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Case report

Atypical femoral fracture in a multiple myeloma patient undergoing treatment with denosumab: A case report and literature review

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ABSTRACT

Introduction and importance: Denosumab is a new standard treatment for bone disease caused by multiple myeloma. There are a few reports of atypical femoral fracture in patients with multiple myeloma, all of which were associated with long-term use of bisphosphonate. Here, we report the first case of denosumab-induced atypical femoral fracture in a patient with multiple myeloma.

Case presentation: A 71-year-old woman with multiple myeloma developed dull pain in her right thigh 8 months after restarting high-dose denosumab following its initial administration for 4 months and subsequent withdrawal for 2 years. Fourteen months later, complete atypical femoral fracture occurred. Osteosynthesis was achieved using an intramedullary nail and she was switched to oral bisphosphonate 7 months after cessation of denosumab. There was no exacerbation of the multiple myeloma. Bone union was achieved and she recovered to her pre-injury level of activities. The oncological outcome was alive with disease at 2 years after surgery.

Clinical discussion: Prodromal symptoms such as thigh pain and radiographical finding of thickening of the lateral cortex in the subtrochanteric region of the femur were attributed to denosumab-induced atypical femoral fracture in the case. A unique aspect of this case worth highlighting is that the fracture occurred after short-term denosumab use. This may be associated with multiple myeloma or other medication including dexamethasone and cyclophosphamide.

Conclusion: Atypical femoral fracture may occur in patients with multiple myeloma who receive denosumab, even for a short period. Attending physicians should be cognizant of the early symptoms and signs of this fracture.

1. Introduction

Multiple myeloma (MM) is a clonal plasma cell malignancy that accounts for slightly >10 % of all hematologic cancers [1]. MM manifests as skeletal-related events (SREs), such as lytic lesions and osteopenia, and is often associated with severe bone pain, pathological fracture, vertebral collapse, and spinal cord compression. Bisphosphonates are generally effective in preventing SREs [2], but the risk of atypical femoral fracture (AFF) is increases significantly with a longer duration of bisphosphonate treatment [3].

Denosumab is a fully human IgG2 class monoclonal antibody to RANKL (receptor activator of nuclear factor-kappa B ligand) and inhibits bone resorption [4]. A recent study demonstrated that denosumab was non-inferior to zoledronic acid in delaying the time to first SRE in patients with MM and achieved longer progression-free survival [5]. The International Myeloma Working Group (IMWG) recommends denosumab for the treatment of newly diagnosed MM (grade A recommendation) and relapsed or refractory MM with evidence of MM-related bone disease (grade B recommendation) [6]. Denosumab has now become one of the gold standard treatments for SREs in MM.

The incidence of AFF is thought to be extremely low when denosumab 60 mg is administered subcutaneously at 6-monthly intervals for osteoporosis [7]. However, patients with bone metastases or MM receive subcutaneous denosumab 120 mg monthly, and there have been recent reports of AFF occurring in patients with bone metastasis receiving denosumab [8,9].

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Here, we report the first case of denosumab-induced AFF in a patient with MM and the treatment strategy. This report follows the SCARE criteria [10].

2. Presentation of case

The patient was a woman who had been diagnosed with MM at the age of 71 years. Bortezomib and dexamethasone therapy was started, with addition of cyclophosphamide (BCd) after a drug eruption caused by lenalidomide. BCd was also effective, and the disease remained stable. She had been receiving denosumab 120 mg at approximately 1-month intervals for 4 months and daily vitamin D to prevent hypocalcemia after the diagnosis of MM. Subcutaneous denosumab administration was selected in the case because it was more convenient than intravenous zoledronic acid, an alternative bone-modifying agent.

Eight months after restarting denosumab following 2 years of withdrawal due to dental treatment, she developed dull pain in her right thigh and was referred to a department of orthopedic surgery at her local hospital at age 74 years. Radiographs revealed localized thickening of the lateral cortex in the subtrochanteric region of the right femur (Fig. 1a), but the images were interpreted as normal and she was misdiagnosed with lumbar radiculopathy due to lumbar spinal canal stenosis. Seven months later, she underwent bone scintigraphy to examine osteonecrosis of the jaw. It showed ^{99m}Tc uptake in the subtrochanteric region of the right femur (Fig. 1b), which was not investigated further. She also underwent radiographs of the femur at a nearby general internist at the same time, which were also interpreted as normal (Fig. 1c). Monthly administration of denosumab was continued.

