

Clinical Quiz

Simultaneous bilateral atypical femoral fractures after alendronate therapy

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Case

A 76-year-old white female presented to the orthopaedic emergency department suffering from severe pain in both femurs after falling from standing height. Hip and pelvis radiographs revealed bilateral diaphyseal femoral fractures.

Medical history included menopause at the age of 37, diaphragmatic hernia and gastroesophageal reflux, hypertension, mitral valve insufficiency and osteoarthritis of the left hip. The patient had first been diagnosed with osteoporosis eleven years ago after a bone density screening test. The baseline dual-energy X-ray absorptiometry (DXA) revealed L2-L4 bone mineral density (BMD) of 0.658 g/cm² - T-score: -4.5 SD. She was put under calcium and vitamin D supplements and oral alendronate treatment ever since.

Nine years after the initial diagnosis of osteoporosis and while under alendronate for 9 consecutive years the patient suffered from substantial back pain. Lateral X-rays of the spine revealed compression fractures of the T¹², L¹ and L³ vertebrae. Magnetic resonance imaging showed lesions consistent with recent osteoporotic fractures. The laboratory examination and the biochemical analysis of bone turnover markers [Ca (mg/dl) (8.2-10.2)=9.9, P(mg/dl) (2.7-4.5)=3.8, iPTH(pg/ml) (10-65)=37.3, 25(OH)D (ng/ml) (20-76)=28.7, NTx(nMBCE) (6.2-19)=11.7, P1NP (ng/ml) (16.3-73.9)=40.4 – all within normal reference values], did not reveal any secondary causes or underlying disease for the occurrence of these fractures.

The patient continued alendronate and after approximately 11 years she reported occasional left thigh pain on weight bearing which lasted for 15 days. Radiographic examination showed a lateral cortical shaft reaction without an evident fracture line. Partial weight-bearing mobilization with assistive device on the affected limb was recommended until pain resolution, and the patient was advised to stop alendronate therapy. Four months later the pain had been considerably improved, however, the patient sustained simultaneous transverse diaphyseal fractures of both femurs after a low energy trauma (Figure 1 a,b). Fractures were osteosynthesised with an intramedullary nail (Figure 2).

The patient was initiated on 1000 mg calcium and 2000 IU of vitamin D per day in order to repair any existing bone remodelling defects. She was advised to have protected weight-bearing with a walker. Bone healing proceeded uneventfully in both of the femurs.

Commentary

The use of bisphosphonates (BP) for the treatment of osteoporosis is effective, well tolerated and considered to have a safety profile when high dosages are administered. Long-term treatment with BP has been recently associated with subtrochanteric and diaphyseal femoral fractures. In addition, there has been increasing interest regarding the occurrence, the aetiology as well as the pathophysiology of these fractures. The International Osteoporosis Foundation and the American Society of Bone and Mineral Research (ASBMR) have published position statements that acknowledge this issue, defining atypical femur fractures and guiding further research¹.

According to the ASBMR Task Force, atypical femoral fractures are most commonly observed in the proximal one-third of the femoral diaphysis, but it is possible to occur anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal femoral metaphysis. These atypical fractures usually occur as

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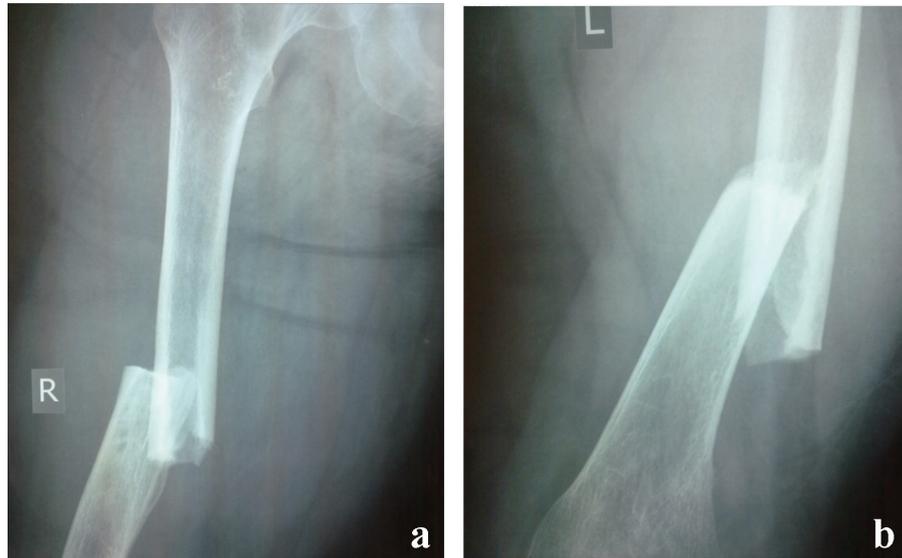


Figure 1a,b. AP radiograph of the right and left femur showing a complete atypical diaphyseal fracture.

a result of no trauma or minimal energy trauma, equivalent to a fall from a standing height or less. The fracture may be complete, extending across the entire femoral diaphysis. Complete atypical femoral fractures are generally transverse although they may have a short oblique configuration, and are not comminuted. Alternatively, the fracture may be incomplete, manifested by a transverse radiolucent line in the lateral cortex. Both complete and incomplete fractures are commonly associated with a periosteal stress reaction and thickening of the lateral cortex at the fracture site or thickening of both cortices. Fractures of the femoral head or within the intertrochanteric region with spiral subtrochanteric extension, pathological fractures associated with local primary or metastatic bone tumors, and peri-prosthetic fractures are excluded from the category characterized as atypical femoral fractures.

