Acta Biomed 2021; Vol. 92, Supplement 1: e2021130 DOI: 10.23750/abm.v92iS1.10452

Case report

Preventive bilateral femoral nailing in atypical femoral fracture non responder to anabolic therapy: case report and mini-review

Elisabetta Neri, Livia Gabriele, Vanna Bottai, Lorenzo Andreani, Enrico Bonicoli, Michelangelo Scaglione

Azienda Ospedaliera Universitaria Pisana

Abstract. Currently bisphosphonates are the main antiresorptive medications used in osteoporosis. However, a prolonged use of these drugs is associated to an increased risk of atypical femoral fractures, especially in patients suffering from others predisposing clinical conditions. This report describes a case of a woman presenting bilateral impending femoral fracture initially treated with bisphosphonates suspension and intramedullary nailing of right femur. Despite anabolic therapy, the patient presented progression of incomplete contralateral femoral fracture which required a second surgical treatment. The aim of this case report is to underline the need to suspect atypical femoral fracture, and, when diagnosticated, to treat them with bisphosphonates suspension, anabolic medication, and eventual prophylactic surgical procedures in non responders patients. (www.actabiomedica.it)

Key words: Atypical femoral fracture, bisphosphonate, teriparatide, osteoporosis, femoral nailing.

Introduction

Osteoporosis causes almost 9 million fractures annually worldwide (1); fragility fractures occur in 40-50% of women and 13-22% of men over the age of 50 years (2).

Several types of therapy are currently used to prevent fragility fractures: antiresorptive drugs (such as bisphosphonates), monoclonal antibodies (such as Denosumab), anabolic drugs (such as recombinant human parathormon), dual action drug (such as strontium ranelate), hormones and hormones receptors modulators.

Bisphosphonate therapy is considered the principal method of osteoporosis treatment; the large use is attributable to wide consensus about its capacity to increase bone mineral density and preventing fragility fractures (3).

However, since when Odvina reported in 2005 the first nine case of spontaneous non vertebral fractures in patients treated with prolonged therapy with alendronate (4), BPs intensive use has been re-evaluated, considering a drug holiday after at least 3-5 years of therapy (5) and always associated with a clinical and metabolic patient reevaluation (6).

A long-term bisphosphonate use (usually for more than 3 years, as described by Second Task Force of the American Society for Bone and Mineral Research-ASBMR) produces a suppression of bone turnover and consequent higher risk of potential micro lesions accumulation. The ending result is a weakened bone that is not able to repair several damages. All these events can produce bone fractures called *atypical fractures (AF)(7)*.

Approximately 70% of patients with a confirmed stress fracture report prodromal pain before diagnosis; despite this, impending fractures often remain misdiagnosed (8).

A case of bilateral impending AFF related to bisphosphonate use with typical radiological and well

documented clinical paths, not responsive to teriparatide treatment will be exposed.

Case presentation

A 75-year-old female patient visited our outpatient due to tight pain in left leg started from 4 years before, increased in previous weeks. She reported a clinical history of anxious depressive syndrome (in treatment with alprazolam), previous surgery ovariectomy (due to ovarian cyst) and appendicectomy; she presented severe osteoporosis, treated for 7 years with pharmacological therapy. Specifically, she took Risedronate 35 gtt/w and Cholecalciferol 25000 IU/15 days for 2 years; then, anti-resorptive therapy switched to Ibandronate 35 mg 1/w, continuing Cholecalciferol supplementation for another year.

In 2016 a post-traumatic no surgical vertebral fracture of D12 occurred. Laboratory investigations excluded secondary hyperparathyroidism. In 2017 bisphosphonate therapy was suspended in favor of beginning treatment with Denosumab 60 mg subcutaneous injection (one injection every six months). Regarding her painful symptoms, general practitioner had recommended to the patient X Ray study of just pelvis and right hip, assuming her pain was caused by hip arthrosis. Therefore, he recommended rest and painkillers therapy.

