Atypical Femur Fractures and Cortical Thickening in Osteoporotic Patients Treated with Bisphosphonates

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Abstract

Background: Patients treated with bisphosphonates (BP) may present atypical femoral fractures (AFF) as a complication with an incidence of 3.2-50 cases per 10,000 person-years. The existence of cortical thickening is sometimes related to the appearance of atypical fracture. So, from the clinical point of view, in patients treated with bisphosphonates, the appearance of cortical thickening must suggest the change of treatment in order to avoid fractures.

Case report: We present a case of atypical fracture, with bilateral cortical thickening as a predictor of atypical femur fracture, in a patient using BP for years. The main symptom developed by the patient through the years BP were taken was bilateral thigh pain.

Conclusion: There is some evidence of a relationship between long-term BP and a specific type of femoral fracture with radiographic features (including cortical thickening) and some clinical features as prodromal pain. However, atypical fractures are uncommon, and with correct indication, the utility of antiresorptives are not discussed. Physicians and patients should know the possibility of AFF and the possible bilateral involvement of this rare complication, in order to assess the risk-benefit of continuing/withdrawing treatment with BPs.

Keywords: Osteoporosis; Bone; Fracture; Atypical; Sub-trochanteric; Bisphosphonates; Denosumab; Femur; Cortical; Thickening

Background

BPs are used by millions of patients worldwide as a first line treatment for osteoporosis, because they are highly effective in the prevention of osteoporotic fractures, providing clear evidence for a reduction in the incidence of fractures. They reduce bone loss by attenuating the ability of the osteoclast to resorb bone, decreasing activation frequency and the rate of remodeling [1].

The safety profile of BPs has been demonstrated after being used for years. However, a recent concern has arisen about the association between the use of BPs and the appearance of atypical femur fractures (AFF), a rare type of atramumatic or minimal trauma femur fracture occurring below the great trocanter [2]. This rare complication, with a rate of 3.2-50 cases per 10,000 person-years, may be due to the prolonged half-life of BP and their effect on fracture remodelling, although there is not a final explanation for the physiopathology of these fractures [3-5].

The possible pathogenetic mechanisms associated with AFF included microdamage accumulation, variations in bone turnover, alterations to the pattern of collagen cross-linking, increased mineralization, reduced heterogeneity of mineralization, reduced vascularity and antiangiogenic effects. In conclusion, it has been demonstrated that bisphosphonates alter the mineralization process, which creates density alterations that affect bone quality.

AFFs occur more commonly in women, Asian race people and people with disadvantaged femoral geometry (varus alignment, smaller canal and larger offset) [3-11]. The risk of AFF increases significantly after 5 years of continuous treatment and decreases after cessation [11]. Therefore, it is important to assess benefit-risk in patients treated with BPs for an extended period of time.

In 2010, the American Society for Bone and Mineral Research (ASBMR) formulated diagnostic criteria for AFF. Thus, to designate a fracture as “atypical”, it must include all the following major criteria:

a) It must be caused by minimal or no associated trauma localized to the sub trochanteric region and femoral shaft;

b) Have a transverse or short oblique orientation;

c) Have a medial spike when the fracture is complete; and

d) Be without comminution.

Minor criteria include cortical thickening, a periosteal reaction of the lateral cortex, bilateral proximal pain and delayed fracture healing, together with the presence of co-morbid conditions and concomitant drug exposure. All major features are needed to define a fracture as "atypical" while minor features may not be present in some cases [1-3].

In 2013, ASBMR published an updated version of a previous report that included revised criteria for AFF. According to the new definition, localized periosteal reaction of the lateral cortex was incorporated as a major criterion. The reasons for changes were a positive correlation between BP use and signs of fatigue fractures, including transverse fracture lines on the lateral cortex, periosteal reactions and a medial spike [9].