At age 75 years (approximately 15 months after onset of pain in the right thigh and 22 months after restarting denosumab), she developed severe pain in the right thigh after low-energy trauma sustained when she tripped over a step. Radiographs revealed a short oblique fracture in the subtrochanteric region of the right femur (Fig. 1d), and she was referred to our department. AFF was diagnosed based on the clinical course and radiological findings and was treated surgically by internal fixation using an antegrade long intramedullary nail (Zimmer Natural Nail) with mini-open reduction via a lateral approach at the fracture level (Fig. 2a). Pathological examination of femoral intramedullary tissue obtained intraoperatively during the reaming procedure detected some viable myeloma cells (Fig. 2b). Denosumab was discontinued after surgery. In postoperative treatment, 1 week of non-weightbearing was followed by approximately 10 weeks of partial weightbearing with double crutches during walking. Gradually, full weightbearing during walking was achieved and crutches were removed. Follow-up radiographs showed good bone formation, and bone union was achieved 7 months after surgery (Fig. 2c). Thereafter, she was started on monthly oral bisphosphonate therapy (minodronate 50 mg) to attenuate the rebound effect of discontinuation of denosumab. The postoperative course was uneventful and she recovered to her pre-injury activities of daily living. BCd therapy was resumed 3 months after surgery. There was no exacerbation of MM and the oncological outcome was alive with disease, with good lower extremity function and an International Society of Limb Salvage score of 96.7 % at 2 years after surgery (Fig. 2d).

3. Discussion

This is the first report of denosumab-induced AFF in a patient with MM. AFF is relatively rare in patients with MM and there have been only 9 reports of AFF in patients with MM to our knowledge (Table 1) [11–19]. These reports include 16 cases of AFF in 10 patients (4 unilateral, 6 bilateral). All cases had prodromal symptoms, such as thigh or hip pain. Long-term bisphosphonates were used in all cases and for a median duration of 9.5 years. Surgery was performed in 15 of the 16 cases. A few reports mention bone union as evident union in 2 fractures [17], insufficient callus formation in 1 [12] and non-union in 1 [13].

There have been two reviews on the incidence of denosumab-induced AFF [8,9]. Yang et al. reported that clinical AFF had an incidence rate of 0.4 % (1/253), and that the incidence of atypical femoral stress reaction based on imaging review was 4.5 % in patients receiving denosumab 120 mg for multiple bone metastases (3/66) [9]. Takahashi et al. reported that the incidence of AFF-related events was 1.8 % (5/277) in patients receiving denosumab 120 mg monthly for bone metastases and identified long-term denosumab and previous treatment with zoledronic acid as risk factors for AFF [8].

Our case has several features in common with bisphosphonate-induced AFF in MM. However, the duration of drug treatment in our case (total of 4.2 years after starting denosumab, 22 months after restarting denosumab) was shorter than the median administration period reported for bisphosphonate-induced AFFs in MM cases [11–19]. The circulatory half-life of denosumab is approximately 26 days, suggesting that the effect of denosumab had disappeared while denosumab was withdrawn for 2 years in our case. Computed tomography images taken during denosumab withdrawal also showed no findings of localized thickening of the right femur (Fig. 3). This indicates that the radiological findings appeared 8 months after denosumab administration and the complete fracture occurred at 22 months after denosumab administration. Takahashi et al. reported 5 cases of AFF in patients who had been treated with denosumab for bone metastases with a mean of 40 doses (range, 15–47 doses) for a mean of 3.6 years (range, 2–4 years) [8]. It should be noted that monthly high-dose denosumab appears to cause AFF even within a short period.

AFF is a stress or insufficient fractures [8,9]. Continuous loading of

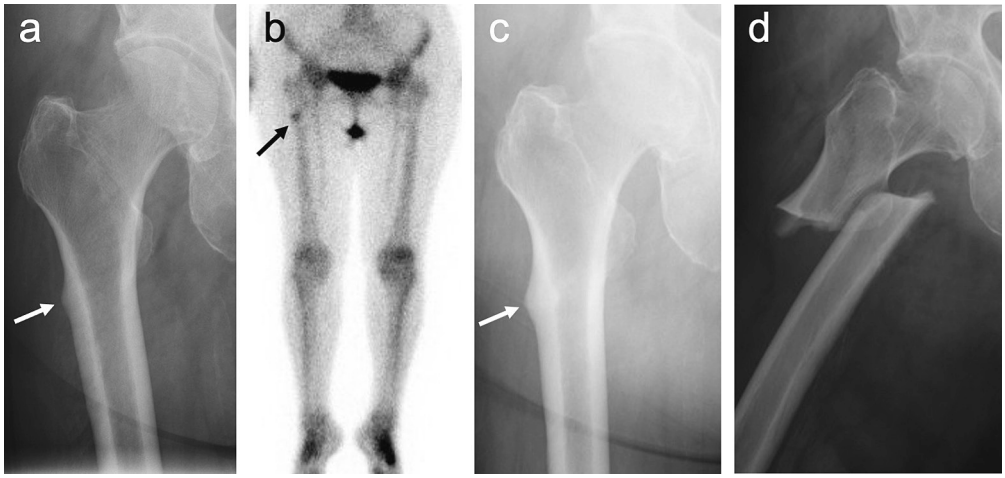

Fig. 1. (a) Anteroposterior radiographs of the right femur 8 months after restarting denosumab showing localized thickening of the lateral cortex in the subtrochanteric region (white arrow). (b) A bone scintigraphy scan showing uptake of ^{99m}Tc in the subtrochanteric region of the right femur (black arrow). (c) Fifteen months after restarting denosumab, localized thickening of the lateral cortex is expanding (white arrow). (d) Antero-posterior radiographs of the right femur after low-energy trauma showing a short oblique fracture and medial spike in the subtrochanteric region.

