Trauma Case Reports 51 (2024) 101005

Contents lists available at ScienceDirect

Trauma Case Reports

journal homepage: www.elsevier.com/locate/tcr

Case Report

Successful treatment of atypical femoral fracture with autogenous bone grafting in a patient on denosumab for bone metastasis from breast cancer: A case report

Taiki Yasukawa [a,b], Sang Yang Lee [b,c,*], Hiro Hasegawa [a,b], Koki Tsuchiya [b], Toshiyuki Shirahata [b], Makoto Yoshimura [a,b], Yoshifumi Kudo [b]

[a] Department of Orthopedic Surgery, Takatsu General Hospital, 1-16-7 Mizonokuchi, Kawasaki-ku, Kanagawa, Japan
[b] Department of Orthopedic Surgery, Showa University School of Medicine, 1-5-8 Hatano-dai, Shinagawa-ku, Tokyo, Japan
[c] Department of Orthopedic Surgery, Keijinkai Shiroyama Hospital, 1 Iizuka-cho, Ota city, Gunma, Japan

ARTICLE INFO

Keywords:
Atypical femoral fracture
Bone metastasis
Denosumab
Bone graft

ABSTRACT

Atypical femoral fractures (AFFs) occur with minor trauma and are believed to be a potential complication of the prolonged use of antiresorptive agents, such as bisphosphonate and denosumab, for the treatment of bone metastasis. In comparison with typical femoral fractures, AFFs have a higher incidence of complications, including implant failure and delayed union or nonunion. This report describes the case of a 42-year-old woman who developed denosumab-associated AFF after denosumab therapy for bone metastasis from breast cancer. Surgical treatment with IMN was performed after open anatomical reduction. To reduce the risk of delayed union and nonunion, the autogenous bone graft obtained from the iliac crest was conducted. The radiograph taken 5 weeks after surgery showed callus formation. Full weight bearing was allowed 3 months after surgery. Six months postoperatively, radiographs and computed tomography images demonstrated bone union. Twelve months after surgery, the patient was able to walk easily without pain. For cancer patients with bone metastasis whose life expectancy may be limited, a decline in physical activity can be fatal. Consequently, it is crucial to avoid a decrease in activities of daily living brought about by delayed union or nonunion. In this regard, autogenous bone grafting is a viable and effective technique for the treatment of AFFs in patients with bone metastases.

Introduction

Atypical femoral fractures (AFF) can occur with minor trauma and are considered as a potential complication of the long-term use of antiresorptive agents, such as bisphosphonate (BP) and denosumab. Denosumab, an inhibitor of the receptor activator of nuclear factor-κß ligand (RANKL), is primarily used for osteoporosis treatment [1]. Although the pathogenesis of AFF has not been fully elucidated, the long-term administration of antiresorptive agents is known to drastically suppress bone turnover, contributing to the development of AFF.

Bone-modifying agents (BMAs), such as BP and denosumab, are used not only to treat osteoporosis but also to reduce the frequency

* Corresponding author at: Department of Orthopedic Surgery, Keijinkai Shiroyama Hospital, 1 Iizuka-cho, Ota city, Gunma 373-0817, Japan.
E-mail address: sangyang@beige.plala.or.jp (S.Y. Lee).

https://doi.org/10.1016/j.tcr.2024.101005
Accepted 30 March 2024
Available online 1 April 2024

