Case Report

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Denosumab and metatarsal fracture healing: potential benefits with delayed remodeling: a case report

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Background: Denosumab is known to enhance callus formation while delaying remodeling. However, its effects on fracture healing are scarcely reported in the literature. This case report, to the best of our knowledge, is the first to report the potential effect of denosumab on a metatarsal fracture in an older adult patient, 4 months after administration, resulting in a favorable clinical course with early weight-bearing 17 days after the fracture.

Presentation of case: A 73-year-old female sustained a right-foot second metatarsal fracture due to the fall of a heavy object. She has a history of diabetes mellitus, hypertension, and osteoporosis. Prior to sustaining the fracture, she received seven doses of denosumab spaced 6 months apart, with the last dose administered 4 months earlier. Furthermore, the patient was treated with a backsplint for 6 weeks. After 17 days, follow-up radiographs showed a large callus formation, with no pain and the ability to bear weight. Subsequent radiographs revealed a large callus with delayed remodeling.

Discussion: This case report suggests that denosumab remains effective for promoting rapid callus formation even 4 months after administration for osteoporosis, despite delayed remodeling. This delay did not seem to have negative effects on the clinical outcomes, as the patient achieved weight-bearing within 17 days after sustaining the fracture.

Conclusion: Denosumab may positively influence fracture healing in older adults with metatarsal fractures, potentially leading to delayed remodeling. However, further studies are needed to confirm these observations.

Keywords: callus remodeling, case report, denosumab, fracture healing, osteoporosis

Introduction

Osteoporosis is a skeletal disorder characterized by decreased bone mineral density and deterioration of microarchitecture, leading to increased fracture risk. Several therapeutic options are available for osteoporosis management, including bisphosphonates, hormone replacement therapy, selective estrogen receptor modulators, and denosumab[1].

Denosumab, a potent monoclonal antibody, blocks the receptor activator of nuclear factor-kappa B ligand (RANKL) by inhibiting osteoclast formation and bone resorption[1,2]. Denosumab has been used in various orthopedic conditions, such as Charcot foot and giant cell tumors of the bone[3,4]. Concerns existed regarding antiresorptive drugs, such as bisphosphonates and denosumab, potentially delaying fracture healing by inhibiting osteoclast activity, which is responsible for bone remodeling. However, recent studies have not supported this negative effect on fracture healing. Denosumab administered at a 60 mg dose every 6 months, even close to the time of fracture, appears not to impede spinal fracture healing nor cause additional complications[1]. Furthermore, recent research has shown that higher doses of denosumab (120 mg monthly for 3 months) had a positive effect on fracture nonunion healing in a small-scale study with three cases[5]. In metatarsal fractures, clinical healing, characterized by radiographic callus formation and resolved point tenderness, typically occurs within 6 weeks[6]. Zenios *et al*.[7] showed that the radiographic union of metatarsal fractures was typically achieved after 3 months. However, to our knowledge, the specific effects of denosumab administered 4 months before metatarsal fracture on the healing process

HIGHLIGHTS

- A 73-year-old female with multiple risk factors for delayed healing experienced rapid recovery from a metatarsal fracture.
- The patient experienced a traumatic metatarsal fracture 4 months after denosumab injection at a dose of 60 mg.
- Denosumab had a good effect on fracture healing and delays callus remodeling.
- The patient regained weight-bearing ability within 17 days after the fracture.

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remain unreported in the literature. Therefore, this case report, adhering to the Surgical CAse REport (SCARE) guidelines[8], aimed to address this gap in knowledge.

Presentation of case

A 73-year-old female presented to the emergency department with right foot pain after being hit by a heavy falling object on 3 January 2023. Her medical history included type II diabetes mellitus, hypertension, and osteoporosis. She had a surgical history of cataract surgery. Moreover, she regularly received insulin aspart, amlodipine, metformin, atorvastatin, alfacalcidol, calcium carbonate, and denosumab (a total of seven injections, administered every 6 months, with the last dose received in September 2023). The patient was a nonsmoking housewife who lived independently and ambulated without assistance. Psychosocial history and genetic information in her family were irrelevant. The patient had no history of head trauma or loss of consciousness. Her weight, height, and BMI were 76 kg, 157 cm, and 30.83 cm, respectively.

