

Case Series

Atypical fractures secondary to bisphosphonate therapy: A case series and pictorial review

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ABSTRACT

Osteoporosis is a ubiquitous and chronic process that affects an increasing number of people each year. Various forms of treatment are currently used including bisphosphonates which have been linked to atypical fractures of the femur. We present a case series of eight osteoporosis patients who developed atypical femoral fractures, while on bisphosphonate therapy. This pictorial review aims to increase awareness of bisphosphonate-related atypical fractures, discuss the current literature recommendations, and provide clear learning points from each case-based discussion.

Keywords: Atypical, Fracture, Bisphosphonates, Osteoporosis, Imaging

INTRODUCTION

The World Health Organization defines osteoporosis as a bone mineral density (BMD) of more than 2.5 standard deviations below the mean.^[1] It is a clinically heterogeneous disease of compromised bone strength with advancing age and estrogen deficiency predominating as the most common etiopathological factors. The National Institute for Health and Care Excellence guidelines recommend bisphosphonates as a first-line therapy to hamper the rate of BMD loss.

Bisphosphonates are bone-sparing agents through the suppression of osteoclastic bone activity which results in lower resorption rate and decreased bone turnover. The longstanding administration of bisphosphonates has been linked to atypical fractures, primarily of the proximal femur. However, it remains a controversial topic due to the lack of scientifically proven direct causative connection. In addition to bisphosphonates, other medications are often used to treat osteoporosis. Among these is denosumab, a monoclonal antibody that blocks osteoclast formation and therefore reduces bone resorption.^[2] Despite a more specific and targeted effect, denosumab confers a similar risk of atypical fractures to bisphosphonates. Nevertheless, denosumab therapy is likely to prevent many more fractures that it can potentially cause.^[3] The absolute risk of bisphosphonate-associated atypical fractures is low, compared to the number of fractures prevented.^[4]

This imaging-focused review demonstrates through a series of cases, the various radiological features of bisphosphonate-related atypical fractures.

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CASE REPORTS

Case 1

A 75-year-old female presented with left hip pain. A pelvic radiograph [Figure 1a] showed thickening of the subtrochanteric lateral cortex of the left femur and a subsequent magnetic resonance (MR) study confirmed a cortical fracture with an associated bone marrow edema [Figure 1b and c]. Retrospective review of a radiograph [Figure 1d and e] acquired the prior year to investigate for the left hip pain, revealed very subtle cortical beaking at the site in question. This initial radiograph [Figure 1d and e] was reported as normal, as the significance of the finding was poorly understood by the general reporting radiologist.

The imaging requests contained no history of treatment with bisphosphonates. When this history was specifically sought, it was found that the patient had been on bisphosphonates for 5 years before presentation. This case was discussed

with the orthogeriatricians and orthopedic surgeons, as no official guidelines on the management of bisphosphate-related atypical fractures were available at the time. The multidisciplinary team discussion recommended prophylactic intramedullary nailing [Figure 1f]. The radiograph [Figure 1f], taken post-internal fixation, demonstrates the further extension of a clear fracture line.

Case 2

An 82-year-old female presented with right hip pain following a fall. The pelvic radiograph [Figure 2a and b] demonstrated lateral cortical beaking in the proximal right femur with evidence of progression from the previous radiograph [Figure 2c] dated 4 years prior. A bisphosphonate-related fracture was queried by the reporting radiologist.

The progressive beaking of the lateral femoral cortex was further assessed with a subsequent pelvic MR study [Figure 2d and e], confirming a cortical fracture. However,



Figure 1: (a) A 75-year-old female presented with the left hip pain. A pelvic radiograph showed thickening of the subtrochanteric lateral cortex of the left femur (solid white arrow). (b) MR coronal T1W sequence demonstrated cortical thickening along the proximal subtrochanteric left femur (solid white arrow) with the hypointensity of underlying bone marrow edema (empty white arrows). (c) MR coronal STIR sequence demonstrated evidence of bone marrow edema in the proximal left femur (empty white arrows). (d) A pelvic radiograph acquired for the left hip pain a year earlier, demonstrated subtle lateral cortical thickening (solid white arrow) in the subtrochanteric left femur. (e) Magnified image of Figure 1d demonstrated the subtle cortical thickening (solid white arrow). (f) Post-fixation radiograph of the left femur demonstrated progression of the fracture line (solid white arrow). MR: Magnetic resonance, STIR: Short-tau inversion signal.

