

Impending atypical femoral fractures associated with bisphosphonates: postoperative diagnosis after hip prosthesis. Clinical cases presentation.

Vanna Bottai¹, Nicola Piolanti², Giuseppe Digrandi², Agnese Menconi³, Damiano Antognetti³, Michele Di Lonardo¹, Michelangelo Scaglione¹, Gloria Raffaetà³

¹Second Orthopedic and Traumatologic Clinic, University of Pisa, Pisa, Toscana, Italy; ²First Orthopedic and Traumatologic Clinic, University of Pisa, Pisa, Toscana, Italy; ³Orthopedic Rehabilitation Department Section, University of Pisa, Pisa, Toscana, Italy.

Abstract. *Background and aim:* Number of hip prosthesis implants in arthritis, number of patients treated with bisphosphonates to prevent fragility fractures and, together, number of atypical femoral fracture's cases are increasing. *Case series:* This article describes two cases of hip arthritis, treated with hip replacement, in patients using bisphosphonates for a long time; in both cases an incomplete atypical femoral fracture was misdiagnosed before the surgery. Authors describe the importance to carry out a complete osteometabolic and radiographic pre-operative examination of patients in treatment with bisphosphonates going to hip replacement, to check the possible presence of incomplete atypical femoral fracture and to optimize surgical and pharmacological treatment. *Conclusions:* In hip prosthesis surgery, prior diagnosis of incomplete atypical femoral fractures can indicate the choice of a different kind of prosthesis stem to optimize surgical results. This can also positively impact to rehabilitation in term of duration and daily activities recovery. (www.actabiomedica.it)

Key words: osteoporosis, atypical femoral fractures, hip prosthesis, periprosthetic atypical femoral fractures, bisphosphonates

Introduction

Atypical femoral fractures (AFFs) are subtrochanteric and shaft femoral fractures often associated with a long use of bisphosphonates (BPs). Their incidence among patients taking BPs for over 10 years is estimate at approximately 107.5/100000-person year.

AFFs are characterized by specific Xray patterns such as transverse or short oblique fracture line, non-comminuted fractures, and presence of cortical spike. They can be bilateral and can present nonspecific prodromal pain (groin or tight pain).

AFFs can be completed or incomplete fractures. Incomplete fractures are characterized by the presence of a lateral femoral cortex thickening. A transverse lucency in the lateral cortex can be also present.

In complete AFFs mainstay treatment is surgical with internal fixation with intramedullary nailing; instead for incomplete fractures surgical treatment is conducted only in patients suffering pain or non-responsive to 2-3 months of conservative therapy, to prevent the onset of a complete fracture (1).

However orthopedic AFFs' management is still variable and there isn't clinical practice guideline.

Recently many cases of AFFs associated with hip prosthesis (atypical periprosthetic femoral fractures PAFFs) are described (2) (3) (4).

Hip prostheses in arthritis are constantly increasing and patients treated with bisphosphonates are increasing together.

It is so plausible that patients affected by symptomatic arthritis and asymptomatic AFFs undergone

to hip surgery without a correct pre-operative AFFs diagnosis.

The Authors present two cases of hip arthritis associated with an asymptomatic incomplete AFFs; in both cases AFFs were diagnosed occasionally post-surgery.

Case 1

A 79-year-old Caucasian woman affected by coxarthrosis unresponsive to conservative treatment, underwent to a right total hip prosthesis after preoperative planning (Figure 1).

Pathological and physiological anamnesis was collected using a standard form. The patient was 155 cm tall, Weight 60 kg, BMI (Body Mass Index) was 24.6 kg/m².

She was affected by hypertension, hyperlipidemia, Asthma, GERD (Gastro-Esophageal Reflux Disease) and assumed Olmesartan, Statin, Aspirin regularly, an occasional pharmacological therapy for asthma.

The patient was also in treatment for osteoporosis with Alendronic Acid/Colecalciferol (70mg/2800UI, 1 admin/week) for 4 years.

