Atypical fracture of the femur in a patient using denosumab – a case report

Jörg Schilcher and Per Aspenberg

Orthopedics, Department of Clinical and Experimental Medicine, Faculty of Health Science, Linköping University, Sweden
Correspondence: per.aspenberg@liu.se

A woman born in 1930 was diagnosed with osteoporosis in 2000, and was started on treatment with alendronate. Her lumbar T-score in 2010 was –3.0. In 2008, she had a displaced atypical fracture of her left femur, which healed uneventfully after intramedullary nailing (Figure 1). No radiographs of her contralateral femur were obtained. She continued taking alendronate until it was stopped in September 2010. In February 2011, she received a single zoledronate infusion. No bisphosphonate was given after that, due to reduced kidney function. She received a first injection of denosumab in April 2012 and then every 6 months, with the last and fourth injection in October 2013.

The patient has been generally healthy otherwise, with no drugs known to influence the skeleton. She took long daily walks until September 2013. At this time—29 months after the last zoledronate injection and after 16 months on denosumab—she noted slight pain in her right thigh and knee. In October, the pain increased and soon necessitated the use of a walking frame. She sought acute medical attention after being unable to rise from a chair on January 5, 2014. Radiographs showed 2 focal thickenings of the lateral diaphyseal cortex, 1 of them with a visible crack (Figure 2). She was operated with an intramedullary nail on the day after.

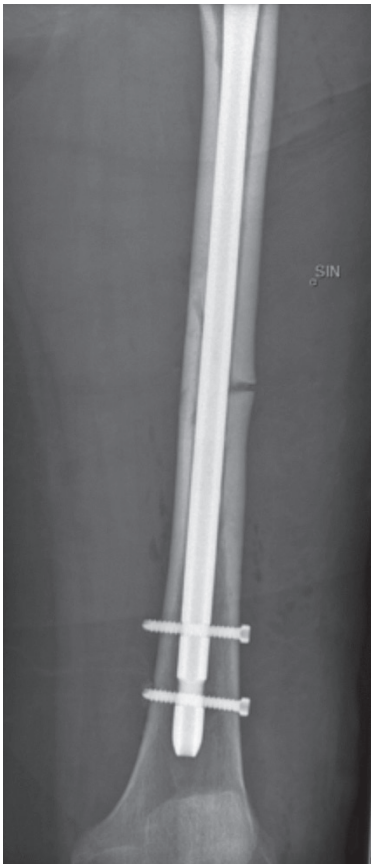

Figure 1. Left femur. Atypical fracture while using alendronate, 2008.