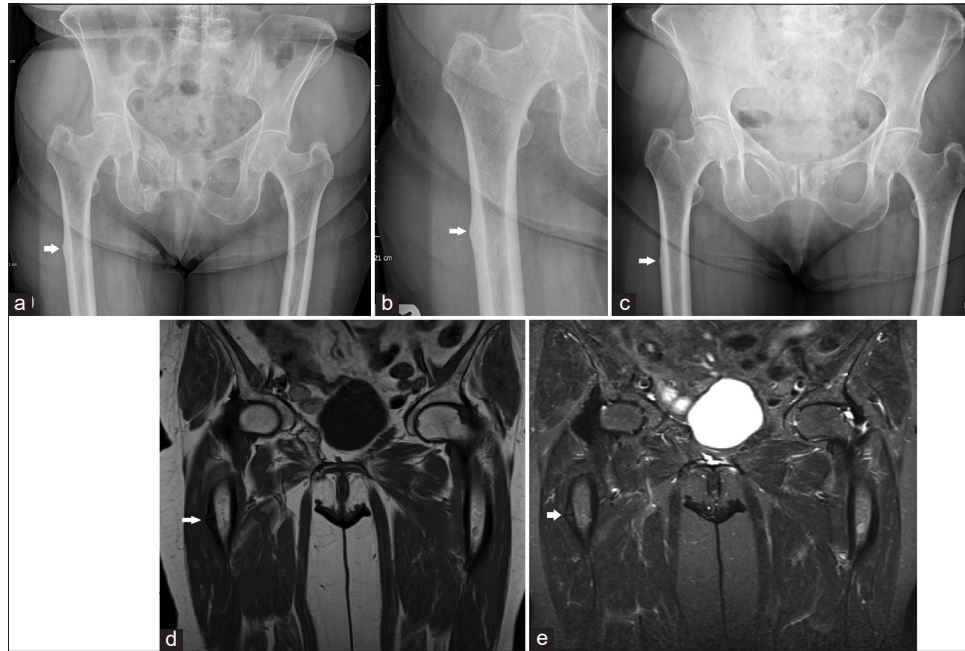


Figure 2: (a) An 82-year-old female presented with post-traumatic right hip pain. The pelvic radiograph demonstrated lateral cortical beaking in the proximal right femur (solid white arrow). (b) Magnified image of Figure 2a, the lateral cortical beaking can be seen (solid white arrow). (c) A pelvic radiograph acquired 4 years earlier, demonstrated subtle lateral cortical beaking in the proximal right femur (solid white arrow). (d) MR coronal T1W sequence demonstrated cortical thickening along the proximal right femur (solid white arrow). (e) MR coronal STIR sequence demonstrated the cortical beaking is solid white arrow with no evidence of bone marrow edema in the proximal right femur. MR: Magnetic resonance, STIR: Short-tau inversion signal.

in this case, there was no evidence of bone marrow edema, indicating stability.^[5,6]

Review of the initial pelvic radiograph [Figure 2c] showed that it was requested to investigate traumatic right hip pain. The pelvic radiograph demonstrated fractures of the right superior and inferior pubic rami and subtle lateral cortical beaking of the right proximal femur. However, due to the presence of acute fractures and the omission of the relevant 4-year history of bisphosphonate therapy from the clinical details, the femoral lateral cortical changes were not reported.

Following the radiological confirmation of the atypical fracture, the bisphosphonates were immediately halted. A follow-up pelvic radiograph a year later showed that the cortical beaking did not progress.

Case 3

A 67-year-old female presented with an episode of right hip pain. The pelvic radiograph [Figure 3a] reported thickening of the lateral cortex of the right proximal femur. This lateral cortical thickening was relatively unchanged from the previous study performed 4 years earlier, for atraumatic left-sided hip pain [Figure 3b]. The possibility of

a bisphosphonate-related atypical fracture was raised by the reporting radiologist. A discussion with the clinical team revealed a 20-year history of bisphosphonate therapy.