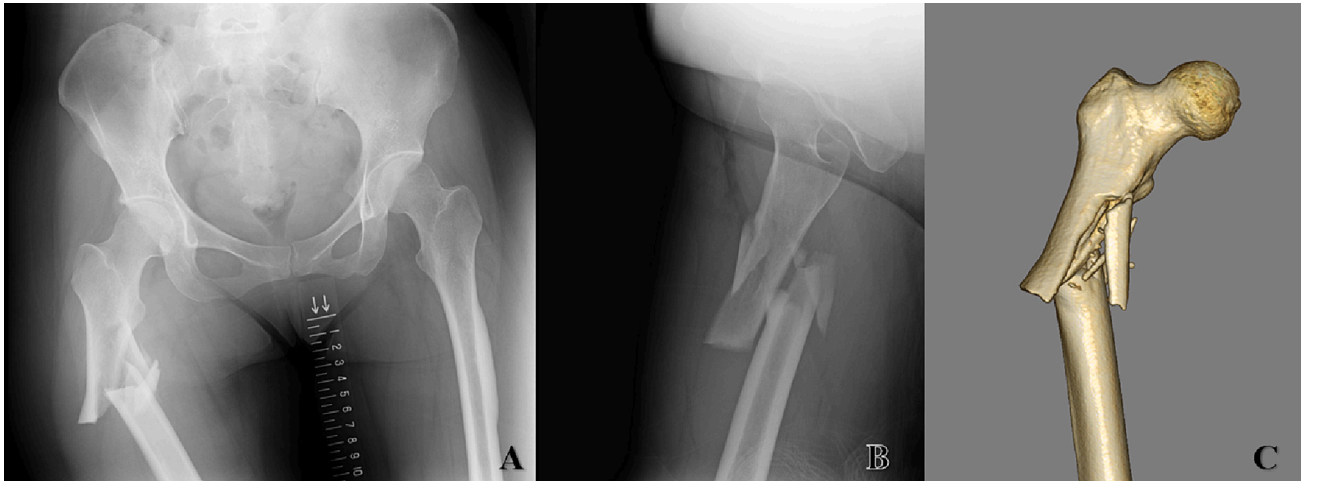

Fig. 1. **(A)** Anteroposterior (AP) and **(B)** lateral radiographs and a **(C)** three-dimensional (3D) computed tomography (CT) image demonstrate a complete subtrochanteric fracture of the right femur, extending through both cortices with a medial spike, accompanied by thickening of the lateral cortex.

and severity of skeletal-related events (SRE), including pathological fractures and spinal cord compression, in cancer patients with bone metastasis [2]. With recent advances in chemotherapy, the prognosis of cancer patients, particularly those with distant metastases, has been improving. As a result, the occurrence of bone metastasis and associated SREs is on the rise, and long-term BMA use is expected to increase in patients at risk of developing AFF [2].

In comparison with typical or osteoporotic femoral fractures, AFFs have been associated with a higher incidence of complications, including implant failure and delayed union or non-union [1,3]. In patients with a high risk of delayed union or nonunion, bone grafts are often used to promote bone union and decrease the risk of revision surgery [4]. Here, we present a case of denosumab-associated AFF in a patient with breast cancer-related bone metastasis that was successfully treated with autogenous bone grafting and intramedullary nailing (IMN).

Case summary

A 42-year-old woman, with a medical history of bone metastasis in the lumbar vertebrae from breast cancer, was admitted to our hospital due to pain in the right thigh. She fell down from a standing position at home. Three months prior to the fall, she began experiencing mild pain in her right thigh. Nine years ago, the patient was diagnosed with breast cancer and treated with hormone therapy. She was administered denosumab injections at a monthly dose of 12 mg for seven years. Radiography showed a complete subtrochanteric fracture of the right femur, which extended through both cortices with a medial spike, accompanied by thickening of the lateral cortex (Fig. 1). Considering the long-term use of denosumab and imaging findings [1], she was diagnosed with AFF.

Following an open anatomical reduction, surgical treatment using IMN was performed. Autogenous bone grafting was conducted to reduce the risk of delayed union and nonunion. After harvesting cortical and cancellous bone from the iliac crest, the cortical bone was crushed into small pieces and mixed with the cancellous bone. A mixed bone graft was then inserted into the fracture site (Fig. 2). The postoperative course was uneventful. Denosumab administration was resumed a month after the operation. As the radiograph taken 5 weeks post-surgery demonstrated callus formation, partial weight-bearing on the right leg was permitted (Fig. 3). Full weight bearing was allowed, 3 months post-surgery. Six months post-surgery, radiographs and computed tomography (CT) images demonstrated bone union (Fig. 4). The patient was able to walk freely without pain, 12 months postoperatively.

Discussion

Compared with typical femoral fractures, AFFs are known to have a higher rate of complications, including implant failure and delayed union or nonunion. Delayed union is characteristic of AFF and one of the minor features of the AFF definition [1]. Shane et al. [1] reported that 26 % of AFF cases exhibited nonunion or prolonged bone union. Moreover, Weil et al. [3] found that only 54 % of 17 AFFs healed without necessitating secondary procedures, such as nail dynamization and revision surgery. In a multicenter review of 179 patients with AFFs, 12 % required revision surgery [5]. Healing time is increased for AFF, with an average postoperative time to union of 7.3 (range, 2–31) months in a meta-analysis of 833 AFFs [6]. Possible reasons for the higher rates of delayed union or nonunion in AFF include altered biological activity and high mechanical stress in the fractured region. In cancer patients with bone metastasis, BMAs are used for preventing SREs. In this context, BMA dosing is typically higher, more frequent, and more prolonged than that for osteoporosis. Consequently, BMAs are likely to exert a greater impact on AFF and may cause greater risks of delayed union or nonunion. Fukui et al. [2] reported that in cancer patients with AFF, 35 % of the cases resulted in nonunion with an average time to union of 15.1 (range, 3–30) months.

