

Atypical femoral fracture after discontinuing long-term bisphosphonate use

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ABSTRACT

Agents that slow bone resorption (antiresorptive) and increase bone formation (anabolic) are used as medical treatment modalities in osteoporosis. Bisphosphonates (BP) are antiresorptive drugs that suppress osteoclastic activity and slow bone resorption and are recommended to be used as first-line therapy in osteoporosis treatment guidelines. For two decades, these drugs have been prescribed in our country and worldwide to treat osteoporosis and reduce the risk of fractures. However, according to the literature, atypical femoral fractures (AFF) are encountered in patients who have been using these drugs for more than five years. In this case report, we present the diagnosis, treatment, and recovery process of a patient who developed AFF after discontinuing long-term use of BP.

Keywords: Atypical femoral fracture, bisphosphonate, intramedullary nailing, osteoporosis

Agents that slow bone resorption (antiresorptive) and increase bone formation (anabolic) are used as medical treatment modalities in osteoporosis. Bisphosphonates (BP) are antiresorptive drugs that suppress osteoclastic activity and slow bone resorption and are recommended to be used as first-line therapy in osteoporosis treatment guidelines.^[1] For two decades, these drugs have been prescribed in our country and worldwide to treat osteoporosis and reduce the risk of fractures.^[2,3] However, according to the literature, atypical femoral fractures (AFF) are encountered in patients who have been using these drugs for more than five years.^[3,4] In this case report, we present the diagnosis, treatment, and recovery process of a patient who developed AFF after discontinuing long-term use of BP.

CASE REPORT

A 74-year-old female patient presented to our outpatient clinic with complaints of pain in the back and right leg. The patient's complaints had begun one month ago after a 45-minute walk; she stated that she had no pain at rest and the pain occurred with movement. At the neurosurgery clinic where she presented with these complaints, magnetic resonance imaging (MRI) of the lumbar region was taken; spinal stenosis and right L5 radiculopathy was diagnosed and operation was recommended. Physical examination revealed painful and restricted lumbar extension, and tenderness to touch on the paravertebral region of the right L4 and L5 spine and the middle lateral part of the right thigh. Abduction and rotations of the right hip were painful. Neurological

Received: November 15, 2020 **Accepted:** December 17, 2020 **Published online:** May 05, 2021

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Cite this article as:

Comlek S, Mutlu A, Özgönel E, Kahraman S, Özgönel L. Atypical femoral fracture after discontinuing long-term bisphosphonate use. D J Med Sci 2021;7(1):52-56.

deficit was not present. When questioned in terms of osteoporosis, the patient had a history of total abdominal hysterectomy and bilateral salpingoophorectomy at 39 years of age and received hormone replacement therapy for one full year. Aside from the past two years, the patient used various anti-resorptive agents. Other than one year of using nasal calcitonin, she stated that she used daily, weekly, and monthly BPs for 1-3 years, and once received an annual dose of intravenous BP. She did not receive osteoporosis treatment for the last two years. In June 2016, the patient was diagnosed with papillary urothelial carcinoma originating from the bladder, and resection of the tumor was performed via transurethral resection of the bladder and intravesical *Bacillus Calmette-Guerin* (BCG) immunotherapy was administered. Based on the patient's clinical history, right thigh X-ray and whole-body bone scintigraphy in addition to lumbar MRIs were requested to investigate pre-diagnoses of metastasis and stress fracture. During this period, the patient's back and right leg pain exacerbated, and epidural neuroplasty was applied at the algology unit. After the intervention, the patient's waist and right leg pain disappeared, while the tenderness to touch persisted in the middle lateral region of the right thigh. X-ray of the right thigh revealed minimal cortical thickening in the lateral region of the mid-diaphyseal femur (Figure 1). Whole-body bone scintigraphy revealed focal increase of osteoblastic activity in the mid-diaphyseal region of the right femur; contrasted MRI and computed tomography (CT) of the right thigh were requested to rule out possible bone metastasis. Magnetic resonance imaging revealed bone edema and mild contrast enhancement, and CT revealed cortical thickening in the affected region (Figures 2, 3). The department of orthopedics took a bone biopsy from the region, which did not reveal any findings in favor of metastasis.