Plain radiography revealed a fracture of the second metatarsal of the right foot (Fig. 1). Laboratory findings showed a normal lipid profile and renal function tests. Glycosylated hemoglobin (HbA1c) level was elevated at 8.7% (normal maximum: 5.75%), and the random blood sugar level was 239 mg/dl (normal: 80–140 mg/dl). A complete blood count analysis revealed a white blood cell count of 6.8×10^3 /µl (normal: $4–10 \times 10^3$ /µl), hemoglobin of 13.3 g/dl (normal: 13–17 g/dl), and a platelet count of 218×10^3/µl (normal: $150–400 \times 10^3$/µl). Calcium and 25-hydroxy vitamin D levels were within normal limits (2.2 mmol/l and 43 ng/ml, respectively). The last dual X-ray absorptiometry (DEXA) scan performed in February 2023 confirmed osteoporosis (the T-scores of the hip and spine were – 2.74 and – 2.2, respectively). The patient was treated conservatively with a posterior splint and instructed on weight-bearing as tolerated on the right lower extremity. On follow-up in the outpatient department, plain radiographs taken 17 days after the fracture showed large callus volume formation (Fig. 2), and the patient had no point tenderness at the fracture site. She initiated partial weight-bearing with a walker frame without medical advice and discontinued the posterior splint use on her own accord. Radiographs obtained 2 months postfracture (Fig. 3A) showed a stable fracture with no evidence of remodeling. Radiographs at 9 months after the fracture (Fig. 3B) revealed no fracture line with initial signs of remodeling. Furthermore, plain follow-up radiographs obtained 1-year after the fracture (Fig. 4) demonstrated incomplete remodeling.

Discussion

Bone healing progresses through four stages: hemomata formation, inflammation[9], soft and hard callus formation, and remodeling[5]. When a vessel is disrupted at the fracture site, a hematoma forms, leading to innate immune system cell infiltration that then attract immune and mesenchymal stromal cells, triggering the inflammatory phase[5,10]. Fibrocartilage tissue covers the fracture area and offers initial support during the soft callus stage. Cartilaginous tissue undergoes maturation, hypertrophy, and mineralization, resulting in the formation of a hard callus composed of woven bone. Finally, remodeling replaces woven bone with lamellar bone for optimal strength[11,12].