A MR study showed subtle periosteal thickening along the lateral aspect of the proximal third of the right femur with no associated bone marrow edema, indicating stability [Figure 3c and d]. The bisphosphonate therapy was stopped and the patient has had no symptoms since.

Case 4

A 52-year-old female presented with right-sided hip pain. The radiograph of the right femur [Figure 4a] revealed a displaced, laterally angulated transverse fracture of the subtrochanteric region.

A pelvic radiograph [Figure 4b] performed following a fall 4 months previously, was reported to be normal. However, a retrospective review of this initial pelvic study identified subtle cortical thickening along the lateral aspect of the right subtrochanteric femur, partially obscured by the radiographic label.

The absence of bisphosphonate use from the requests was highlighted by the reporting musculoskeletal radiologist. A 7-year history of bisphosphonate therapy was identified.



Figure 3: (a) A 67-year-old female presented with an episode of the right hip pain. A pelvic radiograph demonstrated thickening of the lateral cortex of the right proximal femur (solid white arrow). Left femoral fixation also noted. (b) A radiograph of the pelvis acquired 4 years earlier for atraumatic left-sided hip pain, demonstrated subtle thickening of the lateral cortex of the proximal right femur (solid white arrow). The left femoral fixation was also noted. (c) MR coronal T1W sequence in the MR study demonstrated cortical thickening along the proximal right femur (solid white arrow). Metal artifact secondary to the left femoral fixation was noted. (d) MR coronal STIR sequence in the MR study demonstrated the cortical beaking in the proximal right femur (solid white arrow). However, there is no evidence of bone marrow edema. The metal artifact secondary to the left femoral fixation was also noted. MR: Magnetic resonance, STIR: Short-tau inversion signal.

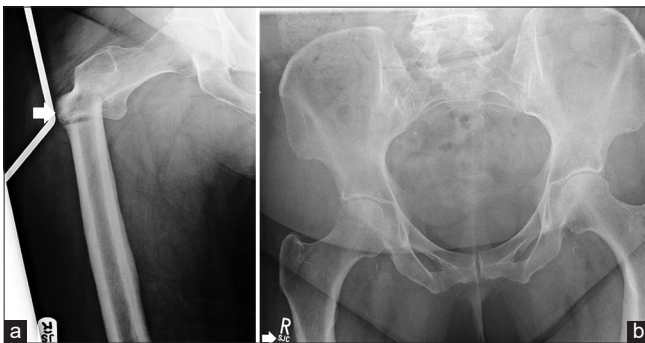


Figure 4: (a) A 52-year-old female presented with right-sided hip pain. The radiograph of the right femur demonstrated a displaced, angulated transverse fracture of the subtrochanteric region (solid white arrow). (b) A pelvic radiograph preformed 4 months earlier, demonstrated subtle lateral subtrochanteric cortical thickening of the right femur, partially obscured by the radiographic label (solid white arrow).

The fracture was managed with intramedullary nailing and the bisphosphonate therapy was stopped by the clinical team.

Case 5

A 77-year-old female presented with persistent bilateral hip pain with a provided clinical history of 20 years of alendronic acid use.

The pelvic radiograph [Figure 5a] demonstrated insufficiency fractures of the pubic rami. Based on the provided medication history, further radiographs of both femora [Figure 5b and c] were also acquired, demonstrating subtle lateral cortical thickening along the mid-shaft of both femurs.

As the patient was symptomatic, a MR study was performed. The bilateral lateral cortical thickening was again visualized [Figure 5d and e]. However, there was no significant bone marrow edema. The bisphosphonate therapy was stopped, and a repeat radiograph a year later showed no progression.

Case 6

A 58-year-old female had a bone scan with single-photon emission computer tomography to evaluate for the presence of possible metastatic deposits. In addition to an avid uptake in the humerus, there was also an avid focal uptake along the proximal right femur [Figure 6a]. A plain film study was advised in the first instance, as the differentials remain wide to include malignancy, trauma, and osteoid osteoma.

The 5-year history of bisphosphonate therapy and the possibility of a bisphosphonate-related fracture were raised by the clinical team at the time of the imaging request.

The plain film of the right hip and femur [Figure 6b] revealed lateral cortical beaking along the mid-shaft of the right femur which was determined to be in keeping with a bisphosphonate-related atypical fracture. Consequently, bisphosphonate therapy was stopped.

