

Case Report

Case of atypical femoral fractures that mimicked the typical imaging findings of prostate cancer-induced bone metastasis

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Abbreviations & Acronyms

ADT = androgen deprivation therapy
 AFF = atypical femoral fracture
 BRI = bone resorption inhibitor
 CT = computed tomography
 IM = intramedullary
 MRI = magnetic resonance imaging
 PC = prostate cancer
 PET = positron emission tomography
 PSA = prostate-specific antigen
 SRE = skeletal-related event

Introduction: Atypical femoral fractures are atraumatic or minimally traumatic fractures and rare side effects of bone resorption inhibitors. Bone resorption inhibitors are frequently used in the treatment of prostate cancer.

Case presentation: A 62-year-old man complained of difficulty in walking and left lower limb pain. Androgen deprivation and denosumab therapy for prostate cancer-induced bone metastasis was initiated 27 months ago. Even though the prostate-specific antigen level did not increase, imaging studies indicated the possibility of bone metastasis. The patient underwent bone biopsy; however, no malignancy was detected. Afterward, he had a fall, causing a complete fracture in his left femur.

Conclusion: Atypical femoral fractures occasionally mimic typical imaging findings and outcomes of bone metastasis. This case is important for recognizing such cases.

Key words: atypical femoral fractures, bone metastasis, bone resorption inhibitors, denosumab, prostate cancer.

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Keynote message

AFFs are a rare side effect of BRIs used in the treatment of PC. BRIs are frequently used for bone management of PC. There is clinical significance for recognizing such diagnostic dilemma.

Introduction

AFFs are minimally traumatic fractures located along the femoral diaphysis in areas just distal to the lesser trochanter and just proximal to the supracondylar flare.¹ AFFs can be caused by obesity, stress, osteoporosis, and low bone turnover. AFFs are a known side effect of BRIs, including bisphosphonates and denosumab.² AFFs account for 0.3% of all femoral fracture cases and 90% of cases occur in women.³ AFFs are categorized as incomplete or complete fractures and can often progress from incomplete to complete.⁴ The incidence of AFFs in cancer patients is 0.05 per 100 000 cases per year, with an odds ratio of 300 (patients administered with BRIs vs patients not administered BRIs).⁵ The incidence of AFF increases when BRIs are administered for longer periods.⁶

PSA levels can be used to detect and monitor PC. Only 1% of PC cases progress when PSA levels are <0.1 ng/mL.⁷ Metastasis without an elevation in tumor marker levels is atypical.

Among newly diagnosed PC cases, 6% are metastatic cases and 80% are bone metastasis cases.⁸ SREs are defined as pathological fractures, spinal cord compression, and radiation therapy- or bone surgery-related events. Bone metastasis causes SRE within 2 years in 41.9% of PC patients.⁹ BRIs decrease the incidence of SRE by inhibiting bone metastasis,¹⁰ however, in rare cases, BRI can cause AFFs.¹

We present an AFF that mimicked typical imaging findings and SREs of PC-induced bone metastasis. Although this is the third case of AFF in PC, to the best of our knowledge, our case report is the first to reveal pathological findings involved with denosumab and contain detailed imaging evaluation such as MRI and PET/CT.

Case presentation

A 62-year-old man was admitted to our hospital for left lower limb pain with no prior history of injury. He reported regularly dismounting a forklift by using his left leg. He was diagnosed with bone-metastatic PC 24 months prior to admission, with a Gleason score of 4 + 4 and an initial PSA level of 219 ng/mL. Thereafter, he was administered denosumab (120 mg) every 3 months and underwent ADT.

An X-ray image of his left femur showed a spike with no clear fracture lines (Fig. 1a). Testing revealed that his PSA was within the normal range at 0.01 ng/mL. However, MRI of his left femur revealed a mass in the bone marrow (Fig. 2a–e), and PET-CT revealed an accumulation of SUVmax 2.7 (Fig. 2f,g). Therefore, we could not dismiss the possibility of bone metastasis. A bone biopsy was performed 16 days post-admission (Fig. 1b), and the results revealed no malignancy (Fig. 3). Pathological findings also revealed osteoblasts prominently covering the cancellous bone with almost no osteoclasts (Fig. 3a,b).