The only mineralometric evaluation performed before the surgery was an heel ultrasound densitometry that reported a T-score of -2.9.

One year before surgery she reported a pathological L1 fracture (Genant 1 type). The reported trauma indeed was inadequate to cause fracture in a healthy bone. She had never smoked in her life, and she never had any other kind of fracture.

Because of the occurrence of a periprosthetic acetabular fracture during the surgery, a delta TT revision cup was used to optimize primary fixation.

At the first post-operative x ray, the presence of a lateral femoral cortex thickening, near the tip of the stem was seen (Figure 2 A, B).

Then a bilateral femoral x ray was done with an occasional finding of radiological patterns of bilateral atypical femoral fracture of the middle third of the shaft (Figure 2 C).

Osteometabolic status was studied with blood exams:

25-OH vit. D3 25.9 mcg/L, Calcium 8.0 mg/dL, PTH 31ng/dL, ALP 45 U/L.

CTX and P1NP were in the normal range.

Inflammatory indices were slightly altered: PCR 3.85 (NR max 0.50 mg/dL), VES 45 mm/h (NR max 30 mm/h).

Serum protein electrophoresis evidenced:

Alpha 1 Globulin 8.4% (NR 2.9%-4.9%), Alpha 2 Globulin 15.9% (NR 7.1% - 11.8%), Beta 1 Globulin 7.4 % (NR 4.7% - 7.2%), Beta 2 Globulin 6.8% (NR 3.2% - 4.5%).

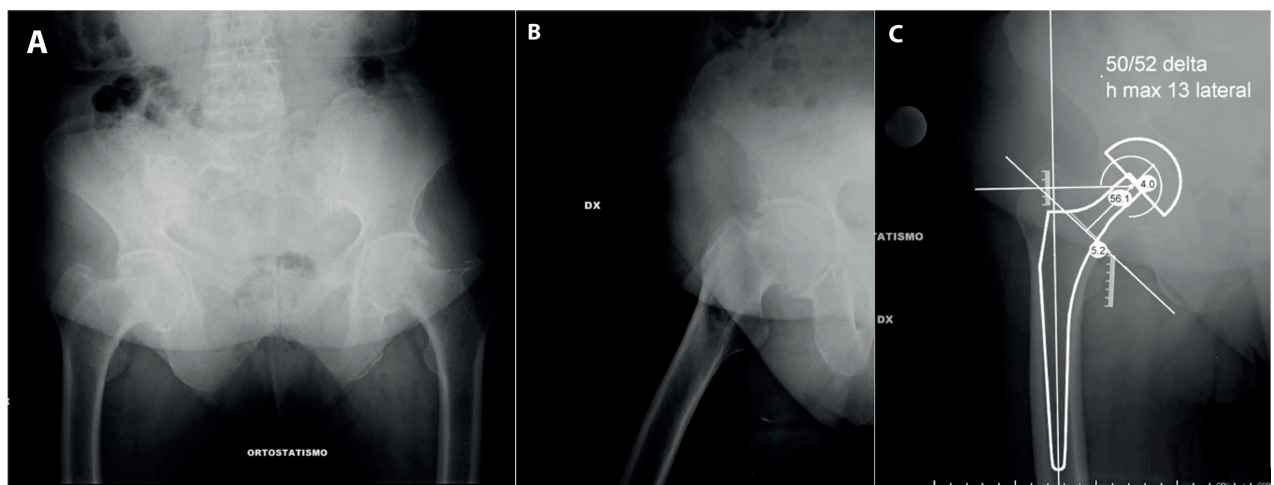


Figure 1. (A), (B) Preoperative x rays, (C) surgical planning. The presence of lateral cortex thickening that allow to make diagnosis of atypical femoral fracture is not showed in these images. For preoperative planning in total hip arthroplasty indeed, in our department we do not perform full length x ray of the femur.