Case 7

A 75-year-old female presented with right hip pain following a fall. The pelvic radiograph [Figure 7a] demonstrated a displaced and laterally angulated, transverse fracture through the proximal shaft of the right femur.

Retrospective review of a pelvic radiographic study [Figure 7b] conducted 5 years previously showed subtle thickening of the lateral subtrochanteric cortex of the right femur. However, due to the absence of bisphosphonate intake in the clinical details, no positive findings were reported on this radiograph.

Liaising with the clinical team revealed an 11-year history of bisphosphonate therapy, which was subsequently stopped. The fracture was treated with intramedullary nail fixation.

Case 8

A 70-year-old female with a background of rheumatoid arthritis presented following a fall complaining of the left

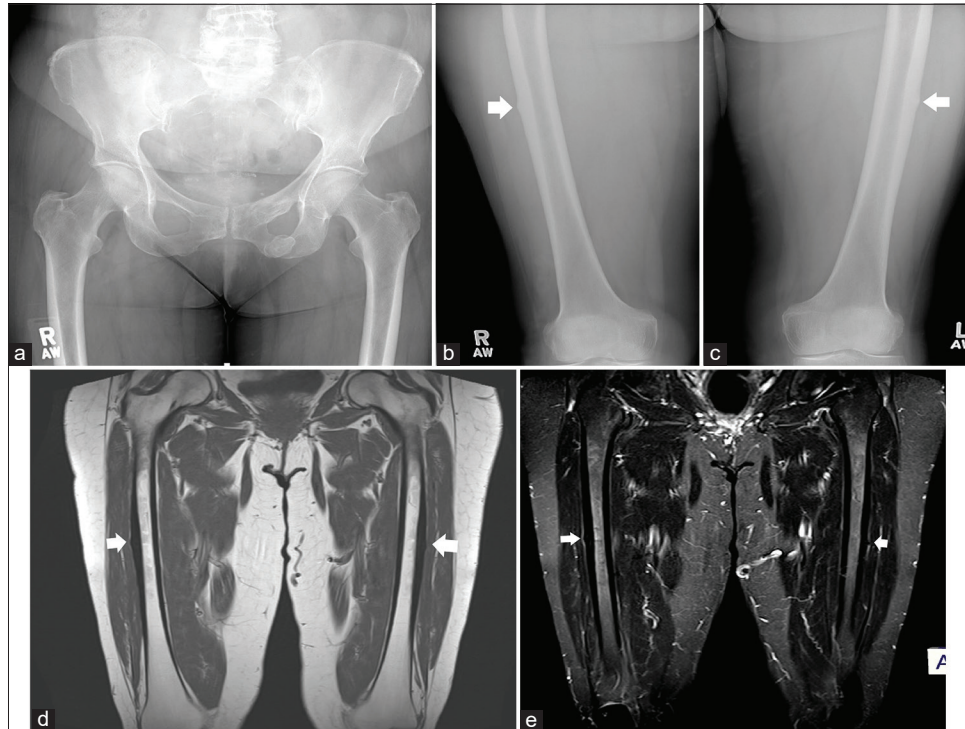


Figure 5: (a) A 77-year-old female presented with persistent bilateral hip pain. The pelvic radiograph demonstrated insufficiency fractures of the pubic rami. (b) Radiograph of the right femur demonstrated lateral cortical thickening along the mid-shaft of right femur (solid white arrow). (c) Radiograph of the left femur demonstrated lateral cortical thickening along the mid-shaft of left femur (solid white arrow). (d) MR coronal T1W sequence in the MR study demonstrated lateral cortical thickening (solid white arrows) along the mid-shaft of bilateral femora. (e) MR coronal STIR sequence in the MR study demonstrated no evidence of bone marrow edema. However, the bilateral cortical beaking is again noted (solid white arrow). MR: Magnetic resonance, STIR: Short-tau inversion signal.

