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CASE REPORT

Bisphosphonate long-term treatment related bilateral subtrochanteric femoral fracture. Can teriparatide be useful?

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Abstract Long-term treatment with biphosphonates has been related to atypical femoral fractures. We report the clinical case of a woman who suffered a proximal diaphyseal oblique fracture of the left femur after uninterrupted 13-year treatment with alendronate. Shortly after surgery, a painful lytic image in the external cortex of her right femur diaphysis was detected. Some papers have suggested surgical treatment to repair femur fractures after long-term treatment with bisphosphonates. Otherwise, two studies have shown healing acceleration of bone fractures with teriparatide. A lytic lesion was treated with teriparatide obtaining progressive disappearance of symptoms as well as bone healing. This outcome may suggest a way of prevention of complete fractures in symptomatic patients with long-term treatment with bisphosphonates.

Keywords Hip fracture · Bisphosphonates · Long-term treatment

Introduction

Bisphosphonates are considered first-line therapy in the treatment of postmenopausal osteoporosis. Their mechanisms of action lead to the inhibition of osteoclasts [1, 2], thereby increasing bone mineral density and lowering the incidence of low-energy fractures, mainly those affecting the spine and hip [3–5]. Alendronic acid was the first bisphosphonate to be approved by the US Food and Drug Administration (FDA) in 1995. Since then its short-term efficacy and safety have been extensively documented [2, 5, 6]. Nevertheless, the side-effects of long-term treatment with bisphosphonates, such as non-traumatic atypical femoral fractures, are beginning to be known. Since 2005 various scientific journals have described the above-mentioned association [7, 8], especially in relation to the use of alendronate [2, 9–14].

We present the clinical case of a patient suffering a proximal diaphysis fracture following an uninterrupted 13-year treatment with alendronate. The patient presented almost simultaneously a symptomatic lytic lesion in the contralateral femur as well as peculiar radiological changes in the medullary cavity.

Case report

A 73-year-old woman suffered a proximal diaphyseal oblique fracture of the left femur, after a banal movement. X-ray studies did not suggest a pathological fracture (Fig. 1a). The patient was operated on 24 h after the fracture, by performing a locked intramedullary nailing with a Grosse-Kempf nail (Fig. 1b). Immediate postoperative evolution was uneventful and she was discharged from the hospital 72 h later.

Subsequently questioned, the patient admitted pre-existing pain in the left thigh for 2 months prior to the surgery, with varying intensity and irregular course. The pain used to intensify when loading the affected limb and partially subsided with administration of nonsteroidal anti-inflammatory drugs. Clinical observation and good response to first-line analgesics suggested only a joint

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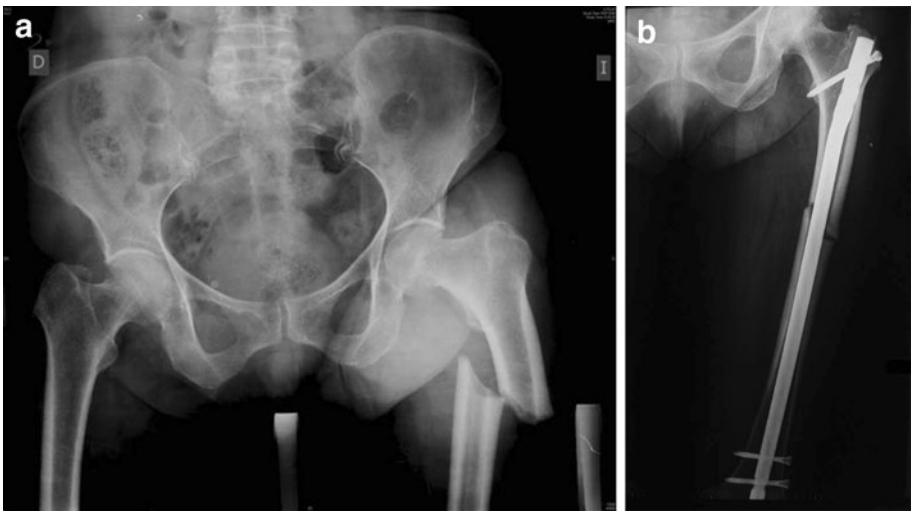