According to the findings, the patient was diagnosed as atypical femoral fracture and blood analysis was requested to assess bone mineral density and osteoporosis. Conservative treatment was planned because it was an incomplete fracture. The patient's treatment consisted of rest, avoiding putting weight on the hip, isometric exercises in bed for the hip and knee, using a cane, and analgesics. Osteoporosis was detected in bone

mineral density test and vitamin D deficiency in the blood analysis, and the patient was given vitamin D and calcium supplements.

Endocrinology was consulted for teriparatide treatment. Since the patient's pain persisted in the thigh region, and radiological improvement was not observed in the follow-up eight weeks later, intramedullary nailing was performed by the orthopedics department (Figure 5). After a 6-week physical therapy and rehabilitation program, the patient was able to move without pain and support. Teriparatide treatment for

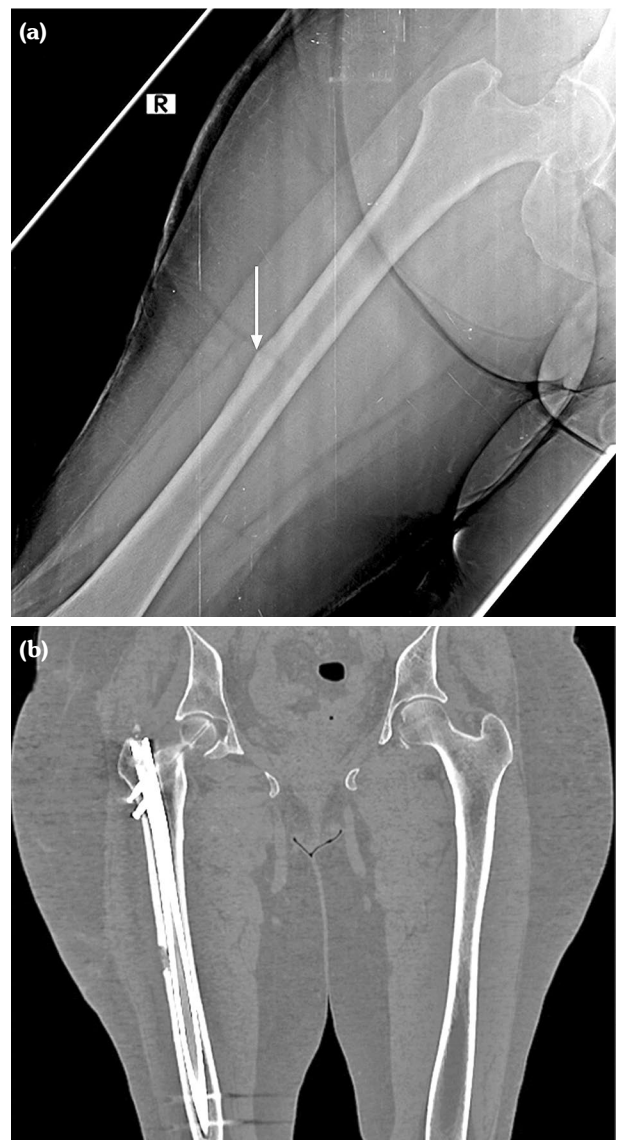


Figure 1. Appearance before and after intramedullary nailing.