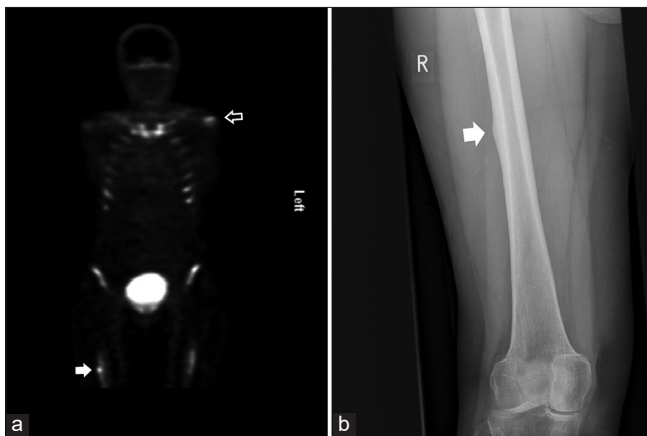


Figure 6: (a) A 58-year-old female had a bone scan with SPECT demonstrated avid uptake in the humerus consistent with known lytic lesion (empty white arrow) and avid focal uptake along the proximal right femur (solid white arrow). (b) Radiograph of the right femur demonstrates lateral cortical beaking along the mid-shaft of the right femur (solid white arrow). SPECT: Single-photon emission computer tomography.

hip pain. A pelvic radiograph demonstrated a displaced and angulated transverse fracture of the proximal left femur [Figure 8a].

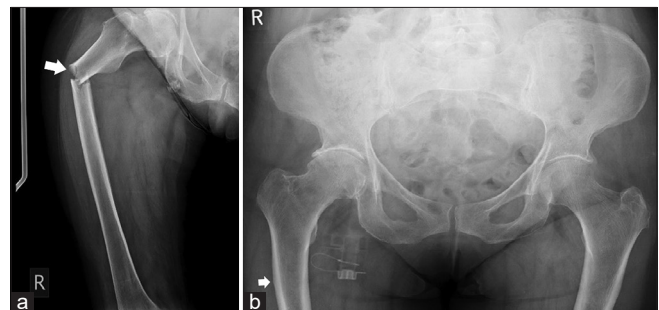


Figure 7: (a) A 75-year-old female presented with traumatic right hip pain. The pelvic radiograph demonstrated a displaced and laterally angulated, transverse fracture through the proximal shaft of the right femur (solid white arrow). (b) Pelvic radiographic study conducted 5 years earlier, showed subtle thickening of the lateral subtrochanteric cortex of the right femur (solid white arrow).

A week before the fall, the patient had a MR study to investigate ongoing left trochanteric tenderness. This MR study [Figure 8b and c] demonstrated left hip joint effusion, focal high Short Tau Inversion Recovery (STIR) at the edge of the scan, within the proximal left femur. These findings were presumed to be due to metal artifact. The reporting radiologist recommended further evaluation with a radiograph [Figure 8d], which revealed a linear fracture line



Figure 8: (a) A 70-year-old female with a background of rheumatoid arthritis presented with traumatic left hip pain. A pelvic radiograph demonstrated a displaced and angulated transverse fracture of the proximal left femur (solid white arrow). (b) MR coronal T1W sequence in the MR study acquired a week earlier, demonstrated cortical thickening along the proximal left femur (solid white arrow). (c) MR coronal STIR sequence in the MR study acquired a week earlier, demonstrated bone marrow edema in the proximal left femur (solid white arrow). In addition, the left hip joint effusion is also seen. (d) Radiograph of the proximal left femur acquired a week prior, demonstrated a linear fracture line and lateral cortical thickening (solid white arrow). MR: Magnetic resonance, STIR: Short-tau inversion recovery.

and lateral cortical thickening in the proximal left femur. The subsequent radiograph reported an atypical fracture.

However, it was only on discussion with the clinical team that a minimum of 20-year history of bisphosphonate therapy was revealed.

A retrospective review of the MR study highlighted the presence of cortical thickening along the lateral aspect of the left proximal femur. The high signal on the STIR sequence was due to subtle marrow edema.

The displaced fracture was subsequently managed with an intramedullary nail.

A summary of these patients can be seen, Table 1.

Learning points

1. Non-degenerative etiology of persistent hip pain should be considered.
2. In the presence of obvious distracting findings, the “satisfaction of search” may result in inadvertently disregarding more subtle signs.

