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Bisphosphonate-induced atypical femoral fracture in tandem: long-term follow-up is warranted

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Summary

Although bisphosphonates (BPs) are mainly used for the treatment of osteoporosis and are generally safe, long-term use and more dosage as utilised in malignant conditions may be associated with the rare adverse event of an atypical femoral fracture (AFF). Occasionally, the risk of developing an AFF persists long after BPs are withdrawn. A 39-year-old woman who underwent chemotherapy and an autologous stem cell transplantation for multiple myeloma presented to us with history of pain in the left thigh. She had received multiple doses of oral and parenteral BPs for about 10 years in view of the underlying myeloma with osteoporosis. Her investigations showed a suppressed CTX of 192 pg/mL, and radiograph of pelvis displayed thickened cortices with beaking of the left femoral shaft, which was suggestive of an AFF. Following discontinuation of BPs, she underwent prophylactic intra-medullary nailing with which her symptoms improved. Five years later, she presented with similar complaints on the right side. Investigations showed that her bone turnover continued to be suppressed with Cross linked C- Telopeptide of type 1 collagen (CTX) of 165 pg/mL and an X-ray done showed AFF on the right side despite being off BPs. A second intra-medullary nailing was done and on follow-up, she has been symptom-free and independent in her daily activities. Discontinuation of BPs may not prevent the incident second AFF and, therefore, thus warranting long-term follow-up.

Learning points:

- Regular screening and follow-up of patients who receive long-term bisphosphonate (BP) therapy should be done.
- Discontinuation of BPs does not preclude the possibility of repeated occurrence of a second AFF.
- Long-term BP therapy warrants regular monitoring and follow-up should an AFF occur

Background

Osteoporosis is a progressive systemic skeletal disorder characterised by a decrease in bone mass and microarchitectural deterioration of bone tissue leading to bone fragility and increased susceptibility to hip, spine and wrist fractures (1). The efficacy of bisphosphonates (BPs) has long been established to reduce the risk of occurrence of hip and vertebral fractures in patients with osteoporosis, as well as in the management of metabolic bone disease such as osteogenesis imperfecta and Paget's disease (2). Although BPs are effective in risk reduction of osteoporotic fractures, their long-term use of is associated with rare but serious adverse events such as osteonecrosis of the jaw and atypical femoral fractures (AFFs). An AFF is a spontaneous or low-trauma, subtrochanteric or femur shaft fracture often complicated by delayed or non-union and bilateral occurrence. AFFs have been reported in patients on BPs and

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in patients on denosumab, but they also occur in patients with no exposure to these drugs (3). We describe the case of a 39-year-old woman who developed AFF on the left side which led to discontinuation of BP treatment after which she sustained a similar fracture on the right side while not on BPs for 5 years.

Case presentation

A 39-year-old woman was diagnosed with multiple myeloma for which she had received three cycles of cyclophosphamide, vincristine, adriamycin and dexamethasone regime-based chemotherapy in 2002. Subsequently, she underwent an autologous bone marrow transplant a year later for persistent disease. She had history of multiple spontaneous rib fractures in 2003 along with flail chest which required hospitalisation during which time she was initiated on parenteral pamidronate 60 mg once a month for 18 months. Her biochemical parameters during that time showed a baseline calcium of 9.3 mg/dL (N: 8.3–10.4), phosphorus of 5.2 mg/dL (N: 2.5–4.5), albumin of 4.8 g/dL (3.5–5.0), alkaline phosphatase of 48 U/L (N: 40–125) and creatinine of 1.1 mg/dL (N: 0.5–1.2).

Subsequently, she remained asymptomatic and was on regular follow-up till 2009 when she presented with low back ache and was found to have multiple osteoporotic fractures involving the lumbar spine (Fig. 1). She was started on alendronate 70 mg once a week, along with calcium and vitamin D supplementation. She was also initiated on hormone replacement therapy in 2009 for premature ovarian failure which she discontinued after 2 years. She was on regular follow-up till 2012 after which she was lost to follow-up. In 2016, she presented with history of insidious onset of pain in her left mid-thigh for the preceding 6 months. There was no prior history of trauma, fever or other joints involvement. On examination, she had an antalgic gait and tenderness over the left thigh. Evaluation at that point showed left-sided cortical thickening and beaking of the left femur (Fig. 2A). Her clinical and radiological features were suggestive of a BP-induced atypical femur fracture. She was advised rest and limitation of weight-bearing. BPs were stopped and she was subjected to prophylactic nailing of the left femur following which there was significant improvement in her symptoms; imaging of the right femur was shown to be normal during this time (Fig. 2B). She was kept on periodic follow-up with supplemental calcium 1000 mg per day and 60,000 units of cholecalciferol once a month with close monitoring of bone biochemistry and serial femoral