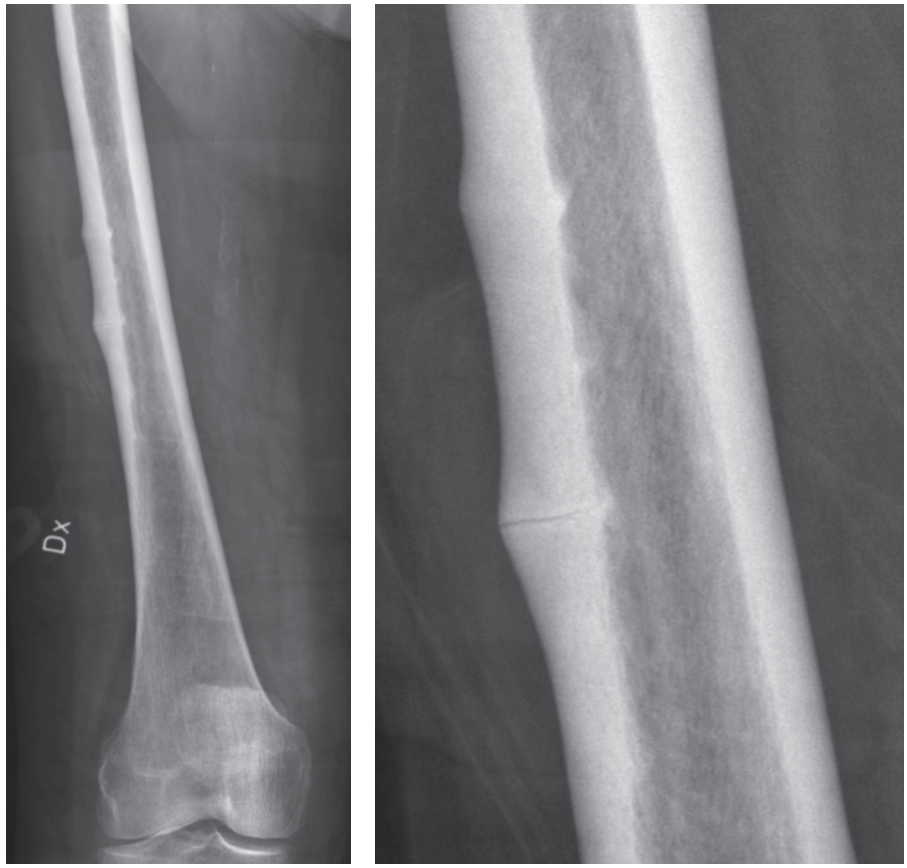

Figure 2. Right femur. Multifocal atypical fractures while using denosumab 2014 (overview and magnification). Note the visible crack.

DOI

Discussion

It is apparent from the current literature that bisphosphonates cause atypical fractures, although rarely, through their anti-resorptive activity. Because denosumab is also anti-resorptive, it should be no surprise if it causes atypical fractures (Aspenberg 2014). The producer warns of this complication in the product label, and mentions that suspected atypical fractures have occurred in their studies, although they do not go into detail.

This is the third case of denosumab-associated atypical fracture reported in the literature that can be reached via PubMed. The first report appeared online in October 2013 (Drampalos 2014) and is printed in this issue of Acta Orthopaedica. The second case was published online in December (Thompson 2013). There is another report of a spontaneous subtrochanteric fracture in a patient receiving denusomab, but that patient had hyperparathyroidism and her fracture did not meet the radiographic criteria for an atypical fracture (Paparodis 2013).

All 3 patients reported with atypical fractures had used a bisphosphonate before switching to denosumab. In the first patient, bilateral fractures occurred 1 and 13 months after the drug switch (Drampalos 2014). The second case also had bilateral fractures. She had rheumatoid arthritis and had used a corticosteroid and immune modulatory drugs. She had been free of bisphosphonates for 12 years when her first atypical fracture appeared, 3 months after the first injection of denosumab. She then had another, incomplete atypical fracture diagnosed 1 year later, after which denosumab use was stopped (Thompson 2013). In our patient, the time between the last zoledronate injection and surgery was almost 3 years. The bisphosphonate-associated risk of atypical fracture diminishes rapidly after use of the drug is discontinued (Schilcher et al. 2011), and the long time after cessation in our case speaks against the bisphosphonate being a cause—although it is possible that the fracture emerged before the patient noted symptoms.

The short duration of denosumab use before the appearance of the atypical fractures in the 3 cases argues in favor of the theory that atypical fractures are a consequence of impaired targeted remodeling of fresh microcracks, rather than being a consequence of generally altered bone material properties (Aspenberg 2014). It is unlikely that a reduction of general bone remodeling for less than a year would increase the brittleness of the femoral cortex.

Atypical fractures occur also in patients without anti-resorptive drugs, and only future epidemiologic studies with radiographic adjudication will tell about the strength of the association with denosumab.

PA has received research support from Amgen related to denosumab.

JS collected the data and PA wrote the manuscript; both authors revised it.

Aspenberg P. Denosumab and atypical femoral fractures. Acta Orthop 2014; 85 (1): 1-2.

Drampalos E, Skarpas G, Barbounakis N, Michos I. Atypical femoral fractures bilaterally in a patient receiving denosumab. Acta Orthop 2014; 85 (1): 3-5.

Paparodis R, Buehring B, Pelley EM, Binkley N. A case of an unusual subtrochanteric fracture in a patient receiving denosumab. Endocr Pract 2013; 19 (3): e64-8.

Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 201; 364 (18): 1728-37.

Thompson R N, Armstrong C, Heyburn G. Bilateral atypical femoral fractures in a patient prescribed denosumab – a case report. Bone 2013 Dec 31. pii: S8756-3282(13)00549-8. doi: 10.1016/j.bone.2013.12.027. [Epub ahead of print]