3. A high index of suspicion is needed to ensure that subtle cortical changes are detected, regardless of the clinical history.
4. Radiologists should be aware that subtle cortical thickening may be the only finding of early atypical fractures.
5. Although the history in the initial radiograph did not support a right-sided pathology, a systematic review of the radiograph including the non-symptomatic side will ensure that early signs are not missed, (Case 3).
6. The subtrochanteric areas should be included on pelvic radiographs and the labels should not obscure any part of the bones.
7. The atypical fractures usually occur in the subtrochanteric region; however, they can also be observed bilaterally and more distally along the femoral midshaft. Therefore, a low threshold to obtain further imaging in symptomatic patients is advisable (Case 5).
8. Atypical fractures may mimic metastatic deposits (Case 6).
9. The absence of bone marrow edema on MR imaging may indicate stable appearance. Stopping the bisphosphonate therapy may help reverse the symptoms.^[5,6]
10. In the absence of marrow edema on STIR sequences, there may only be subtle low signal intensity on the T1W sequence. This should not be mistaken for an artifact (Case 8).
11. Patients can initially be asymptomatic and may develop symptoms if bisphosphonate therapy is continued.
12. Prophylactic nail should be offered when there is an associated bone marrow edema on MR imaging.^[7]

DISCUSSION

Bisphosphonate-associated atypical fractures often occur along the femoral shaft between the subtrochanteric and supracondylar area in a transverse orientation. They are usually non-comminuted and relate to prolonged bisphosphonate use of more than 5 years.^[4] These fractures may be preceded by a prodromal deep groin or thigh pain in the absence of significant trauma, exhibiting a high incidence of bilaterality.^[4]

Recently, several cases have been reported in the literature of atypical tibial fractures with a possible link to bisphosphonate therapy.^[8] The earliest denominating radiological feature of bisphosphonate-linked atypical tibial fractures is periosteal reaction of the proximal lateral cortex that progresses to transverse fracture line in the absence of intervention.^[8,9]

Monzem *et al.* examined in a case-control study the effect of ibandronate between ovariectomized and non-ovariectomized mice. The assessment concluded that bisphosphonate use in combination with low estrogen status (post-oophorectomy) resulted in reduced femoral resilience, increased tibial cortical thickness, and modified the proximal diaphysis of the tibia into a straighter shape.^[10]

Table 1: Summary of cases.

Case No.	Age	Sex	Duration of bisphosphonate therapy	Imaging findings at diagnosis	Initial radiological findings	Management
Case 1	75	Female	5 years	Subtrochanteric lateral cortical thickening, cortical fracture and bone marrow edema.	Missed, subtle cortical thickening of the subtrochanteric lateral femoral cortex.	Prophylactic intramedullary nailing. Bisphosphonates stopped.
Case 2	82	Female	4 years	Lateral cortical beaking of the proximal right femur without bone marrow edema.	Acute pubic rami fractures. Missed, subtle beaking of the lateral cortex of the proximal right femur.	Bisphosphonate therapy was stopped. A follow-up radiograph demonstrated no progression.
Case 3	67	Female	20 years	Lateral cortical thickening of the proximal right femur. No bone marrow edema.	Missed, thickened lateral femoral cortex.	Bisphosphonate therapy was stopped. No further symptoms since.
Case 4	52	Female	7 years	Displaced, angulated transverse subtrochanteric fracture of the right femur.	Missed, subtle thickening of the subtrochanteric lateral cortex of the right femur.	Intramedullary nailing. Bisphosphonates were stopped.
Case 5	77	Female	20 years	Insufficiency fractures of the pubic rami. Subtle thickening of the lateral cortices of the midshaft of bilateral femora. No bone marrow edema.	Not applicable.	Bisphosphonate therapy was stopped. Follow-up radiograph demonstrated no progression.
Case 6	58	Female	5 years	Focal avid uptake along the proximal right femur on SPECT corresponding to lateral cortical beaking on plain film.	Not applicable.	Bisphosphonate therapy was stopped.
Case 7	75	Female	11 years	Displaced, angulated transverse subtrochanteric fracture of the right femur.	Missed, subtle subtrochanteric lateral cortical thickening of the femur.	Intramedullary nail fixation. Bisphosphonates were stopped.
Case 8	70	Female	20 years	Transverse displaced and angulated fracture of the proximal left femur.	Small left hip effusion. Low T1 signal in midshaft of left femur, thought to be metal artifact. Missed: 1. Bone marrow edema in the midshaft of the left femur. 2. Cortical thickening along the lateral aspect of the proximal left femur.	Intramedullary nail fixation.