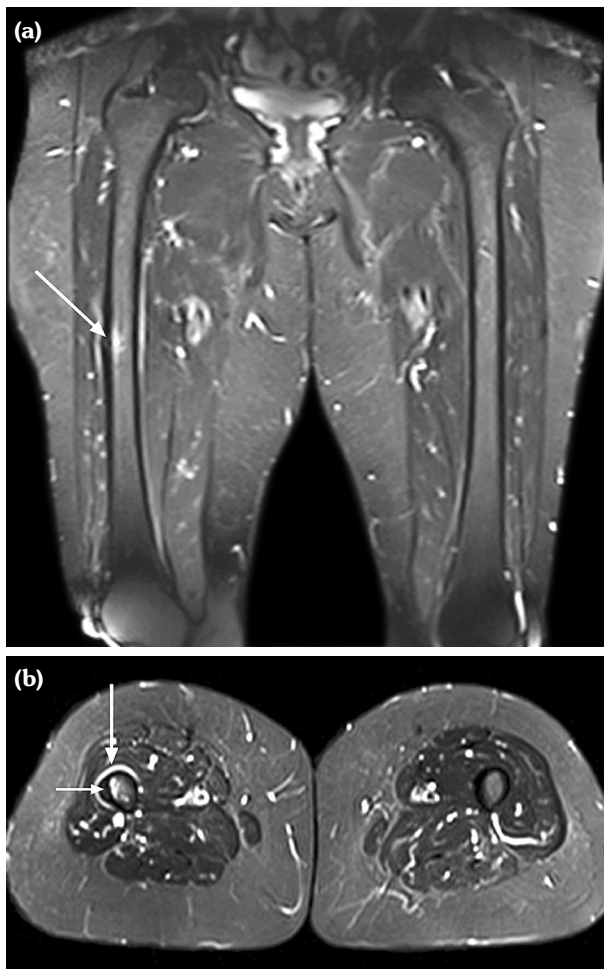


Figure 2. (a, b) In coronal fat-suppressed T2-weighted section, edema is seen in the periosteum and bone marrow in the $\frac{1}{2}$ mid-diaphysis of the right femur (long narrow arrow and short thick arrow); in axial fat-suppressed T2-weighted section, periosteal edema (long narrow arrow), together with focal cortical thickening containing high signal compatible with resorption cavity (short thick arrow).

osteoporosis treatment was initiated one month postoperatively. The patient was informed of possible incomplete fracture in the contralateral femur. Routine pool exercises of hip group strengthening and erector spinae stretches, lower and upper muscle group strengthening, and cardio fitness program was planned and the patient was asked to continue this program.

DISCUSSION

A case report of low-energy femoral fractures in patients using alendronate was first presented

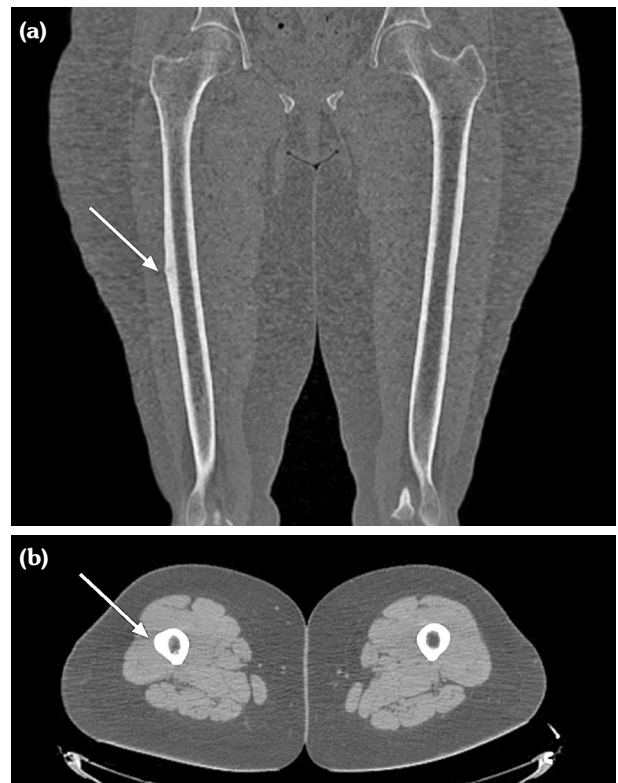


Figure 3. (a, b) 3D CT of the right femur reveals focal cortical thickening shaped as beaking and radiolucency line in the $\frac{1}{2}$ mid-diaphyseal outer cortex.

