condition, should be kept in mind. Radiological features of incomplete fractures should be well recognized and necessary approaches should be made before progression to complete fracture.

Ethics

Informed Consent: Consent form was filled out by the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.B., İ.C.B., B.A, R.G., Concept: S.B., İ.C.B., B.A., R.G., Design: S.B., İ.C.B., B.A., R.G., Data Collection or Processing: S.B., İ.C.B., B.A., Analysis or Interpretation: S.B., İ.C.B., R.G., Literature Search: S.B., İ.C.B., B.A., Writing: S.B., İ.C.B., B.A., R.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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