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ORIGINAL ARTICLE

Atypical Femoral Fractures due to long-term bisphosphonates therapy

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Abstract

Introduction. Bisphosphonates (BPs) represent the main therapy in patients with osteoporosis, although a long-term treatment can lead to atypical fractures.

Material and methods. We conducted a retrospective study between 2008 and 2017 and included 23 female patients with atypical femoral fractures (AFFs). The mean period of BPs therapy administration was 5.2 years. We included 7 subtrochanteric fractures and 18 femoral shaft fractures. Two of the total patients presented bilateral femoral fractures. 18 patients presented prodromal symptoms from 2 to 18 months before the diagnosis of fractures, all of them following low energy trauma. All the patients included in our study underwent surgery with intramedullary nail or gamma nail. The postoperative mean follow-up was 2 years. Results. Of all 23 female patients with a total of 25 fractures – 10 underwent osteosynthesis with gamma nail and 15 underwent osteosynthesis with intramedullary nail. From the total number of patients: 13 patients achieved complete union, 6 presented delayed union and 3 non-union (2 intramedullary nail and one gamma nail), whereas in one patient treated previously with gamma nail we observed implant failure.

Conclusion. The treatment of AFFs after BPs therapy administration represents a challenge for orthopaedic surgeons regarding both surgical technique and postoperative follow-up.

Keywords: osteoporosis, bisphosphonates, atypical femoral fractures, gamma nail, intramedullary nail

Introduction

Osteoporosis represents a metabolic disease characterized by the reduction of mineral bone density and alteration of bone architecture [1] thus being a trigger factor for fractures. Several studies concluded that the incidence of osteoporosis is 50% in females and 25% in males [2]. As life expectancy increased over the years, so did the incidence of fractures in osteoporotic patients. Bisphosphonates (BPs) represent the main therapy in patients with osteoporosis. BPs decrease bone resorption by inhibiting osteoclasts [3], thus improving bone density and reducing the risk of fractures especially those localized in the spine and hip [4]. However, in 2005, Odvina described the reduction of bone turnover secondary to

long-term treatment with alendronate, hence leading to atypical fractures [5].

Materials and methods

We conducted a retrospective study between 2008 and 2017 and included 23 female patients with atypical femoral fractures (AFFs) assessed with the American Society of Bone and Mineral Research (ASBMR) diagnostic criteria (Table 1). The mean age was 69 years old (extreme ages – 57 and 81 years old respectively). The period of BPs therapy administration was between 2 to 7 years until a femoral fracture was produced (the mean period was 5.2 years). We included 7 subtrochanteric fractures and 18 femoral shaft fractures. Two of the total number of patients presented bilateral fractures. 18 patients presented prodromal symptoms from 2 to 18 months before the diagnosis of fractures, all of them following low energy trauma. All the patients included in our study underwent surgery with intramedullary nail or gamma nail. The postoperative mean follow-up was 2 years.

Table 1. The 2014 AFFs diagnostic criteria as determined by the ASMBR task force statements [6]

Major features	Minor features
The fracture is associated with minimal or no trauma, as in a fall from a standing height or less	Generalized increase in cortical thickness of the femoral diaphyses
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	Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex	Bilateral incomplete or complete femoral diaphysis fractures
The fracture is non-comminuted or minimally comminuted	Delayed fracture healing
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")	To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the less trochanter to just proximal to the supracondylar flare

Results

Results were evaluated postoperatively from a radiological point of view in two incidences (anterior-posterior and latero-lateral) at 6 weeks, 3, 6, 9 and 12 months respectively.

Of all 23 female patients with a total of 25 fractures – 15 underwent osteosynthesis with intramedullary nail (Fig. 1) and 10 underwent osteosynthesis with gamma nail (Fig. 2). Regarding the period of time needed for the consolidation of fracture we obtained the following results: 13 patients achieved complete union, 6 presented delayed union and 3 non-union (2 intramedullary nail and one gamma nail), whereas in one patient treated previously with gamma nail we observed an implant failure. The mean period of union was 26 weeks in patients with complete union and 30 weeks when taking into consideration also the patients with delayed consolidation. Among the 6 patients with delayed consolidation – 4 presented subtrochanteric fractures and 2 presented femoral shaft fractures.

In our study, we also practiced biopsy with subsequent histopathological examination from the fracture site (Fig. 3 and 4).