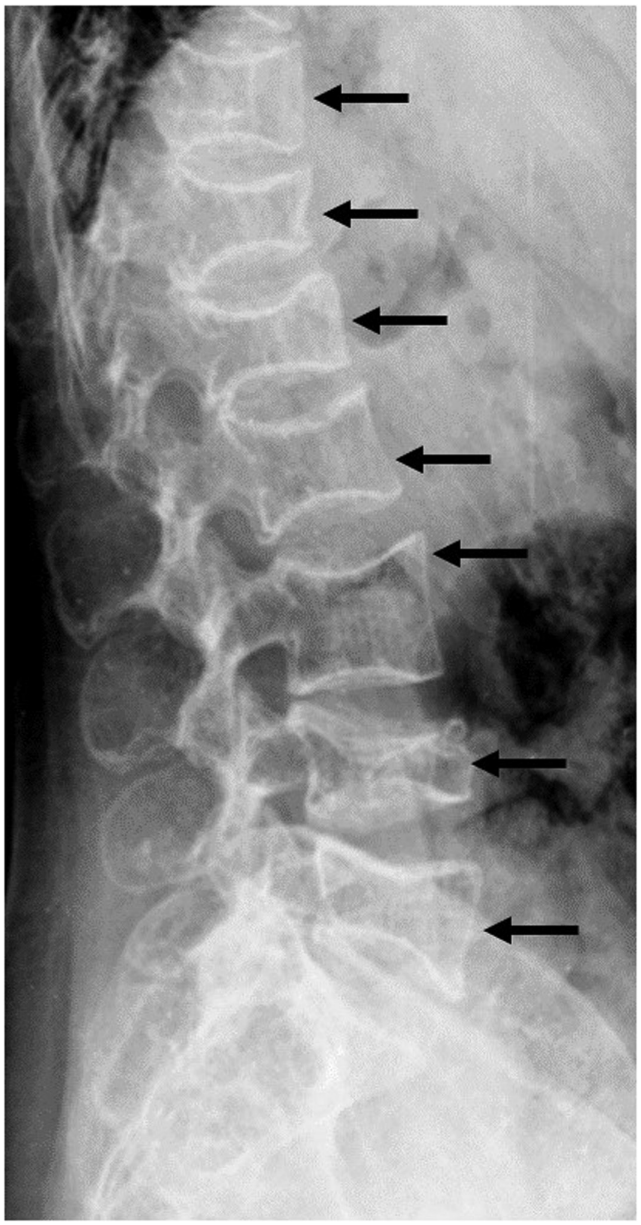

Figure 1
X-ray of spine showing multiple vertebral fractures.

X-rays and she remained off BPs for 5 years. In 2021, she presented with similar complaints of dull aching pain involving her right outer mid-thigh for 1 month which was aggravated by activity. On examination, there was tenderness along the anterolateral border of the thigh in the proximal 1/3rd region. X-ray of the right femur showed beaking of the femoral shaft which was suggestive of AFF (Fig. 3A). A second prophylactic intra-medullary nailing was done during this time (Fig. 3B). Her biochemical investigations and bone mineral density (BMD) are summarised in Table 1.

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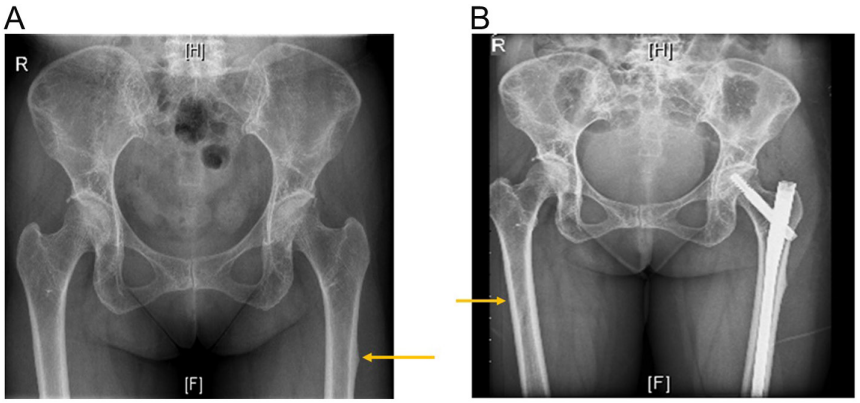

Figure 2
(A) Radiology of pelvis displaying cortical thickening and beaking of left femur. (B) Radiology of pelvis showing right femur without fracture.

