Atypical femoral fracture after long-term use of bisphosphonates: case reports and review of the literature

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ABSTRACT

Bisphosphonates (BPs) have proven successful in reducing fragility fractures and are the most commonly used antiresorptive drugs. However, the reduced bone remodeling that is the source of their immense benefits also gives rise to side effects. The first reports linking atypical femoral fractures (AFFs) to BPs appeared around 15 years ago but, despite the known connection, the process leading to injury is still unclear. AFFs have characteristic radiographic features that must be detected in order to identify the lesion and establish appropriate treatment. Their unique factors make surgery challenging, and indeed the surgical approach is burdened by a higher rate of complications. With the purpose of raising awareness, we describe, in detail, 4 cases of atypical subtrochanteric/diaphyseal femoral fractures treated by our department and provide a review of the recent literature.

KEYWORDS

Atypical, femoral fracture, bisphosphonates, alendronate, zoledronate.

Introduction

In the modern treatment of osteoporosis, bisphosphonates (BPs) are the most commonly prescribed medication [1] since they have proven to be very effective in reducing fragility fractures, mainly vertebral and proximal femur fractures [2,3]. As the latter group is expected to reach 2.6 million fractures/year in 2025 [4], the use of BPs will likely increase as well. Unfortunately, BPs are not short of adverse effects [5] and atypical femoral fractures (AFFs) have emerged as a long-term complication of this therapy [6].

Although the process leading to AFFs is not completely clear, bone remodeling is known to be critical in limiting micro-damage accumulation. It has been suggested that the reduction of bone turnover produced by BPs prevents efficient repair of micro-damage, and can lead to stress fractures [7]. Similar injuries have been associated with other families of antiresorptive drugs [8].

When incomplete, fractures can be asymptomatic or manifest with generic groin/thigh pain, but the majority appear to evolve towards a complete fracture [9]. The radiographic presentation of atypical fractures is characteristic: a transverse radiolucent line going from lateral to medial is accompanied by cortical thickening and a "beaked" appearance [10]. Treatment of complete fractures is strictly surgical. As for incomplete lesions, their likely evolution leads many authors to perform preventive surgery [11,12]. The aim of this paper was to report 4 cases of AFF and to review the recent literature.

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Case report

Case #1: A 78-year-old female patient was brought to the emergency department with pain and functional impairment at right lower limb level. X-rays showed a transverse femoral shaft fracture with signs of lateral cortical thickening and "beaking" (Fig. 1a). She reported that she had been at home walking when she felt intense pain following a particularly heavy step; she also reported that she had been suffering from thigh pain for months. Almost 7 years earlier, although it was after a fall and without prodromal symptoms, she had suffered a similar injury to the left side (also treated by our department, Fig. 1b/c). Suffering from osteoporosis, she had been using alendronic acid/colecalciferol (Vantavo®, Merck Sharp & Dohme Ltd, Netherlands) for the previous 15 years (this treatment had been suspended by her rheumatologist two weeks before the latest injury). The fracture was treated by intramedullary (IM) nailing (Gamma3® Long, Stryker, USA) (Fig. 1d). The patient attended the 1- and 3-month follow-up appointments; at the latter, X-rays showed advanced fracture consolidation (Fig. 1e) and she was walking with no aid.

Case #2: A 71-year-old female presented to the emergency room with complete impairment of the left lower limb. She denied trauma and explained that her leg had "given way" as she sat down on a low chair, adding that she had been limping on the left side for the past 3 months due to groin and thigh pain. Her medical history included hypothyroidism and rheumatoid arthritis for which she underwent recurrent cycles of cortisone. As a precaution against osteoporosis, she had started alendronic acid/colecalciferol (Fosavance®, Merck Sharp & Dohme Ltd, UK) intake 20 years before the injury. Current X-rays showed a subtrochanteric fracture with atypical signs, namely an initially transverse fracture line that formed a spike going medially, lateral cortical thickening, and a "beaked" appearance (Fig. 2a). Osteosynthesis was obtained by IM nailing (Gamma3® Long, Stryker, USA) (Fig. 2b). At the last follow-up (4 months, Fig. 2c/d) she was walking with a cane but without pain.