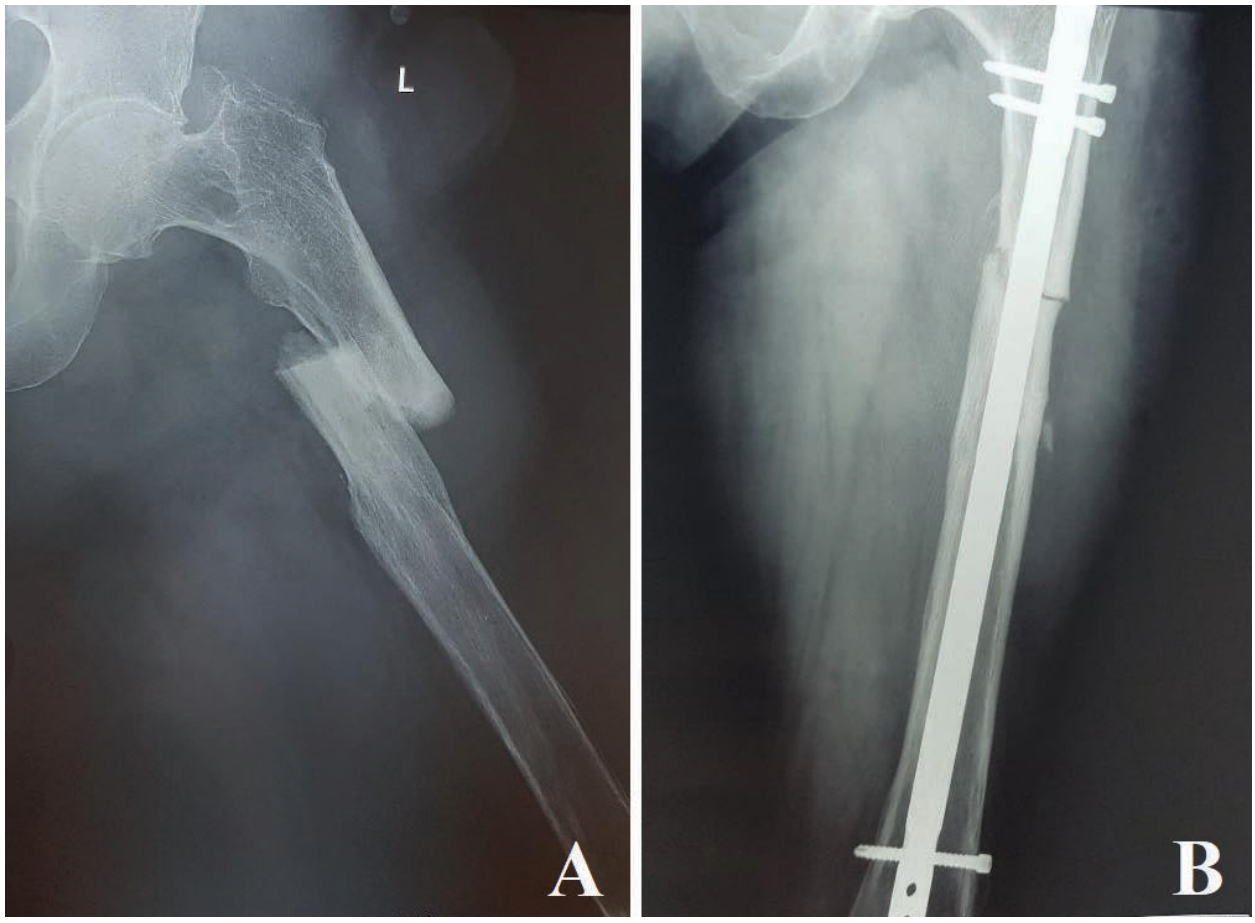


Fig. 1 Left femoral shaft atypical fracture secondary to BPs therapy. (A) Preoperative aspect - X-ray view (anteroposterior incidence), (B) Postoperative aspect – intramedullary nail