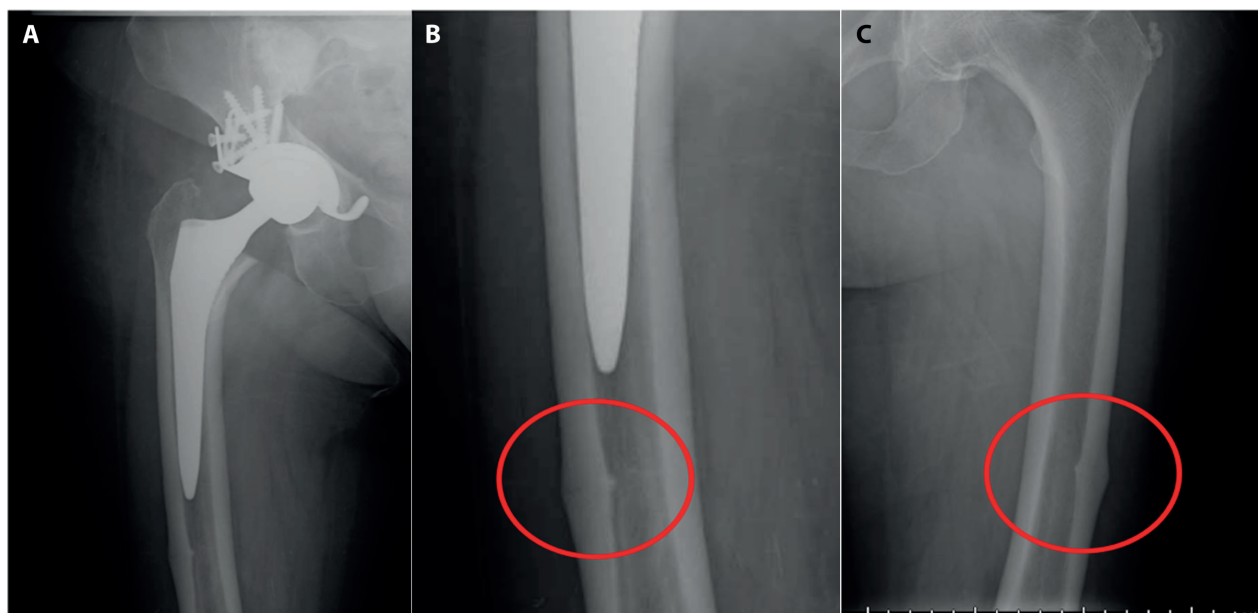


Figure 2. (A) The presence of a lateral femoral cortex thickening was shown in the post-operative x rays. (B) Detail of the fracture with a thin lateral radiolucency line. (C) Contralateral x ray shows atypical femoral fracture also in the left femur.

BPs treatment was immediately stopped, and the patient started anabolic treatment with Teriparatide (20 mcg/day), supplementation with calcium carbonate (500 mg/die) and calcifediol 1,5 mg/10ml (30 drops/week).

To better evaluate the pattern of the AFF in the contralateral side a thigh MRI (Magnetic Resonance Imaging) was done; the presence of cortex edema was found (Figure 3 A) so for 2 months only a partial weight bearing on the left side was allowed.

The radiological exams after six months from anabolic therapy showed the lateral radiolucency line disappears (Figure 3 C).

Anabolic therapy was scheduled for 6 months until pain resolution.

Case 2

A 77-year-old Caucasian woman patient, affected by coxarthrosis unresponsive to conservative treatment, underwent to a left total hip prosthesis.

Pathological and physiological anamnesis was collected using a standard form. The patient was 155 cm tall, weight 60 kg, BMI 33,3kg/m².

She was affected by Arterial hypertension, dyslipidemia, obesity, COPD (Chronic Obstructive Pulmonary Disease), here home therapy was Omeprazole, Atorvastatin, Nebivolol, Tiotropium bromide

The patient reported a condition of osteoporosis, without providing any documentation about it. For this condition she had been taking Alendronate (70 mg/week) for about 15 years in association with cholecalciferol (100000 U.I./month) and calcium carbonate (500 mg/die). She reported smoking history (20 pack/years) for about 40 years, she stopped 10 years ago.

