Title:

Denosumab induced atypical fracture of free vascularised fibular graft 20 years after tumour reconstruction.

Running head: Denosumab fracture in a fibular graft

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/ans.16358](https://doi.org/10.1111/ans.16358)

VT performed the literature review and wrote the manuscript.

ELC obtained the information and wrote the manuscript.

PFM treated the patient, conceived the manuscript, supervised, reviewed and edited the manuscript.

Case report

A 67-year-old female developed sudden, severe pain and an inability to weight bear on her right leg upon standing from a chair. She had a tibial adamantinoma, treated with wide resection and reconstruction with a free-vascularized fibular graft (VFG) twenty-one years earlier (Figure 1 a-d). Eighteen months prior to her current presentation, she was diagnosed with osteoporosis and begun treatment with an anti-resorptive agent, denosumab, 60mg subcutaneously every 6months. She had received a total of three injections, the last dose being one month prior to this presentation. There was no other history of fragility fractures or any other previous anti-resorptive therapy.

Plain radiographs revealed a non-displaced, transverse fracture of the proximal fibular graft. Localized beak-shaped periosteal thickening of the lateral cortex was present at the fracture site (Figure 2 a-c). A further bone-scan of the patient's body demonstrated increased tracer uptake in the proximal right proximal VFG-tibia junction, consistent with the known fracture. Magnetic resonance imaging of the proximal femora did not reveal any additional occult femoral fractures or stress reactions. Laboratory parameters, including full blood count, alkaline phosphatase (ALP) and thyroid stimulating hormone (TSH) were within normal limits. A definitive diagnosis of an antiresorptive-induced insufficiency fracture of the VFG was concluded and denosumab therapy was discontinued.

The patient was treated non-weight bearing in an above-the-knee fibreglass cast for 4 months, which was then replaced with a Sarmiento-type patellar tendon bearing cast and the patient was encouraged to progressively increase weight-bearing by 30% at 6 weekly intervals. Serial radiographs confirmed fracture callus bridging the fracture and bone union through the posterior 3/4 of the fracture (Figure 3). At 8 months post fracture, healing had been achieved clinically as evidenced by the absence of pain, ability to weight bear and restoration of lower limb function.

Discussion

Atypical fractures are a rare complication of long-term antiresorptive therapy (1, 2). In 2010, with a revision later in 2014, the American Society of Bone and Mineral Research (ASBMR) Task Force released a position statement of AFFs, including a criteria list for the classification of AFFs, which outlines several major features and minor features for diagnosis (2).

Despite being widely associated with bisphosphonate use, AFFs are also known to occur in patients receiving denosumab therapy. The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial was a 3-year international randomised controlled trial (RCT) that evaluated the use of denosumab in the prevention of osteoporotic fractures (3). While this initial trial did not report any AFFs, an extended study of the enrolled participants and further follow-up studies continued to report AFFs occurring in the participants (4, 5).

While stress fractures are known to occur in the early recovery period following reconstruction, this fracture of the VFG occurred over 20 years after index surgery. Follow-up imaging 10 years after initial reconstruction demonstrated robust fibular hypertrophy. These features do not support the pattern of stress fractures typically observed in VFG secondary to increased mechanical load (6). In addition, the clinical and imaging characteristics reflect the features of an atypical fracture. Our presented case satisfies all five Major Features of the ASBMR criteria: absence of trauma, complete, transverse fracture, no comminution, and associated thickening of the lateral cortex. In terms of the Minor Features, this case demonstrated delayed fracture healing. In the context of initiating antiresorptive therapy, with a VFG that had demonstrated robust hypertrophy and structural integrity for 20 years, and satisfaction of the ASBMR criteria, it is reasonable to conclude that this is an **antiresorptive-associated insufficiency** fracture due to denosumab.

This case is unique as it is the first to report an **antiresorptive-associated insufficiency fracture** occurring in the site of a well-healed and hypertrophied vascularised bone graft. Atypical fractures in sites other than the femur, such as the ulna, tibia, and fibula have previously been described in the context of bisphosphonates (7-9). A non-femoral site of fracture has also been reported in a patient receiving denosumab (10). Our case highlights that **antiresorptive-associated insufficiency fractures** may occur in weight-bearing sites other than the femur in patients receiving denosumab and that the site of a VFG is also susceptible. With the growing popularity of VFG as a reconstructive option for bone defects, as well as denosumab for the treatment of osteoporosis, clinicians should be aware of this rare complication.

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Figure Legend

1. (a). Adamantinoma of the tibial diaphysis; (b) Resection specimen (c) Antero-posterior and (d) lateral radiograph of vascularised fibular graft reconstruction 20 years later.
2. (a) Antero-posterior and (b) lateral view of proximal VFG fracture (arrows). (c) Beaked shaped cortical thickening at fracture site.
3. Fracture healing over 8 months.

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Date:

2020-10-12

Citation:

Tran, V., Choong, E. L. P. & Choong, P. F. M. (2020). Denosumab induced atypical fracture of free vascularized fibular graft 20 years after tumour reconstruction. ANZ JOURNAL OF SURGERY, 91 (5), pp.E335-E337. <https://doi.org/10.1111/ans.16358>.

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