Fig. 1 **a** Left femur proximal diaphyseal fracture. **b** Locking intramedullary nailing of the left femur

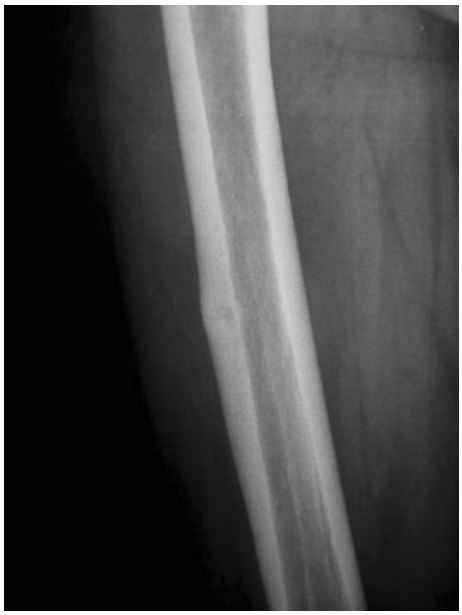

Fig. 2 Lytic image in the external cortex of the right femur diaphysis and double cortical-like image inside the diaphyseal medullary cavity

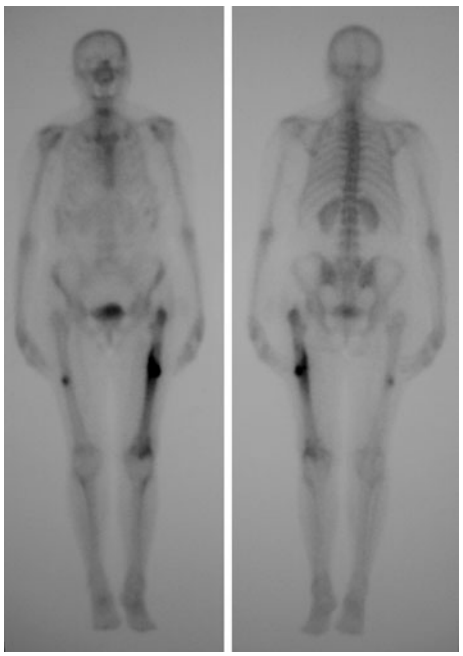

Fig. 3 Bone gammagraphy showing increased deposition in both femurs

degeneration problem. In addition, physical examination or the X-ray studies of the left hip and knee did not reveal any clinical alteration. The fracture occurred in bipedal standing position, while the patient was cooking, rotating the body around the axis of the affected limb, without suffering a fall.

During the month following the above-mentioned surgical intervention, the patient began to suffer from discomfort in the contra-lateral thigh. An X-ray was performed, showing a lytic image in the external cortex of the right femur diaphysis (Fig. 2) and also a double cortical-like image inside the diaphyseal medullary cavity.

The patient was then referred to our hospital, suspecting a possible metastatic process. A bone gammagraphy was performed, showing a focalized deposit in the middle third of the right femur diaphysis and a diffuse increase in deposition of the left femur, corresponding to the surgically treated fracture (Fig. 3). A computerized tomography (CT scan) of the right inferior limb was ordered (Fig. 4a, b), showing the lytic lesion previously described. After analyzing the study together with the Radiology Service and taking into account the pharmacological history of the patient, a neoplastic disease was discarded and bone fragility was considered the most likely etiology of these atypical fractures.