Treatment

In addition to surgical intervention for atypical fracture, she was continued on calcium and cholecalciferol supplementation.

Outcome and follow-up

There has been a significant improvement in the quality of her life; she is ambulant and independent in her activities of daily living during her recent visit in 2022.

Discussion

In this report, we summarise the case of a woman who developed AFF on both sides, in tandem, the second fracture occurring 5 years after the discontinuation of BPs. Osteoporosis is a silent disease until fractures occur, and this leads to heightened societal costs with increased morbidity and mortality (4). BPs are the agents of choice in the treatment of osteoporosis and function by binding to the inorganic components of bone, namely hydroxyapatite, and subsequently targeting osteoclasts by altering their ability to resorb and remodel bone. The two types of BPs available are the nitrogenated and non-nitrogenated forms. Non-nitrogenated BPs include clodronate, etidronate and tiludronate. The nitrogenated forms include alendronate, ibandronate, risedronate, pamidronate and zoledronate. The nitrogenated BPs, in addition, inhibit farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway responsible for the synthesis of cholesterol and other sterols. This interferes with the isoprenylation of GTP-binding proteins, such as Rho, Rab and Rac, which play key roles in osteoclastic cellular activity, eventually leading to osteoclast apoptosis (5).

Currently available guidelines recommend BPs for any adult who has been identified as being high risk for osteoporotic fragility fracture as per standard risk assessment tools. Recognised side effects of BP use include gastrointestinal (GI) irritation, musculoskeletal pain, osteonecrosis of the jaw, and more recently recognised, AFFs. Oral preparations are now able to be given once weekly making the GI side effects much more tolerable. Parenteral preparations, such as pamidronate and zoledronic acid, require even less frequent dosing and do not cause the same GI side effects although flu-like symptoms have been reported (6).

It may be possible that over a long period, BPs accumulate in bone and this may lead to excessive

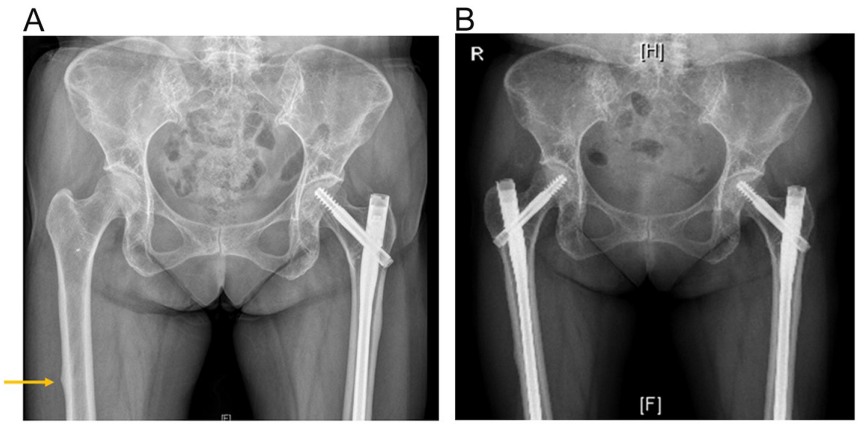

Figure 3
(A) X-ray of right femur with beaking with intra-medullary nailing *in situ* in left femur. (B) Radiology of pelvis after intra-medullary nailing of right femur.

Table 1 Bone biochemistry and BMD at presentation and during follow-up.

Investigations (reference range, units)	**2009**	**2016**	**2018**	**2020**	**2021**
Calcum (8.3–10.4 mg/dL)	9.5	9.6	9.7	10.2	9.3
Phosphorus (2.5–4.5 mg/dL)	4.5	2.8	3.1	4.5	2.7
Albumin (3.5–5.0 g/dL)	5.2	4.8	4.4	4.8	4.6
Alkaline phosphatase (40–125 U/L)	42	39	38	30	36
25 OH Vitamin D (30–75 ng/mL)	27.1	27.9	31.3	32.2	37.4
Parathyroid hormone (11–72 pg/mL)	58	–	64	–	67
Creatinine (0.5–1.2 mg/dL)	0.8	0.7	0.9	0.8	0.8
CTX (220–1088 pg/mL)	–	192	174	165	424
P1NP (16–73.9 ng/mL)	–	12	16	19	42
BMD lumbar spine (g/cm^2) (Z-score)	0.750 (–2.7)	0.790 (–2.2)	0.814 (–2.0)	0.863 (–1.2)	0.867 (–1.1)
BMD femoral neck (g/cm^2) (Z-score)	0.459 (–3.4)	0.469 (–3.2)	–	–	–