Proving a direct causal link between long-term bisphosphonate administration and atypical fractures is yet to be achieved, mainly because of the multifactorial nature of fractures in the elderly population. It is theorized that impaired osteogenesis and the accumulation of microdamage from a severely suppressed bone turnover lead to insufficiency fractures.^[11]

Atypical femoral fractures are divided into complete or incomplete subtypes with strict diagnostic criteria produced

by the American Society for Bone and Mineral Research. These atypical fractures must not be periprosthetic or associated with lytic lesions. Given the high incidence of bilaterality, it is imperative to assess the other femur for evidence of incomplete atypical fractures [Table 2].^[12]

To allow further stratification of these atypical femoral fractures, a scoring system has been proposed in an attempt to predict symptoms and fracture risk. This scoring system takes the radiographic and MR features into consideration.

Table 2: The American Society for Bone and Mineral Research diagnostic criteria for atypical femoral fractures.^[12]

Major criteria	Minor criteria	Exclusion criteria
Proximal fracture line below the lesser trochanter	Periosteal reaction along the outer cortex	The presence of a femoral neck fracture
Distal fracture line above the femoral condyles	Bilateral fracture	Intertrochanteric fracture with subtrochanteric extension
Transverse/oblique fracture line (fracture angle of <30)	Prodromal pain (groin/thigh)	Periprosthetic fracture
Non-comminuted fracture	Increased cortical thickness	Pathological fracture secondary to bone malignancy
No trauma/low-energy trauma	Delayed healing	
Complete fracture (traversing both the medial and lateral cortices)	Comorbidities, such as: <ul style="list-style-type: none"> • Vitamin D deficiency • Rheumatoid arthritis 	
OR		
incomplete fracture, affecting the lateral cortex only	Concomitant treatment; like: <ul style="list-style-type: none"> • Glucocorticoids • Proton-pump inhibitors 	

All the major criterions need to be satisfied

The presence of focal cortical translucency on plain film along with a linear low T2 signal articular lesion (known as, the black line sign) is the most critical radiological factors in predicting symptoms and risk of fracture within 6 months.^[12]

Plain radiographs and CT imaging assist the diagnosis of bisphosphonate-related fractures through identifying a characteristic pattern of focal lateral cortical thickening in the proximal femur with or without a cortical fracture line and a medial spike. In contrast, non-bisphosphonate femoral fractures are usually spiral or oblique and are often comminuted with no focal cortical thickening.^[13]

MR is more sensitive in the detection of impending atypical fractures, with the suggestive findings of lateral cortical thickening represented by a linear high periosteal signal and a normal bone marrow signal on the STIR sequence. It is imperative to look for ancillary signs of potential malignant

pathologies such as soft-tissue mass, endosteal scalloping, and aggressive bone lesions. MR appearances of complete atypical fractures are similar to those of stress fractures, with the fracture line demonstrating low signal intensity on all sequences, surrounded by diffuse bone marrow edema.^[14]

The role of MR imaging extends to fracture monitoring, thereby guiding clinical management, especially in asymptomatic patients of incomplete atypical femoral fractures. Follow-up studies can confirm successful conservative management through the resolution of bone marrow edema.^[14]

Functional studies can be utilized to exclude pathological fractures and enhance the certainty of the diagnosis. The most frequent study used is technetium-99m-labeled methylene diphosphonate scintigram, where an acute fracture will display a hot spot of high uptake in an otherwise normal study.^[14]

In complete atypical fractures, the main aim is to fix the fracture and stabilize the bone. Imminent fractures can be managed conservatively, and prophylactic internal fixation may be considered if the prodromal pain persists.^[15]

CONCLUSION

1. Prolonged use of bisphosphonate therapy increases the risk of atypical fractures.
2. Bisphosphonate-related fractures almost always occur in the femur.
3. Atypical fractures exhibit characteristic radiological signs of focal beaking of the lateral cortex.
4. These fractures are often missed due to lack of awareness or due to poor inclusion of the subtrochanteric region on radiographs.
5. The contralateral hip must always be assessed due to the high incidence of bilaterality.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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