Due to persisting symptoms notwithstanding painkillers, she turned to our specialist in December 2018, that advised left thigh X Ray and MRI (Fig. 1). Bone edema and fracture line was observed in left femur shaft; MRI sign of bone edema and X Ray images of two cortical bump were identified also in contralateral femoral shaft, completely silent in terms of symptoms. In January 2019 she was admitted to the

Table 1. ASBMR 2010 criteria for diagnosis of atypical fracture; modifications introduced by ASBMR in 2013 report are in italicized font

	Major Criteria
1	No trauma or low energy trauma
2	Proximal fracture line under the lesser trochanter and distal fracture line above the femoral condyles
3	Transverse or only slightly oblique fracture line (angle <30°) (ASBMR 2010)/ *Fracture line originates at the lateral cortex and is substantially transverse in orientation, although it may become oblique as it progresses medially across the femur* (ASBMR 2013)
4	No comminuted fracture (ASBMR 2010) *or minimally comminuted* (*ASBMR 2013*)
5	Complete fracture with medial spike, incomplete fracture involving only lateral cortex *Localized periosteal or endosteal thickening of lateral cortex at the fracture site* (*"beaking or flaring"*) (*ASBMR 2013*)
	Minor Criteria
1	Periostal reaction along the lateral cortex (ASBMR 2010)
2	Increased cortical thickness
3	Prodrome pain in the groin or thigh
4	Bilateral fracture
5	Delayed healing (ASBMR 2010) /*delayed fracture healing* (*ASBMR 2013*)
6	Comorbidities: rheumatoid arthritis, Vitamin D deficiency, hypophosphatasia
7	Concomitant treatment: bisphosphonates, glucocorticoids, proton pump inhibitors
	Exclusion Criteria
1	Femoral neck fracture
2	Interthrocanteric fracture with extension to the subtrocantheric fracture
3	Periprosthetic fracture
4	Pathological fracture related to a primary bone tumor or bone metastasis

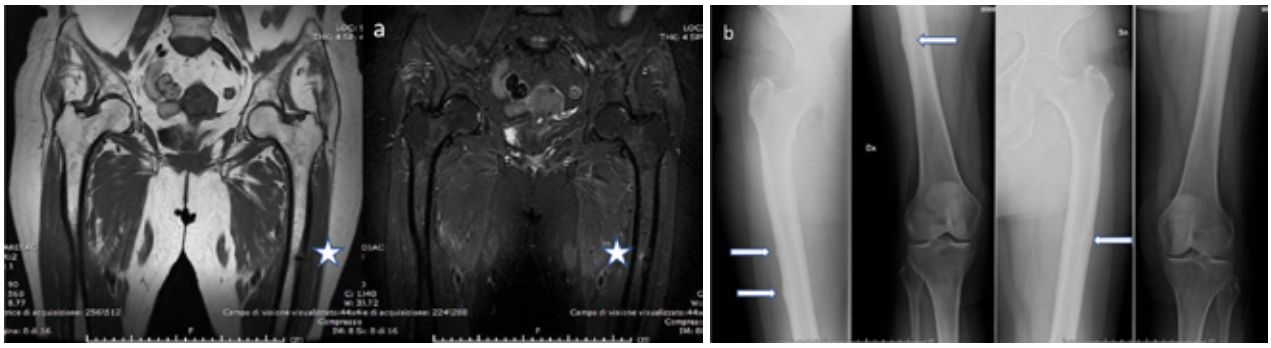

Figure 1. MRI images (a) and X Ray images (b) show the typical impending AFF pattern: bone edema and fracture line (*) and cortical bump (→)