Case #3: A 74-year-old male was referred to us for a left lower limb injury. He had stumbled on an obstacle and fallen on his left thigh with moderate impact. The patient reported a similar injury to the right side 3 years earlier for which he had been treated by our department (Fig. 3a/b/c). He confirmed that he had never experienced any prodromal symptom before either injury. His medical records included gastric cancer 15 years earlier (complete remission) and metastatic prostatic cancer discovered 7 years earlier, when he was prescribed zoledronic acid (Zometa®, Novartis Europharm Limited, UK) for management of bone metastases (this was interrupted at the time of the first fracture). Current X-rays showed a diaphyseal

Figure 1 a) Current right AFF. b) Post-op of the left AFF 7 years earlier and c) control X-rays at 7 years. d) Post-op of current right AFF and e) follow-up X-rays at 3 months.

Figure 2 a) Left subtrochanteric AFF. b) Post-op X-rays after IM nailing. c/d) Follow-up X-rays at 4 months.

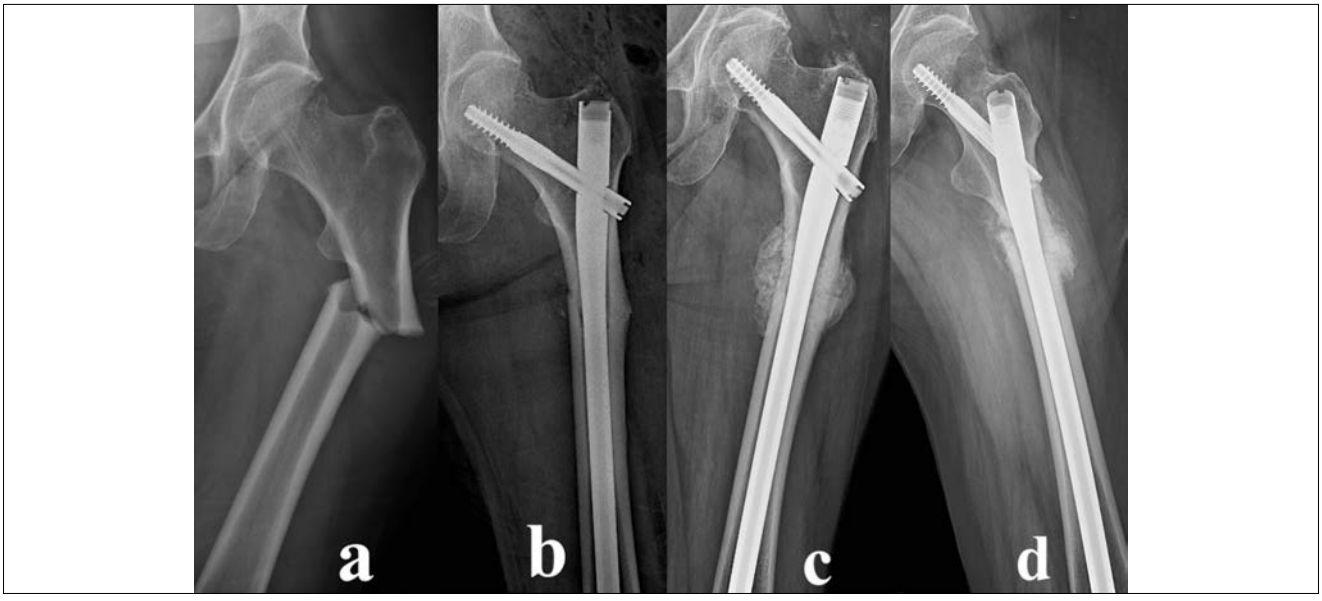

Figure 3 a) Previous right AFF from 3 years earlier with b) post-op X-rays and c) 4-month follow-up. d) Current left AFF. e) Post-op X-rays and f) 4-month follow-up.

fracture with all the aforementioned atypical features (Fig. 3d), similar to the previous injury. IM nailing was the treatment of choice (Gamma3® Long, Stryker, USA) (Fig. 3e), with a reaming biopsy that turned out negative. Radiographic follow-up showed uneventful progression of consolidation up to 4 months (Fig. 3f). When contacted at 7 months from surgery, the patient had returned to his regular life.