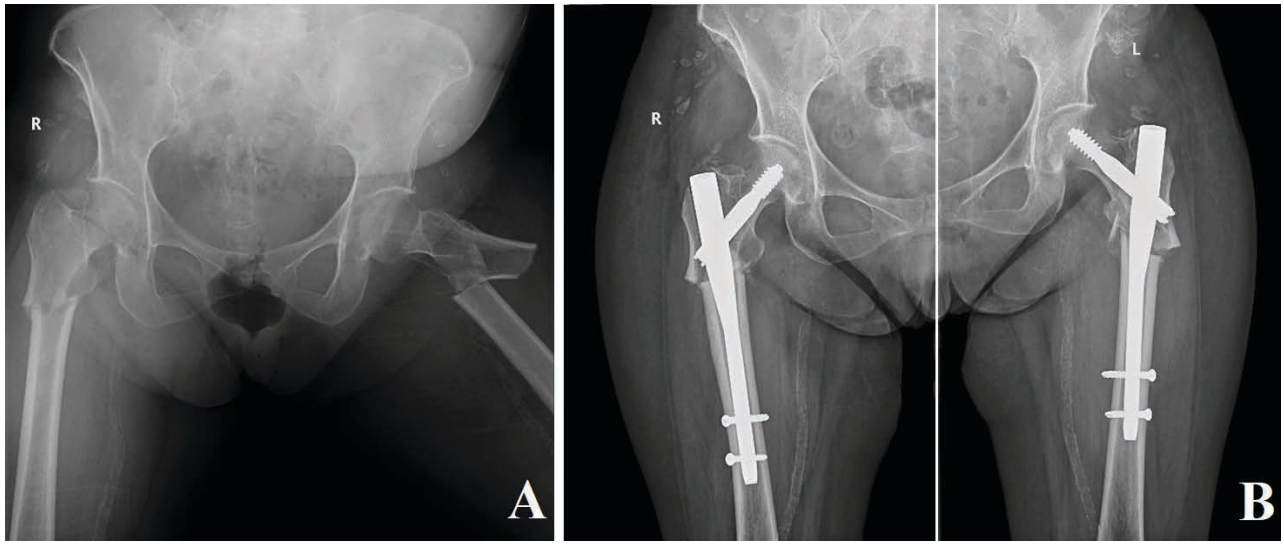


Fig. 2 Bilateral subtrochanteric fracture secondary to BPs therapy. (A) Preoperative aspect – X-ray view (anteroposterior incidence), (B) Postoperative aspect – gamma nail

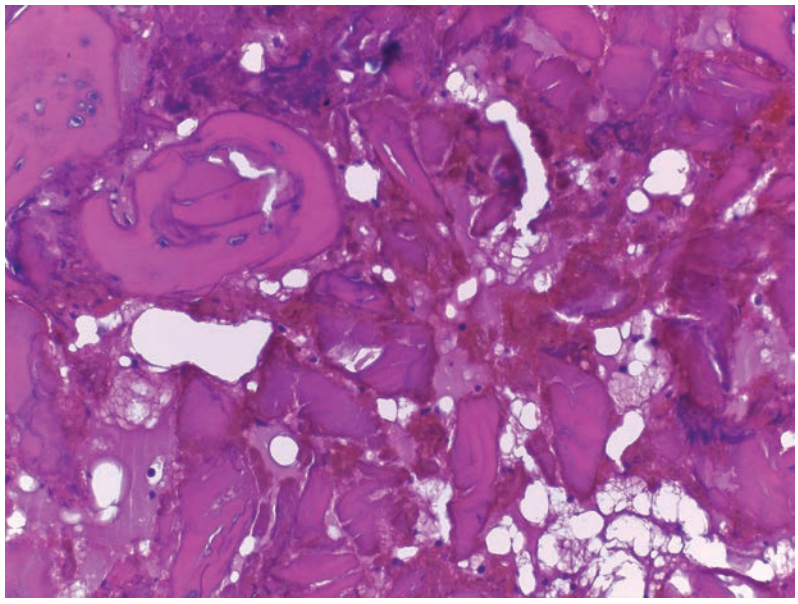
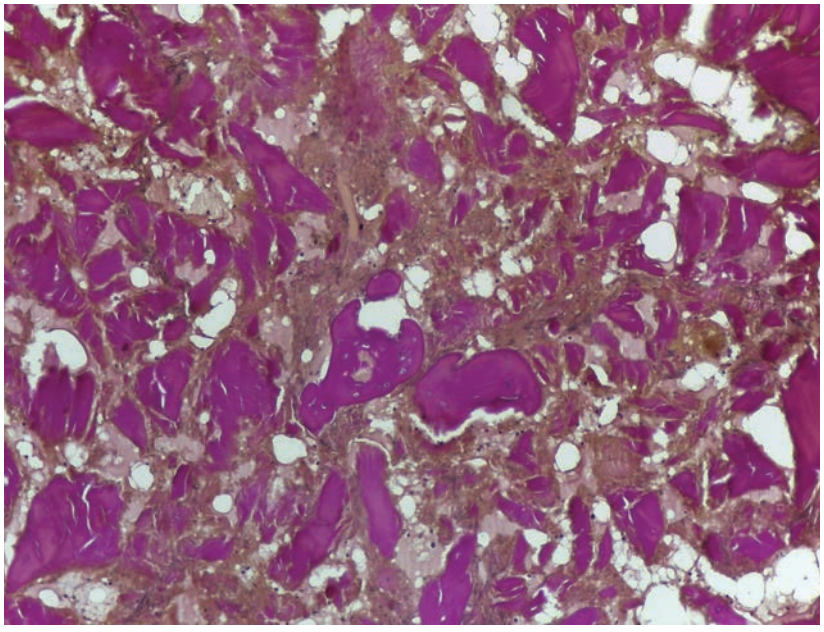


