Atypical metatarsal fracture in a Chinese postmenopausal woman with osteoporosis on long-term denosumab: a case report

Eunice KH Leung[1 #], MB, BS, **Andy KC Kan**[1 #], MB, BS, **Jerome Lau**[2], MB, BS, **CH Wong**[1], MB, BS, **Connie HN Loong**[1], MNurs, **Stephen CW Cheung**[3], FRCR, **YC Woo**[1], MD, **David TW Lui**[1 *], MB, BS

[1] *Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China*
[2] *Department of Surgery, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China*
[3] *Department of Radiology, Queen Mary Hospital, Hong Kong SAR, China*

[#] Equal contribution

[*] Corresponding author: dtwlui@hku.hk

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Case presentation

We report the first case of atypical fifth metatarsal fracture in a 69-year-old Chinese woman following long-term treatment for osteoporosis with denosumab. She had been diagnosed with hypertension in 2007 and was managed with amlodipine and losartan. One year previously in 2006, she had been diagnosed with postmenopausal osteoporosis based on low bone mineral density (BMD) revealed at a health screening. Her height and weight were 150 cm and 54 kg, respectively, with a body mass index of 24.0 kg/m^2. She had no previous history of fracture or parental history of hip fracture.

The patient was initially prescribed raloxifene for 2 years but due to a suboptimal BMD response, she was treated with alendronate for 4 years. Given the prolonged use of alendronate, she was switched to strontium ranelate but this was discontinued a few months later due to intolerance. Dual-energy X-ray absorptiometry at that juncture in 2014 showed the BMD of the L1-L4 level, the left femoral neck, and the left total hip were 0.928 g/cm^2 (T-score= -2.1), 0.646 g/cm^2 (T-score=-2.9), and 0.725 g/cm^2 (T-score=-2.4), respectively. She was started on subcutaneous denosumab 60 mg every 6 months that was continued until October 2021. Her most recent dual-energy X-ray absorptiometry in December 2020 revealed the BMD of the left femoral neck and left total hip were 0.544 g/cm^2 (T-score= -2.3) and 0.715 g/cm^2 (T-score=-1.4), respectively, indicating significant improvement. The BMD of the lumbar spine was not reported due to significant degenerative changes.

The patient presented to the primary care physician in November 2021 with a 2-week history of mechanical right lateral foot pain. She reported no preceding injury but physical examination revealed mild tenderness over the base of the right fifth metatarsal. There was no joint effusion or signs of infection and distal neurovascular status was intact. X-ray of the right foot was performed (Fig a) and she was prescribed analgesics for right foot tendinitis. One month later in December 2021, she complained of persistent right foot pain during her scheduled follow-up at the Osteoporosis Centre of The University of Hong Kong. Physical examination revealed intense tenderness over the lateral side of her right foot, near the base of the fifth metatarsal. Review of the X-ray taken in November 2021 identified beaking over the lateral aspect at the base of the right fifth metatarsal, indicating a periosteal reaction, associated with a transverse radiolucency across the cortex. Repeat X-ray of the right foot (Fig b) revealed a more prominent transverse radiolucency across the same site. A diagnosis of denosumab-related atypical metatarsal fracture was reached given the long duration of antiresorptive treatment (likely related to denosumab since

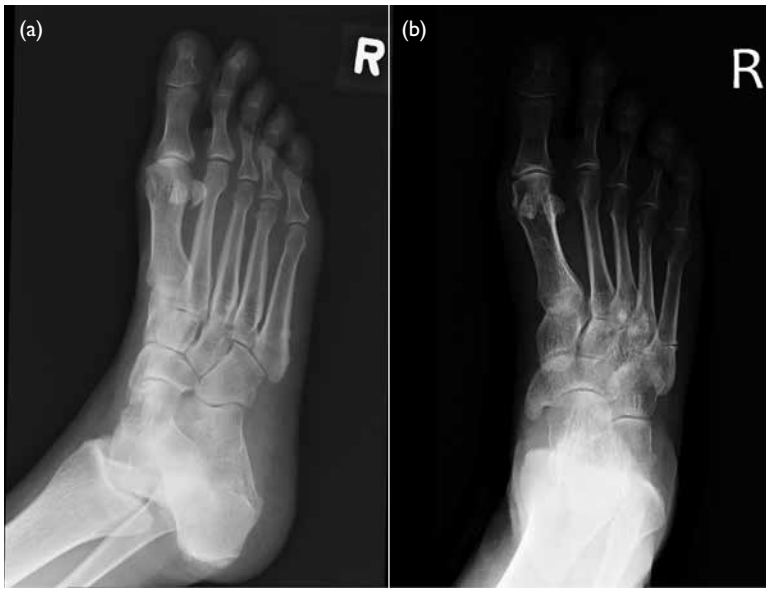

FIG. Incomplete atypical fracture of the right fifth metatarsal of the patient in November 2021 (a) and December 2021 (b)

fracture occurred after 7 years of denosumab), prodromal symptoms and absence of high-energy trauma, along with characteristic radiological findings. Blood tests showed serum calcium level of 2.44 mmol/L (reference range, 2.24-2.63), phosphate level of 0.98 mmol/L (reference range, 0.88-1.45), creatinine level of 60 μmol/L (reference range, 49-82), parathyroid hormone level of 1.7 pmol/L (reference range, 1.3-6.8), and 25-hydroxyvitamin level of 70 nmol/L (sufficient level: 50-220). Although bone turnover markers were not measured, serum alkaline phosphatase level was on the low side at 48 U/L (reference range, 47-124) that could suggest suppressed bone turnover. An X-ray of the left foot was not available, but the patient had no history of left foot pain. For her atypical right metatarsal fracture, she was given a short leg plaster and completed a course of physiotherapy. The fracture healed completely in 6 months. She was started on teriparatide as anti-osteoporosis treatment, and this was tolerated well.