suppression of bone turnover resulting in a decrease in new bone formation and remodelling. This dense, brittle, hypermineralised bone may have micro-cracks within it and be of poor quality, making it more susceptible to fracture. The first report of an AFF was given in 2005 by Odvina *et al.* (7).

AFF is a type of stress fracture and is due to an abnormal load in a normal bone, while an insufficiency fracture occurs due to normal loading forces in an abnormal bone. AFFs are more common in the lower limbs because of the increased load and the geometry of the proximal femur, correlating with the deviation between the anatomical axis and the mechanical axis, producing a lateral transverse rupture, characteristic of a brittle material (8).

In 2013, the American Society for Bone and Mineral Research published the criteria for the diagnosis of AFFs of which four major features are required, and this may or may not be accompanied by minor features (3).

Major features: (all must be met):

1. Fracture line located anywhere between the distal border of the lesser trochanter of the femur to the proximal edge of the supracondylar flare
2. Lateral cortex must be involved (incomplete or complete – normally with medial cortical spike)
3. Transverse or short oblique fracture line with no comminution
4. No or minimal precipitating trauma

Minor features:

1. Localised periosteal reaction at lateral cortex – beaking, flaring
2. Generalised, diaphyseal cortical thickening
3. Prodromal groin/thigh pain
4. Bilateral fracture and symptoms
5. Delayed healing
6. Co-morbidities (rheumatoid arthritis, vitamin and mineral deficiencies)
7. Concomitant use of pharmacological agents (BPs, corticosteroids, proton pump inhibitors)

Neck of femur fractures, fractures relating to primary or secondary bone tumours and peri-prosthetic fractures are not included under AFF.

The pathophysiology of AFF involves a reduced bone remodelling leading to an inability to repair accumulated microdamage that occurs secondary to physiological stress. There is also excessive mineralisation of the bone that makes it more susceptible to fractures as a result of its brittle properties (9, 10). More recently, genetic mutations have been found to influence susceptibility to AFFs following BP therapy, most notably GGPS1 (11).

The overall incidence could be estimated at 7.8/100 000 person-years for patients over 60 years of age. A recent study has shown that this incidence increases with the time of exposure to the drug, from 2/100 000 cases/year for every 2 years of use of BPs to 78 per 100 000 cases/year for every 8 years of use of these drugs (12). The usual treatment is discontinuation of the antiresorptive agent, prophylactic intra-medullary nailing and initiation of teriparatide if not contraindicated (13, 14). In a case control study by Edwards *et al.*, out of 10 587 subjects with malignancy (breast cancer, multiple myeloma, leukaemia, lymphoma), 23 sustained atypical fracture with an estimated incidence of 0.05 per 100 000 person-years. The odds of sustaining an AFF was higher in subjects on alendronate for more than 3 years as compared to those who had received alendronate < 3 years (OR: 6.3 95% CI: 1.5–26.7; $P = 0.01$) (15).

The clinical case described earlier demonstrates the association between the prolonged use of BPs and the occurrence of atypical fracture of the femur. She received multiple doses of oral and parenteral BPs in view of her underlying multiple myeloma with osteoporosis. In the early years of administration of BPs, bone turnover markers

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were not available at the authors' centre. Serum alkaline phosphatase was probably not a reliable marker of bone as it is reported to be normal in multiple myeloma. Following the first AFF, BPs were discontinued. Nevertheless, she developed a similar AFF on the opposite site despite having been off BPs for a minimum of 5 years. This case highlights the importance of regular screening and follow-up of patients who receive long-term BP therapy. It is also interesting to note that discontinuation of BPs does not preclude the possibility of repeated occurrence of a second AFF. Thus, long-term BP therapy warrants regular monitoring and follow-up should an AFF occur.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of her clinical details and clinical images was obtained from the patient.

Author contribution statement
All authors took care of the patient at one point during the patient's hospitalisation, and all authors contributed to the editing of the manuscript.

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