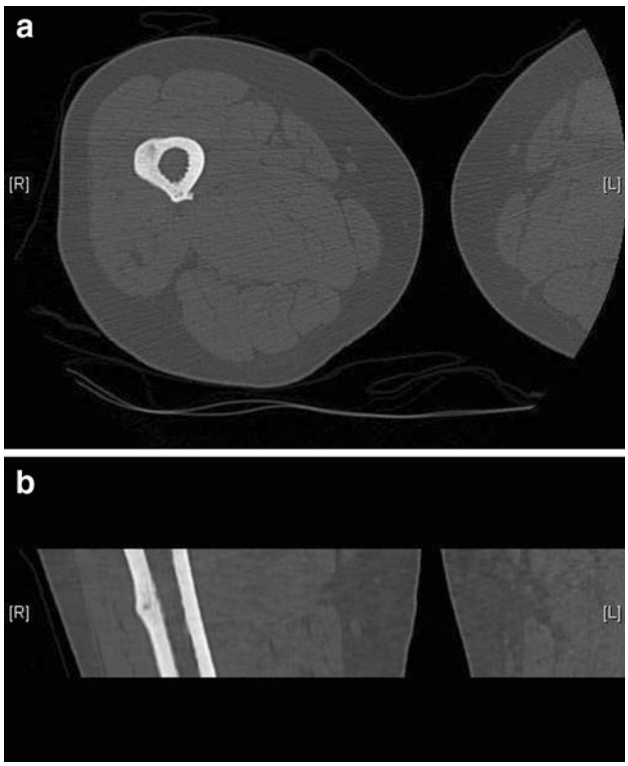

Fig. 4 CT scan of the right femur showing the lytic lesion in axial (**a**) and coronal (**b**) plane

The pharmacological clinical history showed calcium and vitamin D supplements associated with calcitonin intake between 1993 and 1995. Treatment with two daily tablets of 1,132 mg calcium gluconate plus 875 mg calcium carbonate and 10 mg daily dose of alendronate (Fosamax®)was maintained between October 1996 and May 2002. In June 2002, the 10-mg daily dose of alendronate treatment was replaced by the new formulation of one 70-mg tablet weekly, maintaining the calcium supplement. This protocol was followed until the development of the femur fractures. The whole treatment had been based upon bone density measurements in the calcaneus, performed in a private office. The patient did not have risk factors for pathological fractures, was a non-smoker, and had not been previously prescribed corticosteroid treatments.

A dual-energy X-ray absorptiometry was ordered, which did not show changes in the bone mineral density. Alendronate treatment was subsequently discontinued and 20 mcg daily of subcutaneous teriparatide (Forsteo®) was administered for 12 months, associating a 1,500 mg calcium carbonate tablet with 400 UI of vit. D. The objective of teriparatide treatment was to repair the lytic image of the right femur, as surgical treatment by prophylactic intramedullary nailing was considered exceedingly aggressive given the magnitude of the lesion.

Following teriparatide treatment initiation, pain in the right lower limb progressively settled down to complete absence. The lytic image reduced in size more slowly, subsequently reaching full reparation. Teriparatide treatment was finalized following the prescribed period and treatment with denosumab was initiated. Presently, the patient is symptom-free and carries on a normal life.

The need for informed consent was waived by the ethical committee since rights and interests of the patients would not be violated and their privacy and anonymity would be assured by this study design. Authors declare also that their research conforms to the Declaration of Helsinki.

Discussion

The relationship between femoral fractures and long-term alendronate therapy has been documented [9–19]. This type of fracture occurs in post-menopausal women and affects the subtrochanteric region or the femur diaphysis. These fractures occur following low-energy trauma or twisting movements. During the weeks or months preceding the fracture, the patient experiences weakness in the affected limb or pain in the thigh. These symptoms can constitute the prodrome of spontaneous or low-energy fractures. In a group of 17 patients treated with alendronate that presented subtrochanteric fractures Kwek et al. [12] found these same clinical features.