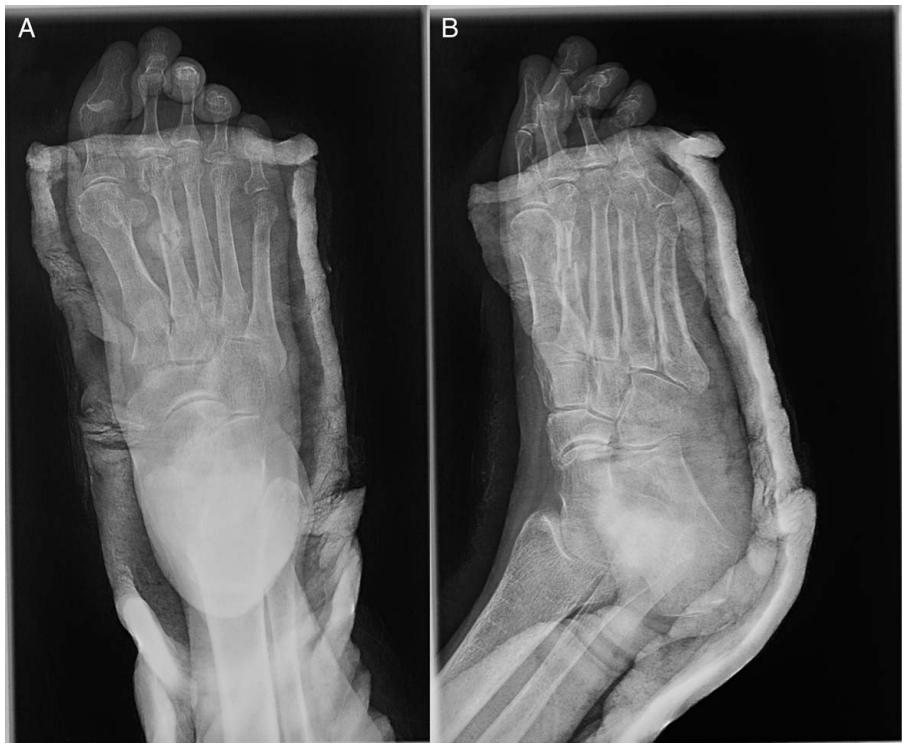

Figure 1. Plain radiographs of right foot AP (A) and oblique (B) day 0 of the fracture.

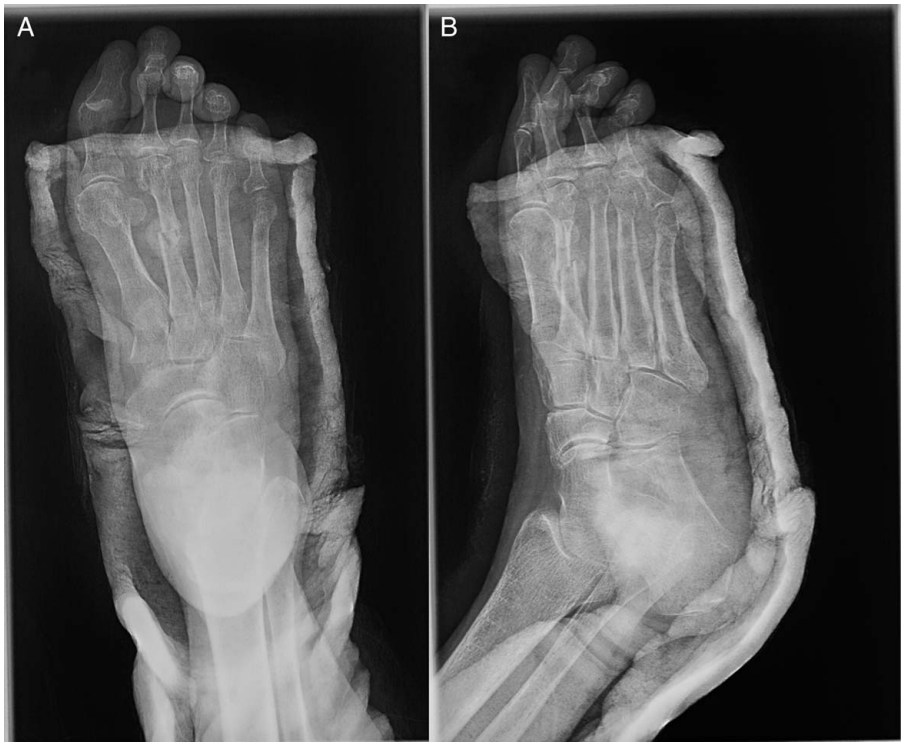

Figure 2. Plain radiographs of the right foot AP (A) and oblique (B) day 17 after the fracture.

Denosumab inhibits osteoclasts, both immature and mature, and suppresses osteoclastogenesis[5]. However, Gerstenfeld *et al.*[13]'s animal study demonstrated significantly greater callus strength in the denosumab group compared with alendronate and control groups. The antiosteoclastic actions of denosumab increase the volume and density of the callus, thereby improving its mechanical strength. In additional, it increases the torsional strength and load-bearing capacity of the callus by delaying callus remodeling[14]. This may explain the delay in radiological fracture remodeling with clinical improvement observed in our patient, despite her early ability to bear weight.