Case History

A 61 year old woman with a history of dyslipidemia in dietary and osteoporosis in treatment with Alendronate 10 mg daily since 2001 with good tolerance and adherence. The patient comes to the emergency service in December 2012 for pain and functional impotence in the right hip, after a fall from their own height. She described pain in

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Taking into account the fact that the median BP treatment duration in patients with AFF is 7 years, we must consider a ‘drug holiday’ in patients without a recent fracture and with femoral neck T-scores greater than 2.5 after the initial therapeutic course [3,8,9]. It is not known whether discontinuation of BPs after 4-5 years in the lower-risk group will lead to fewer AFFs [7]. Patients should be followed by clinical assessment, bone turnover markers and BMD determination [9].

Besides bisphosphonates, AFF has also been reported after treatment with other antiresorptives such as Denosumab, a fully human monoclonal antibody against the RANK ligand and a potent inhibitor of osteoclast-mediated bone resorption, the efficacy of which in the prevention of fracture in postmenopausal osteoporosis was demonstrated vs. placebo in the FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) [10-14].

Stress fractures start with the accumulation of microscopic cracks. Normally, areas with micro cracks are resorbed by osteoclasts and replaced with new bone in a process called “targeted remodelling”. If targeted remodeling is disturbed by antiresorptive treatment, micro cracks might grow and cause stress fractures. The osteoclasts are steered to the area where micro cracks accumulate by RANKL, which is released by osteocytes. RANKL is the particular molecule blocked by denosumab [13]. When denosumab is administered subcutaneously every 6 months, bone resorption capacity generally recovers, at least partially, towards the end of the interval between injections. This could be enough for the skeleton to deal with micro-damaged areas [13]. More than half of patients who were reported with AFF have had thigh or groin pain before suffering a break [3], like our patient.

In these fractures, it is important to differentiate between bone density (quantity of bone) and bone quality (geometry and properties). Tejwani and Peck published that anterior-posterior and lateral radiographs are reliable for distinguishing between femoral fractures related to BP use and those not related to such use [14]. The medical management of AFFs includes: cessation of antiresorptive, correct supplementation of calcium and vitamin D, consideration of teriparatide in cases of poor fracture healing and examination of the contralateral femur, by radiology [10].

BPs are highly effective in the treatment of osteoporosis, thereby reducing the risk of fractures. AFF is a rare but serious condition associated with use of bisphosphonates and new antiresorptives like denosumab, with unclear pathogenetic mechanisms.

There is evidence of a relationship between long-term BP use (usually with a median treatment of 7 years) and a special type of femoral fracture with radiographic features (including cortical thickening as in the case of our patient) and clinical features (prodromal pain and bilaterality). However, atypical fractures are uncommon, and with a correct indication, antiresorptives prevent many more fractures than they cause.

Discussion

We report a bilateral periosteal reaction of the sub trochanteric femur in a patient treated with BPs that develops a right sub capital fracture and was reintervened in January 2013 (extraction of the Expert nail and new fixation with long Gamma nail, with distal block). In addition, an X-ray of the contralateral femur was performed, revealing a diaphyseal lesion and cortical thickening. Prophylactic nailing of the left femur was performed using nail gamma 3, 11 × 26. Biopsies were taken from the latter lesion, without evidence of malignancy. Such cortical thickening and atypical fractures were related to the prolonged use of BPs, withdrawing of this treatment (Figure 1B).

Assessment of the benefits and risks before BP treatment is essential to avoid unnecessary complications, such as AFF. The optimal duration of treatment with bisphosphonates is still unclear. The studies with alendronate and risedronate show that patients with osteoporosis will have an anti-fracture effect for at least 5 years. Continued usage over 5 years needs annual re-evaluation, considering factors such as fracture history, BMD, newly diagnosed disorders, other medications known to affect skeletal tatus [2-6] and as in our case, the appearance of radiographic features such as cortical thickening and some clinical features such as the appearance of prodromal symptoms like aching pain in the thigh [7]. For those patients who are considered to have moderately-elevated risk fracture, continuation of BP therapy should be strongly considered [3].

References