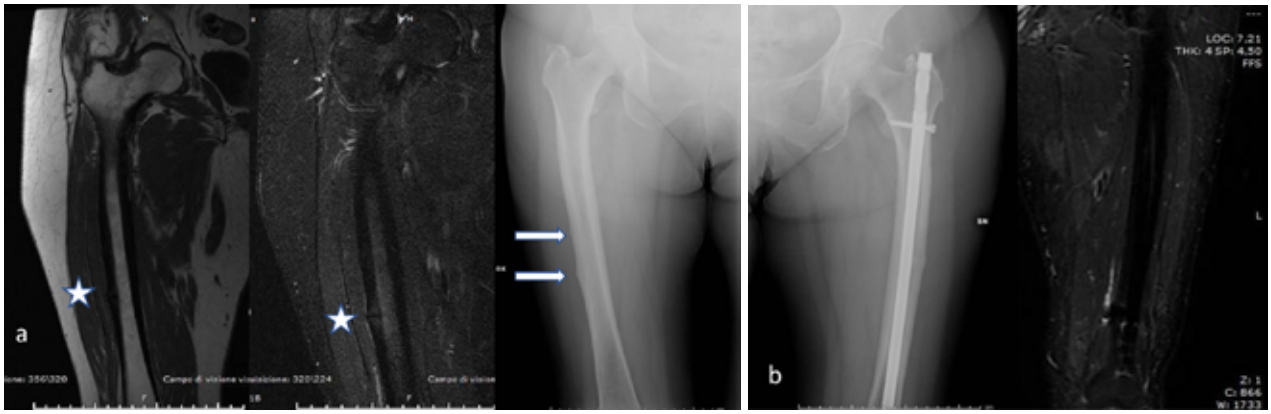

Figure 2. (a) Right femur findings at MRI and Xray images: black line, bone edema and periosteum reaction (*) and cortical bump (→). (b) Left femur follow up images show healing.

hospital to perform a preventive intramedullary nailing. A long recon intramedullary locked nail was used, and the patient had a normal postoperative progress. A dual-energy X-ray absorptiometry (DEXA) scan of the femoral neck and lumbar spine was performed during hospital stay, and a severe osteoporosis (*femoral T-score*: -2,5; *L2-L4 T-score*: -4,5) was found. The therapy for osteoporosis was modified: Denosumab injection was immediately suspended and therapy with Teriparatide 20 mcg/die was started. Right thigh pain decreased and disappeared completely.

After 6 months, another X Ray and MRI of thigh bilateral was performed (Fig. 2): periosteum stress reaction and black line were observed in the right femur shaft associated to mild weight bearing pain; the patient was invited to continuing the anabolic therapy and radiological follow up. Simultaneously complete healing of the left femur treated in first place has been reported.

During the first months of 2020, due to increase of left leg weight bearing pain and to the absence of signs of improvement in radiological images, the patient was addressed to preventing intramedullary nailing and anabolic systemic therapy.

Discussion

First cases of spontaneous femoral fracture associated to BPs therapy were first described in 2005 by Odvina et al (5). They described nine cases of Severe Suppression Bone Turnover (SSBT), a condition of an adynamic or low turnover bone with spontaneous or atraumatic non vertebral fractures, especially in areas rich in cortical bone and characterized by difficulty in healing, within a cohort of patients undergoing long term alendronate therapies. Goh et al described

prolonged alendronate use in 9 out of 13 people affected by AFF (9).

The second report of a Task Force of the American Society for Bone and Mineral Research (ASBMR), reported an AFF relative risk ranging from 3,2 to 50 cases per 100000 person per years in patients taking long terms BPs (10).

AFF is defined by ASBMR with specific diagnostic criteria (8) revised in 2013 (TAB 1). In the case reported, the shaft localization and pattern of lateral cortex incomplete fracture were agreed with major criteria; periosteal reaction along the lateral cortex, cortical thickness, prodrome pain in the thigh, bilateral localization and concomitant treatment with bisphosphonates with minor criteria.

The identification of typical MRI pattern of impending AFF was well explained by Png et al, who describes focal cortical thickening, bone edema, focal cortical abnormality and dreaded black line; all of these features were clearly represented and well documented in our case (11).

Although no accurate BFs dose-relationship in increasing risk of having AFs was detected, many authors noted an increased AFFs incidence in prolonged therapies; in the presented case, the patient had continued antiresorptive therapy for four years, even if assuming different type of medications (12).