CT: Computed tomography.

in 2006.^[5] Later studies referred to these fractures as AFF, describing them as stress fractures. It was found that patients using BP for over 10 years were at risk of developing these types of fractures, and duration of use was directly associated with fracture risk.^[1-3] In our case, the patient had a 10-year history of BP use. The literature states that AFF is most commonly seen in patients between 71-78 years of age; likewise, our patient was 74 years of age.^[4]

Although the mechanism by which BP causes these fractures is unclear, there are several hypotheses for the pathophysiology: disruption of bone turnover and microdamage repair mechanisms, genetic factors, excessive weight-bearing on the femur, and demineralization.^[6] It is suggested that long-term use of BF suppresses the osteoclast system and indirectly disrupts the microdamage repair system and causes microcracks in the bone cortex, leading to AFF. The presence of AFF in patients using

antiresorptive drugs (denosumab) other than BP supports the notion that pathogenesis involves impairment in bone turnover and microdamage repair mechanisms.^[7,8] Mineralization defects are another factor. Atypical femoral fractures are seen in diseases that disrupt bone mineralization (vitamin D deficiency, rheumatoid arthritis, hypophosphatemia, etc.).^[3,9] The prevalence of AFF in patients of Asian origin and excessive weight-bearing on the femur due to pelvis-femur anatomy supports the effects of genetic and anatomical disorders.^[3] The difference of our case from the literature was that the fracture was seen two years after the patient stopped using BP and calcium and vitamin supplements. BPs linger in circulation for a short time, less than 24 hours, while its half-life after binding to bone has been reported to be over 10 years.^[10,11] Our case used BP for over 10 years and did not receive any osteoporosis treatment for the past two years. Our hypothesis regarding our case is as follows: although our patient discontinued using BP, since the half-life of BP in bone is very long, its negative effects on bone turnover continued, while lack of calcium and vitamin D supplementation also impaired mineralization, leading to AFF.

Atypical femoral fractures are that occur in the subtrochanteric femur, characterized by transverse or short oblique configuration, lack of medial spike, non-comminuted fracture pattern, and are non-traumatic or occur after very mild trauma.^[1,3] Atypical fractures can sometimes occur as incomplete fractures, in which only the lateral cortex of the femur is affected in the form of a stress-induced reaction. Png et al.^[12] detected periosteal stress-induced reactions at a rate of 93%, located on the lateral femoral cortex and the medial femoral cortex at the subtrochanteric or midshaft level. Radiographic findings of periosteal stress reaction include focal periosteal beaking, focal cortical radiolucency, and dreaded black line adjacent to the lateral cortex. MRI findings consist of bone edema (periosteal, endosteal, or bone marrow), periosteal or endosteal beaking, focal cortical resorption cavity, and dreaded black line. Our case had typical radiographic and MRI findings.

Min et al.^[13] developed a weighted scoring system to predict the risk of progression of incomplete fractures to complete fractures. The

site, severity of pain, status of the contralateral femur, and the extent of radiolucent line as a percentage of the femoral diaphysis.

Early diagnosis of incomplete atypical femoral fractures is important due to the risk of progression to a complete fracture. According to the literature, it is recommended to discontinue bisphosphonate treatment when incomplete fractures are detected, with close follow-up by reducing weight-bearing in non-symptomatic patients, and prophylactic nailing in symptomatic patients.^[11]

Atypical femoral fractures are reported to occur mostly in postmenopausal osteoporotic women, the incidence of which varies depending on the duration of bisphosphonate use.^[6,14,15] Studies have investigated the bilateral incidence of complete atypical femoral fractures. Dell et al.^[15] reported a 22.5% incidence rate of bilateral femoral fractures.

Our patient was treated with rest, avoiding weight-bearing, and analgesic therapy, as recommended in the literature and in guidelines; surgical treatment was performed when the pain persisted.^[1,3,14] In accordance with the literature, teriparatide treatment, an anabolic agent, was preferred for the treatment of AFF and osteoporosis. Since the patient had little movement due to the resting period and pain, physiotherapy and exercise were added to the treatment to increase muscle strength and aerobic capacity.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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