During surgery, also in this patient, an intraoperative acetabular fracture occurred with consequent positioning of a Delta TT revision acetabular cup, in order to optimize primary fixation.

One month after surgery, during the patient rehabilitation, for the presence of right groin pain a total femur x ray was carried out.

The X-ray evidenced features of atypical fracture on the lateral cortical of the middle third of the right femur diaphysis; after this finding, an x-ray was taken of the entire left femur which showed the presence of a small lateral cortical thickening immediately close to the femoral stem of the prosthesis.

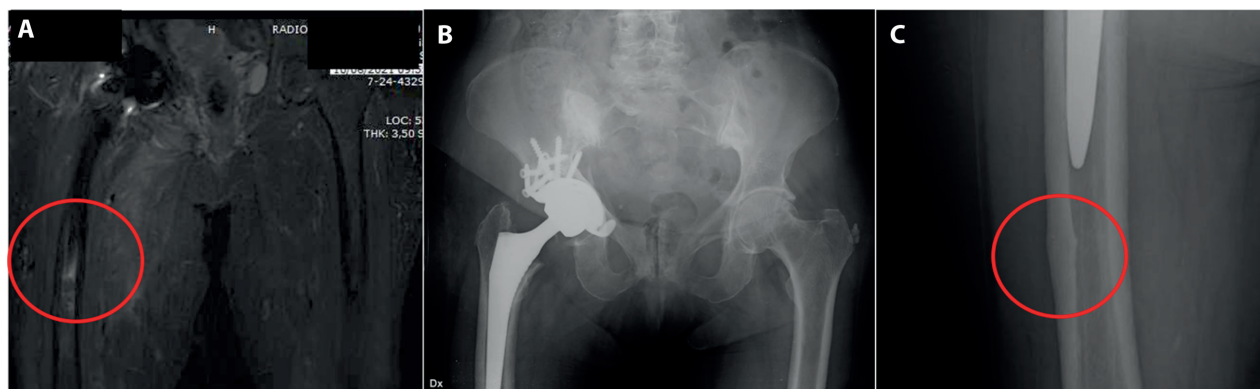


Figure 3. (A) Post operative MRI shows edema only in the right atypical femoral fracture. (B) 6 months x ray shows no signs of implant mobilization (C) after anabolic therapy the thin lateral radiolucency is disappeared.

Osteometabolic status of the patient was studied with:

Dual Energy X-ray Absorptiometry (Dexa):

F.T.: -2.4; F.N.: -2.9; Ward: -4.0; L1-L4: -3.1

Blood exams:

25-OH vit. D3 23.5 mcg/L, Calcium 8.8 mg/dL, PTH 35 ng/dL, ALP 99 U/L.

CTX and P1NP were in the normal range.

PCR 4.25 (NR max 0.50 mg/dL).

Serum protein electrophoresis evidenced substantially all values in the range of normality.

Even if thigh MRI did not show edema of the bone and contiguous soft tissues, due to the presence of pain, only partial weight bearing was allowed.

BFs treatment was immediately stopped, and the patient started anabolic treatment with Teriparatide (20 mcg/day), supplementation with calcium carbonate (500 mg/die) and calcifediol 1,5 mg/10ml (30 drops/week).

Total weight bearing was allowed only two months after the beginning of the anabolic treatment.

In this case the anabolic therapy was scheduled for 24 months, the monitoring of the blood tests did not reveal any alterations, no collateral effects were reported and therefore the patient is still in therapy.

Discussion

BF are commonly used medication in osteoporosis treatment to reduce the risk of fragility fractures.

