CASE REPORT

The first reported case of Atypical Femoral Fracture caused by daily ibandronate prescribed for bone metastases in breast cancer

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SUMMARY

A 55-year-old woman with bony metastatic breast cancer was commenced on daily ibandronic acid to prevent skeletal related events (SREs). Four years later, she began to experience new lower limb and groin pain with investigations leading to the suspicion of further metastatic spread to her left femur. While awaiting radiotherapy for this, she unfortunately tripped and fell sustaining a fracture to the proximal third of her left femur. Radiographic findings of her femur from both before and after the fall were suggestive of an atypical femoral fracture, presumed secondary to her bisphosphonate therapy rather than metastatic spread.

12 years later, following a short history of hip and lower back pain, she was diagnosed with bony metastatic spread. She was commenced on hormone suppressing therapy along with daily ibandronic acid to prevent skeletal related events (SREs). Four years later, she began to experience new lower limb and groin pain and investigations, including plain film radiography and an isotope bone scan, led to the suspicion of further metastatic spread to her left femur.

Plain film radiographs of her left leg (figure 1) ruled out any destructive bone lesions but did demonstrate some non-specific irregularity of the lateral cortex of her proximal femoral shaft. A

BACKGROUND

This case highlights that any oncology patients on bisphosphonate (BP) therapy who present with hip, groin or thigh pain need to be investigated to exclude both bony metastases and atypical femoral fracture.

Atypical femoral fracture (AFF) is a recognised complication of BP therapy when used in the prevention and treatment of osteoporosis. Although rare, the incidence increases with prolonged duration of therapy.

More recently, cases of AFFs have been presented in patients receiving intravenous BPs for the treatment of bone metastatic breast cancer (BMBC) and multiple myeloma.¹⁻³ This case presents an incidence of AFF occurring on oral BP prescribed for BMBC.

This is important because the overall survival of patients with breast cancer is increasing, and the incidence of metastatic bone lesions and associated SREs is relatively high. Therefore, the use of BP therapy is expected to rise and duration of use is also expected to increase. Oral dosing is also much higher in oncological cases for example, ibandronic acid 50mg per day compared with 150mg once in a month in the prescribing for osteoporosis, so AFF may become increasingly prevalent in these patients. Overall, increased awareness regarding AFF is important for all clinicians.

CASE PRESENTATION

A 55-year-old woman with a past medical history of breast cancer, diagnosed in 1998, was treated with neoadjuvant chemotherapy, left mastectomy and postoperative chemoradiotherapy. Unfortunately

Figure 1 Plain film radiograph taken in the weeks prior to patient's fall to investigate her left sided groin pain. Radiological reporting included the following comments: 'There is some irregularity of the lateral cortex of the mid femoral shaft, the appearances are non-specific'. 'Two discrete areas of the cortical bulging at the external aspect of the proximal femoral shaft were noted.'

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Figure 2 Nuclear medicine bone whole body. Reported as: 'Thoracic cage uptake reduced and new focal uptake left femur suspicious for new metastasis. No other new significant abnormalities seen.'

nuclear medicine bone scan (figure 2) demonstrated focal uptake within the proximal left femur, and with corresponding subtle sclerosis on the plain radiograph, was felt to be suspicious for new metastasis.

As treatment, she was scheduled to have radiotherapy to the lesion, however, while awaiting this, she tripped and fell sustaining a fracture to the proximal third of her left femur. Radiographic findings of her femur from both before and after the fall (figure 3) suggested a diagnosis of an atypical femoral fracture, presumed secondary to her bisphosphonate therapy rather than metastatic spread. She was admitted to the Royal Victoria Hospital in Belfast and underwent intramedullary nailing (figure 4). Of note, the patient's biochemical bone profile along with renal function were all within normal limits at time of admission.

DISCUSSION

Bisphosphonates (BPs) have been used for many years for the prevention and management of postmenopausal and

Figure 3 Plain film radiograph (X-ray) of left hip demonstrating a non-committed transverse fracture of proximal diaphysis with medial spike.

corticosteroid-induced osteoporosis. More recently oncologists have been using them in the treatment of BMBC and although, it does not appear to influence overall survival, it has been shown to effectively reduce the associated risk of SREs.^{4 5} Median survival durations of breast cancer are also increasing and with this, we are entering a new era, experiencing side effects to treatments which would not previously have presented due to the natural progression of disease.