For cancer patients with bone metastasis, in whom life expectancy may be limited and a decline in physical performance can be

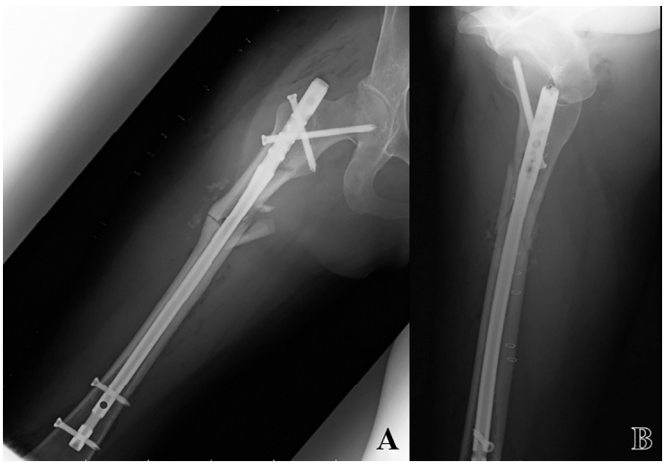

Fig. 2. (A) Anteroposterior (AP) and **(B)** lateral radiographs of the right femur immediately after intramedullary nail fixation with autogenous bone grafting.

Fig. 3. **(A)** Anteroposterior (AP) and **(B)** lateral radiographs taken 5 after surgery show a callus fomation focusing on bone graft.

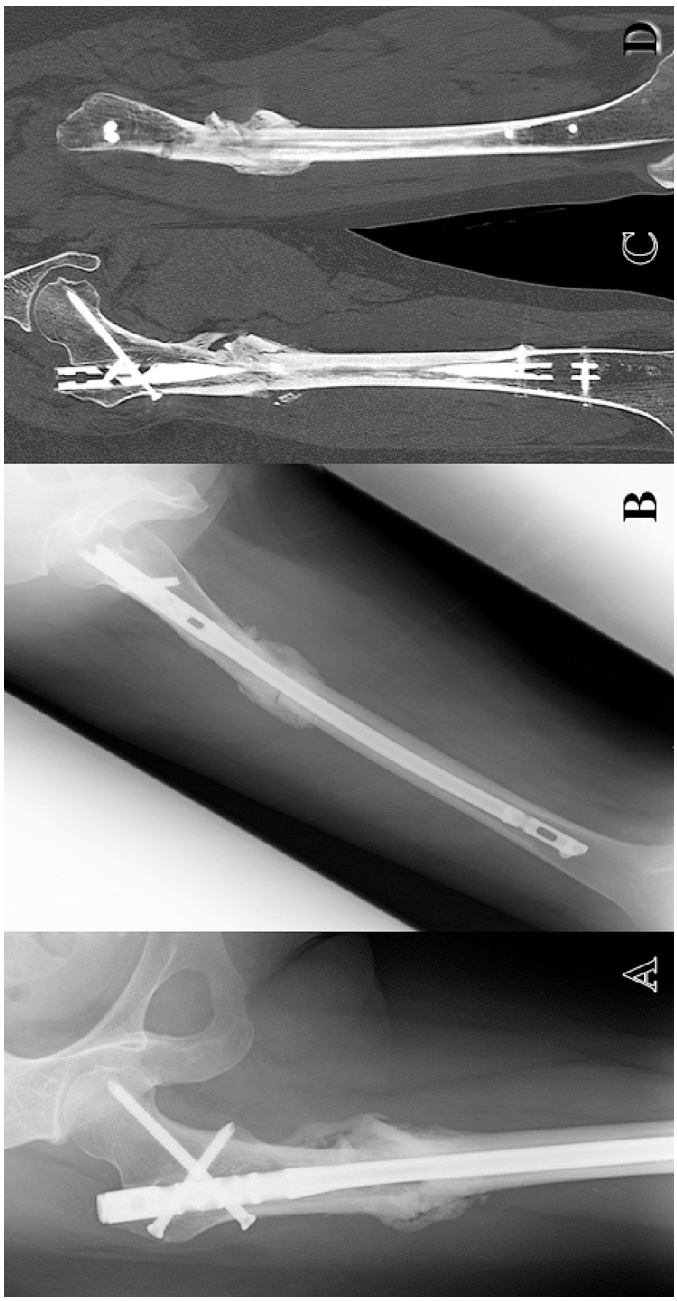

Fig. 4. **(A)** Anteroposterior (AP) and **(B)** lateral radiographs and **(C)** coronal and **(D)** sagittal computed tomography (CT) images taken 6 months after surgery show bone union.