Case #4: A 67-year-old female had a three-month history of bilateral hip pain radiating to the thigh. Pelvis X-rays revealed atypical signs located at the proximal third of both femurs, and so, after repeating X-rays of both femurs, she was brought to our attention. The study revealed a synchronous bilateral incomplete AFF, with the characteristic signs of lateral cortical thickening, a "beaked" appearance, and a transverse radiolucent line (Fig. 4a/b). The patient was under proton-pump inhibitor (PPI) treatment for hiatal hernia. She had been diagnosed with osteoporosis 16 years earlier. She had initially been treated with alendronic acid/colecalciferol (Fosavance®, Merck Sharp & Dohme Ltd, UK), which she continued for 10 years, until it was replaced with e.v. zoledronic acid (Aclasta®, Novartis Europharm Limited, Ireland).

Figure 4 a) Right incomplete AFF. b) Left incomplete AFF. c) MRI study.

Antiresorptive therapy was completely discontinued 18 months before our evaluation. The patient was prescribed protected weight-bearing and an MRI was requested. Thirty days later, her symptoms were unchanged and the diagnosis was confirmed by MRI (Fig. 4c). Informed of the risk of a complete fracture and of the indication for preventive treatment, the patient refused surgery. She was clinically re-evaluated at 3 months, when the symptoms were again unchanged and she renewed her decision to avoid surgery; a 6-month follow-up with a new MRI is currently scheduled.

Discussion

Although the long-term use of BPs for the treatment of osteoporosis has been deemed safe [13], a minor part of the population experiences adverse effects. The relationship between BPs and AFFs is unclear and many studies have tried to identify a precise connection. Schilcher *et al*. [14], consulting Swedish national patient registries, considered a population of 12,777 women who suffered femoral fractures in 2008. Among those with subtrochanteric/shaft femoral fractures, radiographs were reviewed and the diagnosis of AFF was confirmed in 59 cases. The authors found a high prevalence of BP use among patients with AFFs, however the relative risk remained very low. A similar conclusion was reached by Lenart *et al*. [15].

On the other hand, Abrahamasen *et al*. [16], who examined data from the Danish National Hospital Discharge Register, reported that the total number of subtrochanteric fractures declined with adherence to BP treatment, and that people with

subtrochanteric fractures were not more likely to be under BP treatment.

Black *et al*. [17] performed secondary analyses of the results of 3 trials and reached a similar conclusion. A common limitation of these last studies is the lack of X-ray assessment and therefore the inability to differentiate, among low energy subtrochanteric fractures, between those with typical as opposed to atypical findings. It is therefore possible that a switch from the first to the second kind takes place among patients under BP therapy, without variation of the total number. However, it must be noted that AFFs have been described in elderly patients not previously treated with BPs, suggesting that these fractures are not caused by therapy alone, but rather become more common with BP treatment [18].

The female sex, PPIs and corticosteroids have also been indicated as possible co-factors [19–22]. In spite of these possibilities, it is widely accepted that subtrochanteric fractures account for a minor part of all femoral fractures even under BP therapy and that, given the immense beneficial effects of this treatment, its benefits outweigh the risks [7,23,24]. Among our cases, all patients were either under active treatment or had been treated with BPs. Cases #3 and #4 had been put on a drug holiday, respectively 3 years before fracture and 1 year before developing prodromal symptoms. This circumstance is compatible with the prolonged effect of BPs.

The clinical presentations of AFFs are variable, with 34%-76% of patients reportedly experiencing prodromal symptoms [25–27]. The most common symptoms include slow onset of pain at the level of the hip/thigh in the months preceding a complete fracture, but some reports found signs of incomplete fractures as long as 3 years before completion [28]. The final presentation resembles that of subtrochanteric or diaphyseal fractures, with shortening and obvious deformity. Regarding prodromal symptoms, our experience reflects the literature, as these symptoms were not consistent between the cases: #1 presented right thigh pain, however it was not present before the left-side injury; #3 never suffered from prodromal pain.