BPs work by inhibiting bone remodelling through their action on osteoclasts. Evidence suggests that AFFs are stress

Figure 4 Plain film radiograph of left hip and femur demonstrating intramedullary nail fixation. Note: two discrete areas of the cortical bulging at the external aspect of the proximal femoral shaft were noted (arrowed) in figure 1.

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.

In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.

Major features^a

The fracture is associated with minimal or no trauma, as in a fall from a standing height or less

The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur

Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

The fracture is noncomminuted or minimally comminuted

Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")

Minor features

Generalized increase in cortical thickness of the **femoral diaphyses**

Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh

Bilateral incomplete or complete femoral diaphysis fractures

Delayed **fracture** healing

Changes are in bold.

ASBMR = American Society for Bone and Mineral Research; AFF = atypical femur fracture.

^a**Excludes** fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia).

Figure 5 ASBMR task force 2013 revised case definition of AFFs. Changes are in bold. ASBMR, American Society for Bone and Mineral Research; Aff, atypical femur fracture. ^aExcludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia).

fractures.⁶ Repetitive loading on bone can lead to micro cracks and eventually stress-type fractures, and when suppression of the normal bone remodelling mechanism occurs through the use of BPs, natural repair of such areas is significantly reduced. Localised periosteal thickening ('beaking') which is seen in the images above (figure 1) represents the cortical hypertrophy of remodelling in the micro-damaged areas. These micro cracks coalesce and become critical-sized defects leading to incomplete then complete AFFs.

AFFs are so called because they display distinct radiological features compared with typical osteoporotic femur fractures. Specific criteria for definition were published by the American Society of Bone and Mineral Research (ASBMR) in 2010 and revised in 2013 (figure 5).^{6,7}

AFFs are frequently associated with prodromal pain in the thigh, hip or groin pain before suffering an overt break. Therefore, any patient on BP therapy experiencing these symptoms, an AFF must be ruled out; initially by X-ray, but should this be negative and clinical suspicion remains high, abone scan/femur MRI should be arranged. These may reveal the 'beaking' which suggests a fracture could be imminent. AFFs can be bilateral, therefore, the contralateral side should also be imaged. In our example, the patient satisfied ASBMR's case definition of AFF by exhibiting all five of the major features and two out of four minor features (increase in cortical thickness of the femoral diaphysis and prodromal pain).

Prophylactic nail fixation is recommended for incomplete fractures accompanied by pain.^{8,9} For those with minimal pain, a trial of limited weight bearing can be considered, however, if there is no symptomatic and radiographic improvement after 2–3 months of this conservative therapy, prophylactic nail fixation should be strongly considered with the high risk of progression to complete fracture.⁷

Usual practice is that once an AFF has been diagnosed, treatment with BP is stopped with referral to a local expert. The risk of AFF may decline but data is limited.⁶ It is worth noting that although most cases of AFF are associated with BP use they also occur in patients who have never been treated with BPs. They are also associated with medications such as the RANKL inhibitor denosumab, proton pump inhibitors and glucocorticoids and conditions including rheumatoid arthritis.

Given concerns about an increasing risk of atypical femur fractures with long-term BP treatment when prescribed for osteoporosis, the need to continue treatment should be re-evaluated periodically, assessing the benefits and risks of treatment individually, particularly after 5 or more years of use.¹⁰

If AFF in oncology patients is increasingly recognised, the same principles may need to be applied.

Learning points

- ▶ Atypical femoral fracture (AFF) is rare but significant complication of bisphosphonate (BP) therapy and the incidence increases with duration of the therapy.
- ▶ All oncology patients on BP should be asked regarding thigh, hip or groin pain and if present radiological imaging sought not only to exclude bony metastases but also to look for the distinctive features of AFF. If present ensure prompt referral to orthopaedics.
- ▶ Higher BP doses are used in bone metastases cases and with increasing breast cancer survival it is likely we may start to see increased incidence of AFF in oncology patients.

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