Their efficacy in increasing BMD (Bone Mineral Density) is confirmed in many studies. Patients treated with BPs are rapidly increasing all around the world; consequentially also the relative number of side effect are increasing but, in many cases, absolute risk of serious adverse effects is less than the important potential for reducing the fracture risk.

Total hip prosthesis is a large used treatment to reduce pain and to improve the quality of life of the patients with hip osteoarthritis; for this reason, patients undergoing to prosthetic treatment are continuously increasing.

BP's effect is also investigated on periprosthetic bone mineral density (BMD) in females with postmenopausal osteoporosis (5).

Alhambra et coll. reported a 59% reduced risk of revision surgery in patients treated with oral bisphosphonate, when bisphosphonates are started after arthroplasty surgery; many reports highlight the positive effect of oral or endovenous BP in periprosthetic bone remodeling, implant survival and functional outcomes.

Since the first description of AFFs a relationship between BPs' use and atypical femoral fractures was supposed.

AFFs are one of the most important collateral effects of a long BPs treatment and it is supposable that more people could suffer from this adverse effect due to the increased prescriptions of these drugs.

Nowadays it is also evaluated a role on the onset of atypical femoral fractures in patient treated with BPs of varus proximal femoral geometry and

other radiographic parameters, such as hip-axis length (HAL) and center-edge angle (CE) (6).

The exact pathogenic mechanism of AFFs is still unclear. Nowadays it is hypothesized that BPs suppress bone turnover and can determinate a microdamage accumulation (7).

Furthermore, BPs can change the normal mechanical properties of bone tissue by different mechanisms.

All these mechanisms together can induce the onset of AFF.

Recently Marozik et coll. studied the potential relationship between genes variation and the different response in patients treated with BPs.

PAFFs were firstly excluded from AFFs definition because the presence of the femoral stem could be considered a known risk for femoral fractures, but recently several cases in Literature report PAFFs in patients undergoing bisphosphonate treatment presenting similar radiological and histological features than AFF (8).

PAFFs incidence is increasing so that they cannot be still considered a rare event (9) and physicians should suspect a PAFF in case of low-energy or atraumatic periprosthetic fracture in bisphosphonate users associated with radiographs features of AFF.

Correct diagnosis of AFFs and PAFFs is also important to undertake a correct treatment to promote bone healing; it is established that AFFs and PAFFs undergone to delayed healing more than femoral fractures non associated with BPs.

Diagnosis of coxarthrosis is mainly based on clinical and radiological evaluation of the hip bone. Preoperative planning is focused to choose the correct implant considering both hip geometry and bone quality.

In most cases femoral shaft segments are not evaluated during pre-operative planning; therefore, BPs' use is not always assessed, and tight pain is often misdiagnosed as arthritic symptom.

Osteometabolic patient's status is not routinely studied before hip replacement, causing sometimes the occurrence of surgical complications, intraoperative or postoperative, due to an impaired bone metabolism (10).

Authors describes two patients who underwent to hip replacement in coxarthrosis. Pre-operative planning was carried out using standard hip and pelvis X ray; no question about use of BPs was carried out.

In both cases AFFs' diagnosis was occasional and happened later than surgical treatment. Femoral stem, in both cases, didn't reach the AFF's site.

Patients stopped BP's use at the time of the diagnosis and began anabolic therapy.

Weight bearing on the lower limb affected by AFFs was proscribed for 2 months because of the presence of pain or edema at the MRI.

In both cases, an intraoperative acetabular fracture occurred; we cannot assert that BPs induced this surgical complication. However, the coexistence of a PAFF's in the same patients, led us to ask if BPs played a role on acetabular bone microarchitecture.

In scientific literature (1,4,7) no correlation is reported between a specific BPs's molecule and the onset of AFF's, now a day, it remains unclear if there is a direct effect of BPs in AFF's occurrence. However, AFF's often affect patients under BPs treatment, especially for long period. In our experience there is not a prevalence of a specific BP and AFF in accordance with literature.