Discussion

The American Society for Bone and Mineral Research Task Force published a report in 2014 on the case definition of atypical femoral fracture (AFF),[1] which refers to fracture located along the femoral diaphysis just distal to lesser trochanter to just proximal to the supracondylar flare. Major and minor diagnostic criteria were proposed. The pathophysiology is postulated to be related to oversuppression of bone turnover impairing normal bone remodelling in response to physiological stress. Prolonged bisphosphonate use has been associated with rare adverse events of atypical fractures (3.2-50 cases per 100 000 person-years).[1] Atypical femoral fractures related to denosumab use have been reported, but they are even rarer (0.8 per 10000 person-years).[2] Our patient had been taking alendronate for 4 years and denosumab for 7 years. It was very likely that bone turnover had been severely suppressed. In line with this, her serum alkaline phosphatase level was at the lower end of the reference range.

Less commonly, atypical fractures involving long bones other than the femur have also been reported among patients prescribed bisphosphonate or denosumab, including the tibia and ulnar.[3] Notably, atypical metatarsal fractures associated with bisphosphonate use for osteoporosis have

TABLE. Reported cases of atypical metatarsal fractures during treatment for osteoporosis[3-5]

Age/ Sex	Osteoporosis treatment at the time of metatarsal fracture	Previous fracture history	Co-morbidities	Fracture site	Presentation	Radiological findings	Treatment of fracture	Subsequent osteoporosis treatment
63/F[3]	Alendronate	Nil	Hypertension	Diaphyseal-metaphyseal junction of the right fifth metatarsal base	Aching sensation and discomfort over the right foot for 3 weeks, then progressive pain in the right foot for 1 week, worsened with movement	X-ray and CT of the right foot: an incomplete transverse fracture at the inferolateral aspect of the diaphyseal-metaphyseal junction of the right fifth metatarsal	Percutaneous surgical fixation with a proximal approach, then short leg cast followed by thermoplastic splint	Alendronate discontinued; for calcium and vitamin D supplements
24/F[4]	Alendronate	Left neck of femur fracture Right subtrochanteric femoral fracture	Post-adrenalectomy for ectopic ACTH syndrome, on low-dose steroids	Shaft of the right fifth metatarsal	Insidious onset of dull pain in the right foot, persisted for 3 months despite analgesics and physiotherapy; worsened with movement	X-ray of the left foot: an incomplete transverse fracture at the shaft of the left fifth metatarsal with lateral cortical thickening	Plaster	Alendronate discontinued; given 6 months of teriparatide 20 μg SC
59/F[5]	Alendronate	Cuboid fracture	N/A	Shaft of the left fifth metatarsal	Insidious onset of dull pain in the left foot, which failed to resolve with analgesics for 5 months and splint for 6 weeks	X-ray of the left foot: an incomplete transverse fracture at the shaft of the left fifth metatarsal with lateral cortical thickening Whole-body bone scan: a stress fracture in the left fifth metatarsal	Surgery: open reduction, internal fixation and bone graft	Alendronate discontinued; given 6 months of teriparatide 20 μg SC

Abbreviations: ACTH = adrenocorticotropic hormone; CT = computed tomography; F = female; N/A = not available; SC = subcutaneous

been reported in only three cases.[3-5] Our case is the first of atypical metatarsal fracture associated with denosumab. Atypical metatarsal fractures associated with antiresorptive agents, as illustrated in our patient and other case reports (Table), share several characteristics and are distinct from typical fifth metatarsal fractures. They were all associated with prodromal pain with no history of high-energy impact. More importantly, the radiological features fulfil some of the criteria of AFF proposed in the American Society for Bone and Mineral Research 2013 consensus,[1] including a fracture line originating in the lateral cortex and periosteal reaction. Although the atypical metatarsal fracture in our patient was temporally related to the long duration of denosumab, the possibility that alendronate had caused abnormal microarchitecture that persisted and was perpetuated by denosumab therapy could not be excluded since she had also been prescribed alendronate for 4 years.

When AFF is diagnosed, antiresorptive agents should be stopped. The risk of AFF of the contralateral femur declines after discontinuation of bisphosphonate. Adequate vitamin D, calcium supplementation and teriparatide can promote healing and reunion of atypical femoral fracture. Surgery promotes healing and relieves pain for AFF. Incomplete AFF has been successfully treated with prophylactic intramedullary nailing. Unlike AFF, the treatment for atypical metatarsal fractures is less well defined. The decision about treatment involves a patient-physician discussion, although the presence of a longer transverse radiolucent line across the shaft favours surgical management.

Although bisphosphonate and denosumab are safe and efficacious, rare side-effects of atypical fractures have been reported. Our case highlights the importance of clinician vigilance for atypical fractures when patients on long-term antiresorptive agents complain of pain over the long bones (not limited to the femur) to enable timely management to reduce morbidities and re-evaluate the anti-osteoporosis strategy.

Author contributions

Concept or design: All authors.
Acquisition of data: EKH Leung, AKC Kan, YC Woo, DTW Lui.
Analysis or interpretation of data: EKH Leung, AKC Kan, SCW Cheung, YC Woo, DTW Lui.
Drafting of the manuscript: EKH Leung, AKC Kan, YC Woo, DTW Lui.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient for publication of this case report and any accompanying images.

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