Fig. 3 Cortical bone fragments with extensive aseptic devitalisation (bone lamellae fragmentation and necrosis). The viable bone fragments present basophilic tinctorial and bone resorption in the periphery. Rare chronic inflammatory elements (lymphocytes). Non-necrotic areas with a big quantity of bone, increased trabecular thickness, small and few Haversian canals. Rare osteoclast-like cells in the resorption areas of the viable bone tissue (H.E. ob.20x)

Fig. 4 Mostly devitalized bone tissue, fragmented bone lamellae, whereas in the center – still viable bone material with dystrophic Haversian canal. Rare lymphocytes between bone lamellae (van Gieson ob.10x)



Discussions

Once published, the results of Odvina study suggesting a causal relationship between long-term treatment with BPs and AFFs, a sustained research activity was initiated regarding this pathology. Consequently, ASBMR published several major and minor criteria for the diagnosis of AFFs, the first ones being published in 2010 and afterwards revised in 2014. For a certain diagnosis of AFFs, at least 4 major criteria are needed, the minor criteria being just orientative [6]. Recognizing an AFF is very important mainly because its postoperative evolution and adjuvant treatment differ from those of a regular fracture. ASBMR recommends the cessation of treatment with BPs, surgical intervention with intramedullary nail in incomplete fractures if the patients have severe pain and conservatory treatment of incomplete fractures in case of absent or moderate pain [7].

In 2010, Dell and Green described an increased incidence of AFFs proportionally with the period of BPs administration. Thus, in case of a 2 year treatment with BPs, the incidence was 2:100000 whereas in case of 8 years of treatment with BPs, the incidence was 78:100000 [8]. Schilcher and Michaelsson revealed a reduction of AFFs with 70% per year after interrupting BPs therapy [9].

Other studies revealed a reduction of bone turnover with subsequent microfractures and decreased bone mechanical resistance in patients with long-term treatment with BPs hence leading to atypical fractures. Similar results were obtained in studies performed in animals with bone metabolism comparable with the human one [10,11].

The influence of BPs therapy on bone metabolism is translated through prolonged time of fracture union and increased incidence of delayed union. The results of our study regarding the mean union were the following: 26 weeks for patients with complete union and 30 weeks when the ones with delayed union were also taken into consideration. Most studies described a mean period of union of AFFs of 6 months [12], although some suggested even 10 months [13]. In addition, an increased incidence of delayed union was registered in female patients with subtrochanteric fractures, the results being very similar to those presented by Lee et al. [12], possibly due to the concentration of muscles in this region, which may lead to higher difficulty in obtaining and maintaining fracture reduction.

Conclusions

The treatment of AFFs after BPs therapy administration represents a challenge for orthopaedic surgeons regarding both surgical technique and postoperative follow-up.

The positive effect of BPs over osteoporosis should not be neglected, though a follow-up of patients must be performed both from a clinical and biological point of view.

Regarding subtrochanteric fractures secondary to BPs therapy, an increased incidence of postoperative complications and a higher difficulty in obtaining fracture reduction were observed, sometimes even the open reduction being necessary.

Conflict of Interest statements

Authors state no conflict of interest.

Informed Consent and Human and Animal Rights statements

Informed consent has been obtained from all individuals included in this study.

Authorization for the use of human subjects

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent commite

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