Conclusion

This couple of cases are full of interest because they contribute to lead the attention to the lack of specific guidelines of pre-operative management in patients affected by arthrosis undergoing to hip replacement and in treatment with BPs among scientific literature.

In both these cases, the identification of an incomplete atypical femoral fracture was random and postoperative; however, it was possible to implement a specific non-surgical treatment (BPs suspension and anabolic therapy with suspension from loading for 30 days) and this avoided the evolution into complete fractures.

The use of bisphosphonates is effectual and safe; however, long term BPs may increase the risk of developing AFF in some patients. This does not affect the usefulness of BPs in the prevention of osteoporotic fractures. Long term BPs should be investigated, suspicious cases critically evaluated and, only in these selected cases, BPs stopped before surgery.

List of abbreviations: AFFs: Atypical Femoral Fractures; BPs: Bisphosphonates; PAFFs: Atypical Periprosthetic Femoral Fractures;

BMI: Body Mass Index; GERD: Gastro-Esophageal Reflux Disease; COPD: Chronic Obstructive Pulmonary Disease; MRI: Magnetic Resonance Imaging DEXA: Dual Energy X-ray Absorptiometry; BMD: Bone Mineral Density; HAL: Hip-Axis Length; CE: Center-Edge Angle

Conflict 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

Consent: Written informed consent was obtained from the two patients. With this consent, the patient authorizes the surgical treatment and also the collection and publication of clinical data about his case for scientific and educational purposes even outside the institution.

References

1. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014 Jan;29(1):1–23.
2. Meling T, Nawab A, Harboe K, et al. Atypical femoral fractures in elderly women: a fracture registry-based cohort study. *Bone Joint J* 2014 Aug;96-B(8):1035–1040.
3. Bottai V, De Paola G, Celli F, et al. Histological study of atraumatic periprosthetic fractures: does atypical periprosthetic fracture exist? *Clin Cases Miner Bone Metab* 2017 May-Aug;14(2):136–139.
4. Robinson Jde D, Leighton RK, Trask K, et al. Periprosthetic atypical femoral fractures in patients on long-term bisphosphonates: a multicenter retrospective review. *J Orthop Trauma* 2016 Apr;30(4):170–176.
5. Huang TW, Wang CJ, Shih HN, et al. Bone turnover and periprosthetic bone loss after cementless total hip arthroplasty can be restored by zoledronic acid: a prospective, randomized, open-label, controlled trial. *BMC Musculoskelet Disord* 2017 May 22;18(1):209.
6. Taormina DP, Marcano AI, Karia R, et al. Symptomatic atypical femoral fractures are related to underlying hip geometry. *Bone* 2014 Jun;63:1–6.
7. Hagen JE, Miller AN, Ott SM, et al. Association of atypical femoral fractures with bisphosphonate use by patients with varus hip geometry. *J Bone Joint Surg Am* 2014 Nov 19;96(22):1905–1909.
8. Mondanelli N, Facchini A, Troiano E, et al. Periprosthetic Atypical Femoral Fractures Exist: A Retrospective Study at a Single Institution. Prevalence on 115 Periprosthetic Femoral Fractures Around a Primary Hip Stem. *Arthroplasty* 2021 Jun;36(6):2189–2196.
9. Lee YK, Park CH, Kim KC, et al. Frequency and associated factor of atypical periprosthetic femoral fracture after hip arthroplasty. *Injury* 2018 Dec;49(12):2264–2268.
10. Bottai V, Dell'Osso G, Celli F, et al. Total hip replacement in osteoarthritis: the role of bone metabolism and its complications. *Clin Cases Miner Bone Metab* 2015 Sep-Dec;12(3):247–50.

Correspondence:

Received: 4 April, 2022

Accepted: 12 May, 2022

Damiano Antognetti,

University of Pisa, Orthopedic Rehabilitation Department
Section, Pisa, Toscana, IT

E-mail: damianoantognetti@gmail.com

ORCID: 0000-0002-0438-2494