Kim et al conducted a large cohort study based on healthcare utilization database of two states of USA, collecting data regarding 17028 oral bisphosphonates users for 10 years; average age was 79,9 years and 97% were women; 104 diaphyseal or subtrochanteric spontaneous fractures occurred (1,46 fractures per 1000 person-year among bisphosphonates users) (13).

The age-adjusted incidence rate for AFF described by Dell et al. in a large review in 2018 reported 1,78/100.000 person-years with BP use from 0,1 to 1,9 years and 113,1/100.000 person-years with BP use from 8 to 9 years, reporting also a higher risk in Asians than in Whites and in women than in men. However, they concluded that patients at high risk for osteoporotic fractures should not be discouraged from initiating BFs therapy (14).

Atypical femur fractures are most commonly note in proximal femur, especially in proximal one-third of the shaft, but may occur in every location of femoral shaft; generally, are transverse or slightly oblique fractures, complete or incomplete, associated with a typical periosteal stress reaction and thinning of cortical at the fracture site. Prodromal symptoms, such as thigh pain, may be present. Even though AFFs are more commonly related with bisphosphonate (BP) exposure, this kind of fractures are reported also in individuals with no history of BP treatment (5).

Although ASBMR did not included peri-implant fracture into criteria for the AFs diagnosis, several studies have identified many cases of periprosthetic fractures with radiographic features similar to AFFs (15-17).

Moreover, Giannotti et al. described histological examination in a case report of pseudoarthrosis in periprosthetic fracture with atypical radiological characteristics (18).

Typically, AFFs are more difficult to be surgically treated, presenting high rate of delayed healing until nonunion (19).

AFF must be considered every time thigh or hip pain occurs in patients following prolonged antiresorptive therapy, also in wearers of hip prosthetic implants, especially in case of comorbid conditions (eg: hypophosphatasia, vit D deficiency) and during use of pharmaceutical agents (such as BFs, glucocorticoids and PPI); XRay and MRI are indicated for timely diagnosis (14,21,22). If stress reaction is identified, BPs therapy must be immediately stopped and a course of teriparatide may be considered (20); if also dreaded black line is radiographically appreciable and pain continues for more than 2 or three months, prophylactic nailing can be considered; all these concepts are well expressed by Dell et al, who proposed a sort of guideline.

Moreover, drug holiday after 5 year bisphosphonate treatment is demonstrated to reduce to 18,5% the risk of contralateral AFF; in this case, despite antiresorptive suspension and anabolic treatment with teriparatide, there was an evolution towards contralateral impending AFF that became symptomatic, requiring another preventive surgical procedure.

In this case report the authors noted that while the left femoral atypical fracture preventively surgically treated with reaming and intramedullary nailing associated with teriparatide promoted bone healing

and resolution of pain, on the right femur pharmacological therapy alone did not recover enough to avoid the progression from impending to complete atypical fracture.

For this reason, patient can be considered no responder to anabolic therapy.

Conclusions

Despite wide lectures concerning BP's related risk of AFF, specialized doctors and general practitioners must not forget the high utility of BFs in preventing fragility fractures that overcome the onset of adverse events.

However, AFF is an occasional complication with respect to the high number of osteoporosis related fracture.