The majority of the patients often describe a prodromal pain in the groin or thigh several weeks or even months before the occurrence of the fracture. Radiographic findings of stress fractures typically include a periosteal callus that appears hazy and indistinct initially which later solidifies, as an attempt of bone repair. They usually resemble stress fractures and pseudo-fractures while the healing process may be delayed.

The aetiology of atypical femoral fractures and its relationship with the prolonged use of BPs remains unclear. A variety of pathogenic mechanisms have been proposed in the literature. These mainly focus on alterations to the normal pattern of collagen cross-linking, on changes to the maturity of cross-links formed by enzymatic processes and the advanced glycation end-product accumulation, on microdamage accumulation, on increased mineralization and simultaneously its reduced heterogeneity, on variations in rates of bone turnover, and finally on reduced vascularity and anti-angiogenic effects of BPs^{1,3,5}.



Figure 2. AP radiographs of right and left femur, 9 months post-operatively.

Several case reports and case series reporting atypical femoral fractures after prolonged BP use have been recently published²⁻⁵. The majority of the reported fractures have occurred contralateral or bilateral sequentially or with a simultaneous complete and an incomplete contralateral fracture. To our knowledge, there are very few reports presenting simultaneous bilateral complete atypical femoral fractures or simul-

taneous bilateral femoral fractures without any previous use of a pharmacological agent with effect on bone metabolism beside BPs. Our patient meets all of the major and many of the minor features of the atypical femoral fractures proposed by the ASBMR Task Force Report¹. In our case, the fractures resulted from minimal trauma - a fall from a standing height during simple daily activities - while the prodromal symptoms were not bilateral but focused only in the left thigh. The duration of pain symptoms was relatively short and had been fully eliminated after stopping BPs and protected weight-bearing walking. The lack of evident fracture line as well as the short period until pain relief justifies the decision of conservative treatment. In any case, continuation of BP treatment should be prohibited while use of teriparatide offers a reliable alternative especially in those patients that have evidence of poor healing after surgical treatment of the fractures⁵. Our patient had no signs of delayed healing or pseudoarthrosis in both of the femurs and use of an anabolic agent was regarded unnecessary.

In summary, the present case highlights the need for close observation of those treated with BPs, in order to identify prodromal symptoms of atypical femoral fractures, thus avoiding such complications.

References

1. Shane E, Burr D, Ebeling P, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2010;25(11):2267-94.
2. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg Am* 2009;91(11):2556-61.
3. Ovaska MT, Mäkinen TJ, Madanat R. Simultaneous bilateral subtrochanteric fractures following risedronate therapy. *J Orthop Sci* 2011;16:467-470.
4. Alshahrani F, Kendler D. Femoral fractures in osteoporotic patients on bisphosphonates. A case report. *J Clin Densitom* 2012;15(3):380-4.
5. Gomberg SJ, Wustrack RL, Napoli N, et al. Teriparatide, vitamin D, and calcium healed bilateral subtrochanteric stress fractures in a postmenopausal woman with a 13-year history of continuous alendronate therapy. *J Clin Endocrinol Metab* 2011;96(6):1627-32.

Questions

1. Which of the following is not a feature of atypical femoral fractures related to long-term BP use?
 - A. Location in the subtrochanteric region and femoral shaft
 - B. Transverse or short oblique orientation
 - C. Minimal or no associated trauma
 - D. BP use for over 7 years

Critique

In the report of the Task Force of the ASBMR (2010) for this type of fractures duration of BP therapy ranged from 1.3 to 17 years. In the vast majority of cases reviewed by the task force the fractures happened with no or minimal trauma and had a transverse or slightly oblique pattern along the femoral diaphysis.

The correct answer is D.

2. Which of the following is not a possible pathogenetic mechanism for the occurrence of such fractures?
 - A. Microdamage accumulation
 - B. Increased mineralization
 - C. Secondary hyperparathyroidism

Critique

BPs may intensify damage accumulation, due to the potent inhibition of osteoclasts that have a key role to bone damage repair. In addition, BP treatment, by reducing bone turnover, increases overall mineralization and bone stiffness. If bone stiffness surpasses a certain limit, bones become more susceptible to fractures. On the other hand, co-administration of vitamin D and calcium supplements with BPs is prohibitive for the development of secondary hyperparathyroidism.

The correct answer is C.