The characteristics of AFFs have most recently been defined in the second report of the American Society of Bone and Mineral Research Task Force, which identified 5 major features: no or minimal trauma; a fracture line starting from the lateral cortex and extending medially, transverse with possible oblique orientation; complete fractures might have a medial spike; minimal or no comminution; periosteal or endosteal thickening of the lateral cortex. To qualify as an AFF, the lesion must be located from just distal to the lesser trochanter to just proximal to the supracondylar flare and possess at least 4 out of the 5 major features [10]. If the patient undergoes radiological examination during prodromal symptoms, it might be possible to identify an incomplete fracture; this is usually characterized by a transverse radiolucent line involving only the lateral cortex which will be thickened and have a "beaked" appearance.

Many authors reported bilateral localization. Probyn *et al*. [29] examined the X-rays of 124 AFFs and discovered an opposite-side fracture in 63% of the cases. Meier *at al*. [30], albeit in a smaller group of patients, reported contralateral AFFs in 28% of cases. Finally, if conventional X-rays are not conclusive, bone scintigraphy or MRI should be performed [31]. In our current experience, bilateral involvement is always to be suspected. Our cases #1 and #3 had both suffered a previous AFF to the opposite side several years earlier, and case #4 presented with bilateral involvement.

The treatment of incomplete fractures is debated, but the recent literature veers towards a surgical approach. Ramchand *et al*. [32] described a case of incomplete bilateral fracture that improved months after BP suspension, but recurred bilaterally once a different antiresorptive therapy was introduced. Indeed, the majority of incomplete fractures seem to evolve into complete fractures when treated conservatively with suspension of BP therapy and with the introduction of protected weight-bearing. Instead, treating an incomplete AFF with prompt preventive surgery avoids the need for troublesome reduction maneuvers, and reduces complications and hospitalization time [9]. If conservative treatment is chosen, periodic X-ray monitoring should be performed to assess healing or spot signs of progression. In 2017, Min *et al*. [33] described and evaluated a scoring system with the purpose of identifying impending (within 6 months) AFFs. In their experience, a fracture could be considered impending when the score was ≥8, with a positive predictive value of 100% and a sensitivity of 75%. However, the results did not exclude a possible evolution into a complete fracture after the 6-month period for scores <8.

Since these fractures revolve around difficult healing, a surgical approach with cephalomedullary nailing is preferred to one with plating [34]. The latter is usually chosen if cortical thickening has severely deformed the canal or in cases of pre-existing arthroplasty.

The surgical approach to AFFs, whether complete or incomplete, requires special attention and complications are frequently reported. In a controlled study of 25 AFFs, Prasarn *et al*. [35] reported a complication rate as high as 68% (iatrogenic fractures during nailing and implant failure after plating). Also, Lai et al. [36] identified an 18% risk of complications (understood as reoperation or nonunion at 12 months) in a group of 66 patients. As already mentioned, these fractures have been associated with an increase in healing time. Bogdan *et al*. [27] retrieved data on 161 patients and discovered that 22% of them took >6 months to heal. Thompson *et al*. [37] obtained complete follow-up data on 20 AFFs and reported that 4 patients (20%) healed in >6 months, with 2 of them taking >1 year.

Conclusions

Bisphosphonates are undoubtedly a valuable resource for the prevention of fragility fractures and their positive effects greatly outweigh the risks connected with their long-term use. Orthopedic surgeons treating AFFs must be aware that these rare fractures are burdened with higher complication rates than typical fractures.

Moreover, since AFFs go through an incomplete phase which is susceptible to preventive treatment, all practitioners should be watchful for prodromal symptoms, which may allow an early diagnosis. Finally, whenever an AFF is identified, the opposite side should be systematically evaluated because bilateral presentation is frequent.

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