Our patient presented with several risk factors for impaired healing of metatarsal fractures. Cakir *et al.*[15] showed that being overweight, having diabetes mellitus, and being a female could negatively affect the healing outcomes of metatarsal fractures. However, despite all the risk factors, healing occurred in our patient's case within a short time, which suggests a high efficacy of denosumab in promoting fracture healing 4 months after administration. Tetsunaga *et al.*[16] analyzed the pain relief effect of denosumab in fresh osteoporotic vertebral fractures and found rapid pain relief, suggesting faster fracture stabilization with favorable short-term outcomes. Similarly, our patient reported no point tenderness at the fracture site 17 days after the event. A previous randomized clinical trial supports our findings. It showed that denosumab at a dose of 60 mg every 6 months did not impede fracture healing or cause complications even if taken at or before the time of the fracture[1].

While a prior study suggested some recovery of remodeling biomarkers in denosumab-treated patients 4 months after injection, another study reported remodeling suppression by approximately 70% at 6 months compared with alendronate[17]. In the present case, callus remodeling remained delayed even at the one-year follow-up mark. Although the 4-month interval between fracture and the last denosumab dose might have allowed some remodeling, the subsequent dose (2 months after the fracture) likely exerted its expected inhibitory effect. Given the patient's lack of side effects, complete clinical stability of the fracture, and the potential risk of rebound osteoporosis upon discontinuation, we decided not to postpone the next dose of denosumab[18]. The patient did not receive any additional interventions, such as biophysical modalities (e.g. electromagnetic field therapy or low-intensity pulsed ultrasonography)[19,20], or systemic medications, such as teriparatide, which have shown promise in promoting fracture healing[21]. We plan to follow-up this patient with radiographic evaluations every 3 months to document remodeling progression and determine the timeframe for its completion in denosumab-treated patients.

This is the first reported case of denosumab's effect on metatarsal fracture healing in an older adult with osteoporosis and multiple risk factors that highly impair fracture healing, considering the 4-month interval between the last denosumab dose and the fracture. While radiographic remodeling remained minimal throughout the 1-year follow-up, a single case report cannot definitively attribute rapid healing to denosumab. However, when considered alongside previous clinical and experimental studies, this case strengthens the rationale for further investigation. Future levels 1 and 2 studies are warranted to explore the effects of denosumab on fresh limb fracture healing, the long-term remodeling process after fracture with extended