The aim of our report is to underline the importance of an early diagnosis of AFF or impending AFF which must be suspected and investigated with X Ray and MRI when patient under BPs treatment reports thigh pain. Patient may be subjected to metabolic bone profile, addressed to antiresorptive suspension, limitation of weight bearing and beginning of anabolic therapy. If thigh pain is associated, preventive rodding should be performed.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Hernlund E, Svedbom A, Ivergård et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013; 8(1):136
2. Caggiari G, Leali PT, Mosele GR, Puddu L, Badessi F, Doria C. Safety and effectiveness of teriparatide vs alendronate in postmenopausal osteoporosis: A prospective non randomized clinical study. Clin Cases Miner Bone Metab 2016; 13(3):200-203
3. Koh A, Guerado E, Giannoudis PV. Atypical femoral fractures related to bisphosphonate treatment: issues and controversies related to their surgical management. Bone Joint J 2017 Mar; 99-B(3):295-302
4. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005; 90:1294-1301
5. Shane E, Burr D, Ebeling PR, 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; 25:2267–2294
6. Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical Femur Fractures: Review of Epidemiology, Relationship to Bisphosphonates, Prevention, and Clinical Management. Endocr Rev 2019 Apr 1; 40(2): 333-368
7. Adler RA, El-Hajj Fuleihan G, Bauer DC et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res 2016 Jan;31(1):16-35
8. Giannini S1, Chiarello E, Tedesco G, et al. Atypical femoral fractures. Clin Cases Miner Bone Metab. 2013 Jan;10(1):30-3
9. Goh SK, Yang KY, Koh JSB et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br 2007; (3):349–353
10. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral frac- tures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2014; 29(1):1–23
11. Png MA, Koh JS, Goh SK, Fook-Chong S, Howe TS. Bisphosphonate-related femoral periosteal stress reactions: scoring system based on radiographic and MRI findings. AJR Am J Roentgenol 2012;198(4):869-877
12. Abrahamsen B, Eiken P, Eastell R. Cumulative alendronate dose and the long- term absolute risk of subtrochanteric and diaphyseal femur fractures: a register- based national cohort analysis. J Clin Endocrinol Metab 2010; 95:5258–5265
13. Kim SY, Schneeweiss S, Katz JN, et al. Oral bisphosphonates and risk of subtrochanteric or diaphyseal femur fractures in a population-based cohort. J Bone Miner Res 2011 May; 26(5):993-1001
14. Dell R, Greene D. A proposal for an atypical femur fracture treatment and prevention clinical practice guideline. Osteoporos Int 2018 Jun; 29(6):1277-1283
15. Sayed-Noor AS, Sjoden GO. Two femoral insufficiency fractures after long-term alendronate therapy. Clinical Orthop Relat Res 2009; 467:1921-1926
16. Lee JYY, Soh T, Howe TS, Koh JSB, Kwek EBK, Chua DTC. Bisphosphonate-associated peri implant fractures: a new clinical entity?. Acta Orthopaedica 2015; 86(5):622-626
17. Robinson Jde D, Leighton RK, Trask K, Bogdan Y, Tornetta P 3rd. Periprosthetic Atypical Femoral Fractures in Patients on Long-term Bisphosphonates: A Multicenter Retrospective Review. J Orthop Trauma 2016; 30(4):170-176

18. Giannotti S, Bottai V, Dell'Osso G, et al. Pseudoarthrosis in atypical femoral fracture: case report. Osteoporos Int 2013; 24:2893–2895
19. Prasarn ML, Ahn J, Helfet DL, Lane JM et al. Bisphosphonate-associated femur fractures have high complication rates with operative fixation. Clin Orthop Relat Res 2012 Aug; 470(8):2295-301
20. Im G, Lee S. Effect of Teriparatide on Healing of Atypical Femoral Fractures: A Systemic Review. J Bone Metab 2015 Nov; 22(4):183-9
21. Marshall RA, Mandell JC, Weaver MJ, Ferrone M, Sodickson A, Khurana B. Imaging Features and Management of Stress, Atypical, and Pathologic Fractures. Radiographics 2018; 38(7):2173-2192
22. LeBlanc ES, Rosales AG, Genant HK, et al. Radiological criteria for atypical features of femur fractures: what we can learn when applied in a clinical study setting. Osteoporos Int 2019; 30(6):1287-1295

Correspondence:
Received: 15 August 2020
Accepted: 4 October 2020
Elisabetta Neri, Via Paradisa 2, 56124 – Pisa (PI), Italy.
phone and fax number: 050992025
E-mail: elisabetta.neri7@gmail.com