The patient fell from a standing position and completely fractured his left femur 20 days post-admission (Fig. 1c). On the following day, he underwent IM nailing. He was discharged, with walking sticks, 48 days post-admission, and denosumab was discontinued. The final diagnosis was AFF based on pathological findings and clinical course 4 months after hospitalization.

Discussion

This case revealed a complete atraumatic, noncomminuted, and transverse fracture of the left femur, which fulfilled all the major diagnostic criteria for AFF (Table S1).¹ The clinical course suggested progression from an incomplete to complete fracture. Long-term use of BRI is recently considered a cause of AFF.² Our literature review revealed the rarity of AFF cases caused by PC. Only three such cases have been reported to date^{11,12} (Table 1), in which all patients received ADT and BRI therapy for more than 2 years.

The adequate duration and timing of BRI therapy in PC remain unclear. ADT elevated significant incidence of fractures and osteoporosis in PC patients.^{13,14} Combined ADT

and BRI may be related to the occurrence of AFF. However, AFF is a very rare disease, and a recent meta-analysis presented that BRIs were effective in osteoporosis caused by ADT.¹⁵ Even if there is a risk of AFF, adequate administration of BRI should be clinically recommended for bone management in PC.

We could not dismiss the possibility of bone metastasis. The characteristics of the fracture often made it difficult to differentiate developing stress fractures like AFF from malignancies.^{16–18} In this case, the result of MRI and PET-CT also mimics bone metastasis (Fig. 2). Bone biopsy should be considered when image examination cannot confirm diagnosis. Currently, there is no established method of distinguishing bone fracture and metastasis except biopsy, and we hope that unnecessary treatment and biopsy will be prevented by further accumulation of cases.

In this case, AFF might have been caused by denosumab. Pathological findings were consistent with suppressed bone turnover caused by BRI.¹⁹ Low bone turnover can cause micro-damage accumulation and additional fractures. AFF affects 28% of the contralateral femur.¹ Incomplete AFFs often progress to complete fractures. Discontinuation of BRIs is recommended for treatment.

Conclusion

This is a rare case of AFF related to BRI administration. It was difficult to discriminate between AFF and bone metastasis through X-ray, MRI, and PET-CT. When treating bone metastasis by PC with BRIs, the possibility of AFFs should be considered. The incidence of AFFs caused by PC remains unknown, and further study is required to clarify this.

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Conflict of interest

The authors declare no conflict of interest.

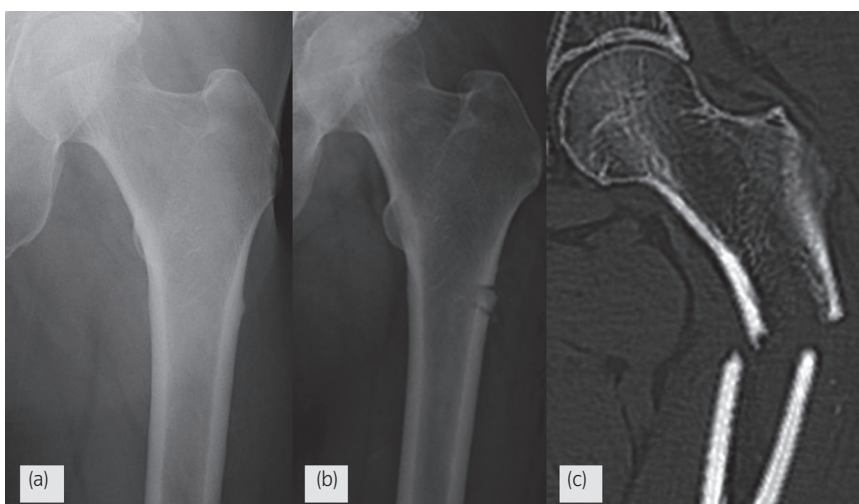


Fig. 1 (a) X-ray image of the left femoral region showing hypertrophic bone. (b) X-ray examination findings following bone biopsy of the left femur. (c) CT image showing that the left femur was completely fractured following a fall from a standing position.