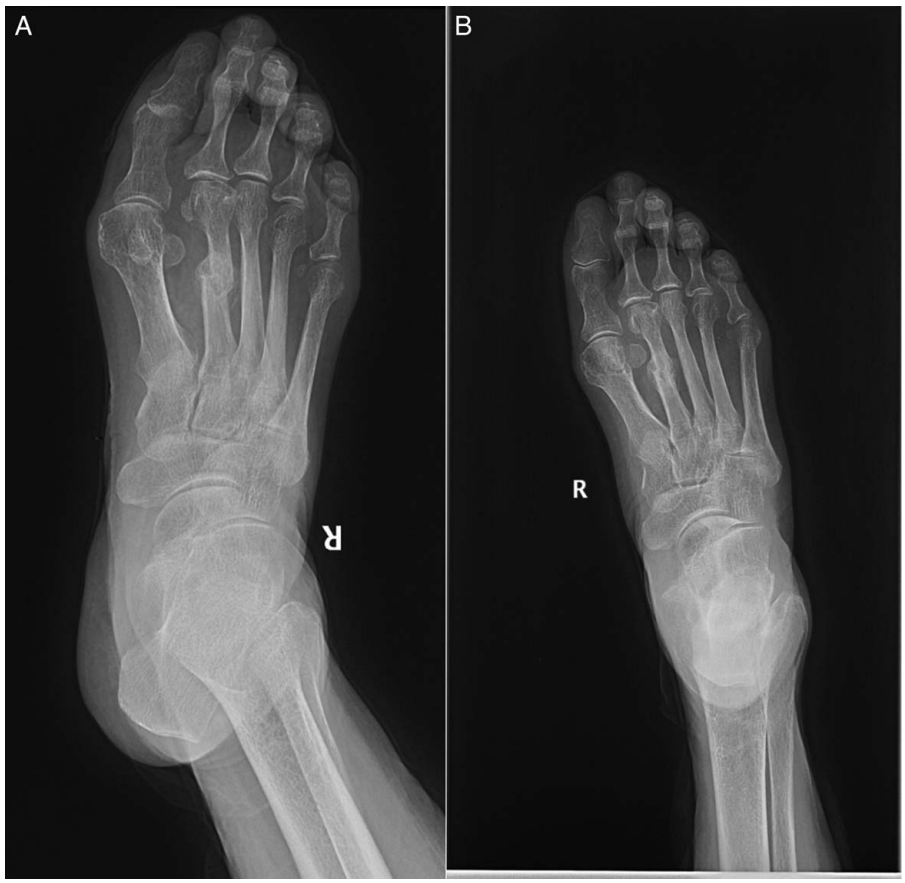

Figure 3. Plain radiographs of the right foot 2 months (A) and nine months (B) after the fracture.

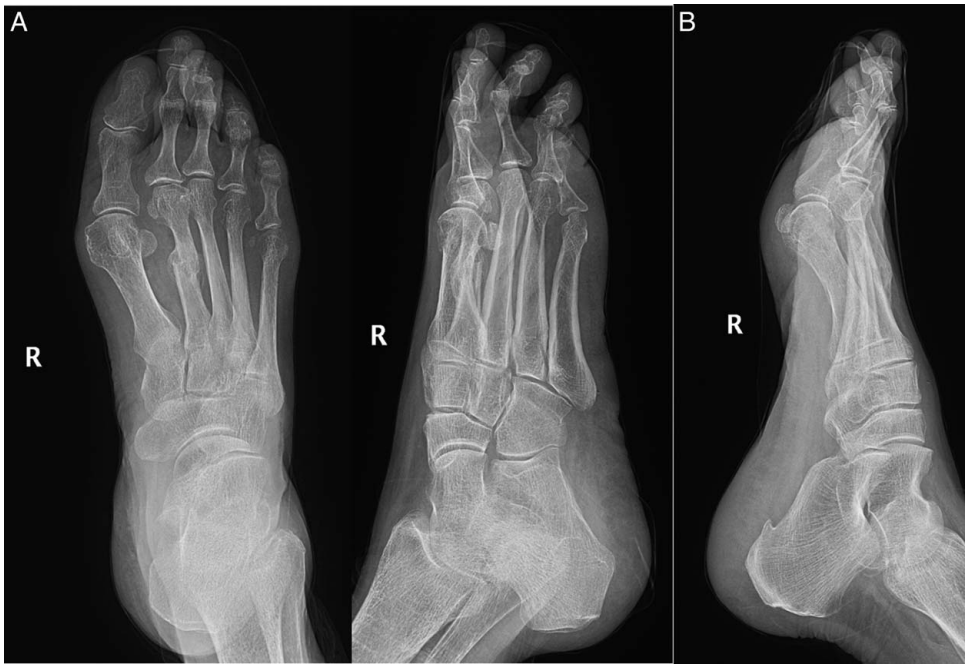

Figure 4. Plain radiographs of the right foot AP (A), oblique (middle), and lateral (B) 12 months after the fracture.

follow-up, and functional outcomes when administered at the standard 60 mg dose every 6 months.

Conclusion

This case suggests that denosumab at the usual dose (60 mg every 6 months) may be beneficial for metatarsal fracture healing, although it appears to delay remodeling. Further studies are needed to confirm the efficacy of denosumab in the treatment of metatarsal fractures.

Ethical approval

Ethical approval for this study was provided by the Health Education and Training Administration (Qassim Health), Kingdom of Saudi Arabia, Registration Number: H-04-Q-001 on 19 of February 2024. Ethics approval code: 607/45/11386.

Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of the journal.

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Author contribution

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