fatal, a decrease in activities of daily living due to delayed union or nonunion should be avoided, and a more reliable treatment option should be considered. Strong fixation and good reduction are essential for bone union. IMN is the gold standard for the operative fixation of complete AFFs. In the present case, we performed IMN after open anatomical reduction. The administration of teriparatide, an anabolic agent used for osteoporosis treatment, has been found to improve bone healing and reduce time to union in AFFs [7]. However, teriparatide is contraindicated in cancer patients with bone metastasis. To facilitate bone union and diminish the need for revision surgery, we performed autogenous bone grafting after IMN in the current case. To date, the efficacy of bone grafting for AFF remains unclear. In nine cases of AFF nonunion, bone healing was achieved with bone grafting and double plating, with an average time to union of 14 (range, 7–32) months [8]. Some studies have recommended the use of bone marrow grafting during the primary fixation of fresh AFF. Iwasaki et al. [9] reported a case of incomplete AFF that was successfully treated with bone marrow transplantation and IMN. Bone union was achieved at 7 months postoperatively. Lovy et al. [10] reported that the injection of bone marrow aspirate concentrate (BMAC) from the iliac crest into the fracture site after IMN significantly reduced the time to union compared to controls (3.5 versus 6.8 months, $p < 0.001$). The union rate, 1 year post-surgery, in the BMAC group was 100 %, whereas that in the control group was 77 %. Because bone grafts contain osteogenic, osteoinductive, and osteoconductive properties, three essential components for fracture healing, bone grafting may alter impaired local bone biology and increase biological activity in the AFF.

This case report had several limitations. First, since bone biopsy was not performed, the possibility exists that the fracture may be due to bone metastasis. However, based on the presence of major AFF features and clinical history, we concluded that the patient was diagnosed with an AFF. Second, as this was a case report, the true validity of bone grafting could not be assessed. Bone union could have been achieved without bone grafting, as there was no negative control. Future efforts involving a larger number of cases and comparative studies employing groups without bone grafting are needed to confirm the validity of bone grafting for AFF.

Conclusion

We report a case of AFF associated with denosumab therapy in a patient with bone metastasis from breast cancer, in whom bone union was successfully achieved through autogenous bone grafting. Autogenous bone grafting is a useful and effective technique for the treatment of AFF.

Informed consent

The patient has provided written informed consent to publish the case report.

Funding

None.

CRediT authorship contribution statement

Taiki Yasukawa: Data curation, Writing – original draft, Writing – review & editing. **Sang Yang Lee:** Writing – review & editing, Investigation, Methodology. **Hiro Hasegawa:** Writing – review & editing. **Koki Tsuchiya:** Writing – review & editing. **Toshiyuki Shirahata:** Writing – review & editing. **Makoto Yoshimura:** Data curation, Methodology, Writing – review & editing. **Yoshifumi Kudo:** Writing – review & editing.

Declaration of competing interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] E. Shane, D. Burr, P.R. Ebeling, et al., Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research, J. Bone Miner. Res. 25 (2010) 2267–2294.
[2] T. Fukui, K. Oe, T. Kawamoto, et al., Multicenter study on atypical femoral fractures in patients with bone metastases taking bone- modifying agents, J. Bone Oncol. 40 (2023) 100478.
[3] Y.A. Weil, G. Rivkin, O. Safran, M. Liebergall, A.J. Foldes, The outcome of surgically treated femur fractures associated with long-term bisphosphonate use, J. Trauma 71 (2011) 186–190.
[4] A.L. Jones, R.W. Bucholz, M.J. Bosse, et al., Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects. A randomized, controlled trial, J Bone Joint Surg Am. 88 (2006) 1431–1441.
[5] Y. Bogdan, P. Tornetta III, T.A. Einhorn, et al., Healing time and complications in operatively treated atypical femur fractures associated with bisphosphonate use: a multicenter retrospective cohort, J. Orthop. Trauma 30 (2016) 177–181.
[6] A. Koh, E. Guerado, P.V. Giannoudis, Atypical femoral fractures related to bisphosphonate treatment: issues and controversies related to their surgical management, Bone Joint J. 99–B (2017) 295–302.
[7] N. Miyakoshi, T. Aizawa, S. Sasaki, et al., Healing of bisphosphonate-associated atypical femoral fractures in patients with osteoporosis: a comparison between treatment with and without teriparatide, J. Bone Miner. Metab. 33 (2015) 553–559.

[8] M.T. Nagy, G. Pydisetty, T.A. Kwaees, K. Saldanha, Outcome of revision surgery for bisphosphonate related subtrochanteric fracture non-union following failed intramedullary nailing, Injury 52 (2021) 582–588.
[9] R. Iwasaki, M. Sakamoto, T. Rokkaku, et al., Intramedullary nail fixation with autologous bone marrow transplantation in an incomplete atypical femoral fracture patient: use of bone marrow extracted from the hollow reamer, Case Rep. Orthop. 2020 (2020) 2878651.
[10] A.J. Lovy, J.S. Kim, J. Di Capua, et al., Intramedullary nail fixation of atypical femur fractures with bone marrow aspirate concentrate leads to faster union: a case-control study, J. Orthop. Trauma 31 (2017) 358–362.