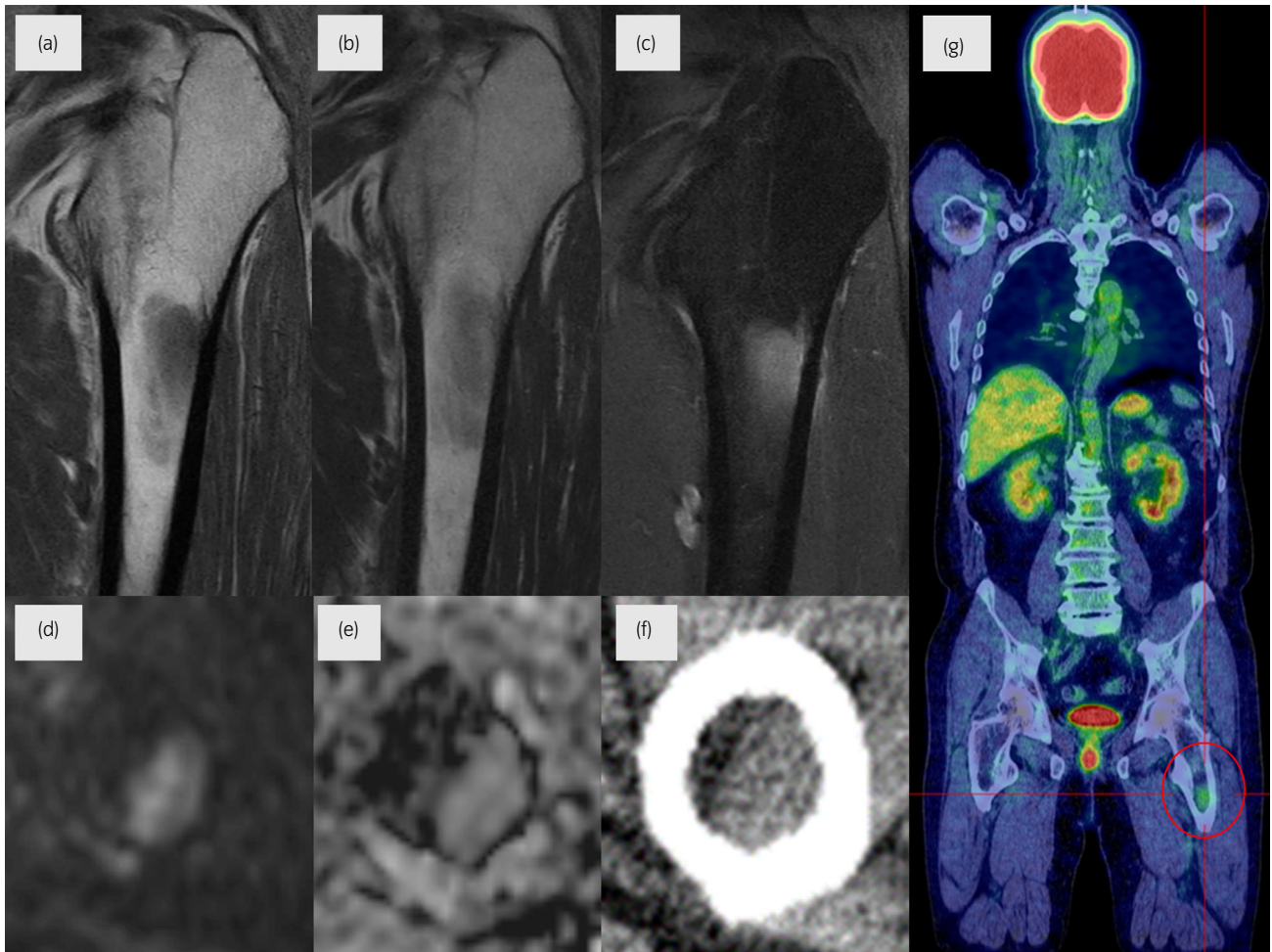


Fig. 2 (a) T1-weighted magnetic resonance image showing that the mass in the left femur demonstrates the same low signal as the surrounding muscle. (b) T2-weighted magnetic resonance image showing that the mass in the left femur demonstrates the same low signal as the surrounding muscle, but the border is unclear. (c) Contrast-enhanced T1-weighted magnetic resonance image showing homogeneously contrasted bone marrow. (d) Diffusion-weighted magnetic resonance image showing a mildly high signal in the mass in the left femur. (e) The apparent diffusion coefficient of the magnetic resonance image shows a mildly high-intensity signal. (f) CT image of the left femur: the increase in signal intensity allows for the recognition of the bone marrow. (g) PET-CT imaging revealing a mild accumulation of SUVmax 2.7 in the portion of the left femur where pain was experienced (shown within the circle).