Radiologically, it has been described marked cortical thinning of the bone and a transverse fracture line [18, 19]. Nevertheless, Goh et al. [11] has reported an X-ray image of cortical hypertrophy in the subtrochanteric region of the femur. Occasionally, a parallel reaction to the contralateral cortex has been observed, which is considered the first stage of these fractures. These radiological changes, together with the frequent delay or nonunion, could be due to inhibition of bone turnover, causing a non-dynamic alteration of the bone. A study [20] of bone biopsies of patients treated with alendronate for a period between 3 and 8 years confirmed that the severe bone turnover suppression, with a reduced or absent osteoblast activity, was the fundamental cause of the fractures. As a consequence of this suppression there is marked thinning of the osteoid and reduction in osteoblast/osteoclast surface. The end result is a decrease of the bone matrix, possibly leading to failures in the microfracture reparation and secondary mineralization process, with a deterioration of the biomechanical properties of the bone [20, 21].

All these changes are enhanced by the long mean lifetime of biphosphonates. Alendronate has a mean lifetime of 10.9 years [21]. A study [22] has demonstrated that following a 5-year alendronate administration, the biochemical markers of bone turnover remain suppressed at least for three more years after treatment interruption. Another

study [23] shows that a dose of alendronate of 10 mg a day for 10 years causes a bone accumulation thereof around 75 mg per 2 kg of mineral.

The described case is that of a postmenopausal woman who presented with a non-traumatic diaphyseal femoral fracture associated with cortical hypertrophy, following long-term alendronate treatment without a clear indication. This type of condition has previously been described in other studies [2, 11–13, 17, 24–26]. A delay in bone healing was reported following the surgical intervention, which was ascribed to the lack of compression of the fracture site, but could have been due to the suppression of bone turnover produced by the biphosphonate treatment, similar to a case previously documented in literature [17]. Other possible etiologies of pathological or insufficiency fractures are osteomalacia, osteogenesis imperfecta, bone tumors (primary or metastatic) and Paget′s disease. Nevertheless, neither the clinical analyses nor the results of complementary tests suggested the above-mentioned possibilities. On the contrary, the contralateral fracture showed a unicortical peak associated with hypertrophy of the cortex and a peculiar X-ray image characterized by the presence of a second cortical line within the medullary cavity.

There are six documented cases [10, 19, 24–27] of bilateral femoral fracture associated with the use of biphosphonates, all of which occurred consecutively and required surgical intervention on both femurs. What critically differentiates this case from the published ones is the sequence of the bone lesions and the pharmacological teriparatide treatment of the second fracture.

Recombinant teriparatide [human PTH (1–34)] was approved by the FDA on 2002, for treatment of osteoporosis in men ad postmenopausal women with high risk for fracture. Teriparatide is currently the only bone-forming osteoporosis drug available for clinical use and increases bone turnover with a greater stimulation of formation than resorption. Bone turnover markers also rise during treatment with teriparatide, with markers of bone formation rising early and rapidly, followed by rises in bone resorption markers [28]. Teriparatide was chosen due to its twice documented effect [29, 30] on fracture healing acceleration. In our patient we observed the progressive disappearance of symptoms and the healing of the lytic lesion.

The administration of biphosphonates in patients with osteoporosis is a useful therapy. Its extended use after 3–5 years should be evaluated yearly. An editorial from 2005 [31] recommends discontinuation after 5 years of treatment and subsequent treatment with parathyroid hormone if the patient is at high risk of fracture. Biphosphonates could be abandoned in patients that present a low or moderate-low risk of fracture (no previous fracture, T-score ≥ -2.0 and absence of other major risk factors) following completion of the above-mentioned period.

We recommend paying special attention to the presence of spontaneous, non-traumatic pain in patients that have followed long-term biphosphonate treatment and performing X-ray studies, including when appropriate CT scan, MRI or both, in order to an early detection of atypical fractures. In these cases it would be advisable to discontinue biphosphonate treatment, with the possibility of starting teriparatide therapy in case of detecting a lytic lesion.

Conflict of interest The authors declare that they have no conflict of interest related to the publication of this manuscript.

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