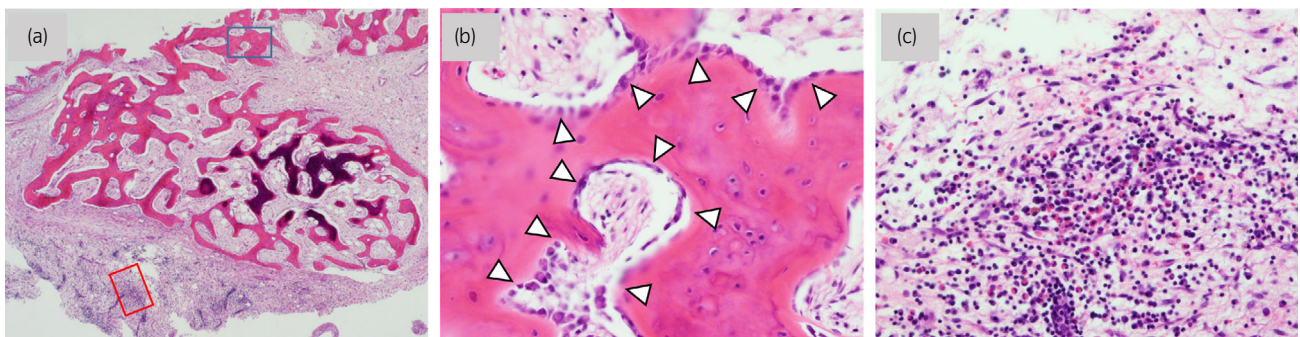


Fig. 3 (a) Bone marrow biopsy specimen (hematoxylin-eosin staining). Malignancy was not observed. (b) An enlarged image of the bone marrow cancellous bone (shown within the blue square in a). The cancellous bone was completely covered by several osteoblasts (arrow), but few osteoclasts were observed. (c) An enlarged image of the bone marrow showing osteomyelitis, with invasion of lymphocytes, plasma cells, and eosinophils (shown within the red square in a).

Table 1 Review of studies of atypical femoral fractures in prostate cancer patients

Case No.	Author	Year	Age	Sex	Bone metastasis at diagnosis	Treatment for PC	Time between pain and complete AFF, months (location of AFF)	Time for anti-resorptive medications, months (medication)	Treatment for AFF
1	Reddy and Gupta ¹¹	2012	70	Male	No	ADT	0 (right femoral)	24 (zoledronic acid)	IM nailing, teriparatide
2	Austin <i>et al.</i> ¹²	2017	86	Male	Yes	ADT	5 (right femoral)	42 (denosumab)	IM nailing, radiation
3	Our case	2019	62	Male	Yes	ADT	2 (left femoral)	27 (denosumab)	IM nailing, stop denosumab

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Major features of the ASBMR[†] Task Force 2013 Revised Case Definition of AFFs.

Editorial Comment

Editorial Comment to Case of atypical femoral fractures that mimicked the typical imaging findings of prostate cancer-induced bone metastasis

The article by Nezu *et al.* is an interesting one which highlights the increasing incidence of newer disease entities as a side effect of advancements in bone resorption inhibitor (BRI) therapy.¹ Although medication-related osteonecrosis of jaw

(MRONJ) has been an established complication of bisphosphonates and denosumab, other osteopathological lesions are now being known to occur and the treating physician needs to be aware of it. By reporting a case of atypical femoral fracture (AFF) in a patient who had received denosumab, the authors have brought out how to tackle the clinical dilemma as well as made efforts to focus on the proper investigation tools which will be a guide for others in the future.

BRI have been in use for nearly two decades with the introduction of bisphosphonates in 2001 and the receptor activator of nuclear factor kappa B ligand inhibitor denosumab

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