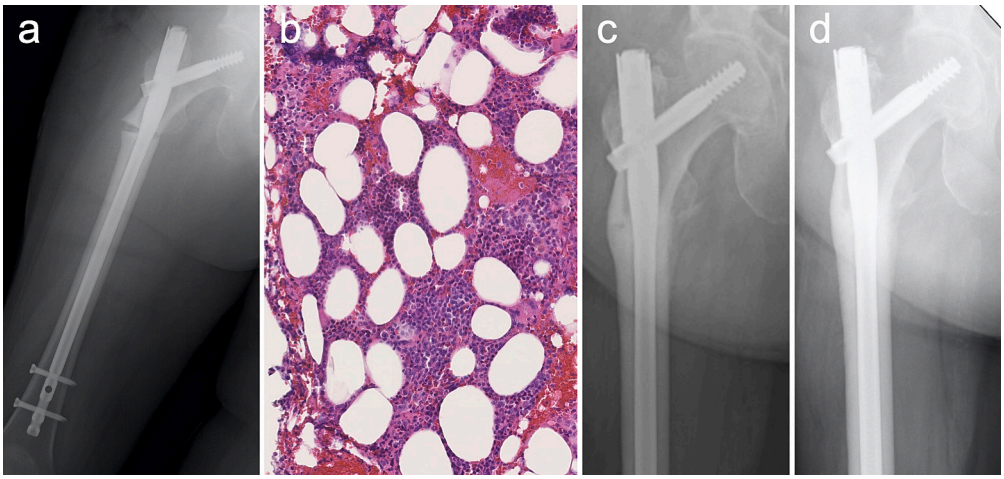

Fig. 2. (a) Anteroposterior radiographs of the right femur after internal fixation of the fracture with an antegrade long intramedullary nail. (b) Pathological examinationof femoral intramedullary tissue detected some viable myeloma cells (hematoxylin-eosin staining). (c) Bone union achieved 7 months after surgery. (d) Plain radiograph at final follow-up, 2 years after surgery.

Table 1
Summaries of previously reported cases of atypical femoral fracture in multiple myeloma.

Case	Sex	Age (y)	Side	Fracture type	Prodromal symptoms	Duration of BPs / Dmab	Number of drug doses	Treatment	Duration of bone union
Wernecke et al. (2008) [11]	M	72	Bilateral						
			Right	Incomplete	Thigh/groin pain	6.6 y (ZOL), 5 y (PMD)	N/A	THA	N/A
			Left	Complete	Thigh pain	6 y (ZOL), 5 y (PMD)	N/A	BHP	N/A
Grasko et al. (2009) [12]	M	57	Left	Complete	Thigh pain	7 y (PMD), 3 y (ZOL)	88 (47 PMD, 41 ZOL)	IM	Callus formation, fractured nail (1 y)
Napoli et al. (2010) [13]	F	56	Left	Complete	Hip pain	2 y (PMD), 4 y (ZOL)	N/A	IM	Non-union (6 mo)
Puhaindran et al. (2011) [14]	F	64	Bilateral						
			Right	Complete	Thigh pain	9 y (PMD)	58 (PMD)	IM	N/A
			Left	Incomplete	Thigh pain	9 y (PMD)	58 (PMD)	Prophylactic IM	N/A
Ward et al. (2012) [15]	M	79	Right	Incomplete	Hip/thigh pain	10 y (ZOL, PMD)	N/A	Prophylactic IM	N/A
Chang et al. (2012) [16]	N/A	N/A	Bilateral						
			Right	Complete	N/A	(PMD or ZOL)	N/A	Operative repair	N/A
			Left	Complete	N/A	(PMD or ZOL)	N/A	Operative repair	N/A
	N/A	N/A	Bilateral						
			Right	Complete	N/A	(PMD or ZOL)	N/A	Operative repair	N/A
			Left	Complete	N/A	(PMD or ZOL)	N/A	Operative repair	N/A
Tonogai et al. (2014) [17]	F	53	Bilateral Right	Complete	Thigh pain	6 y (INC), 2 y (ZOL)	78 (70 INC, 8 ZOL)	IM	Bone union (4 mo)
		56	Left	Complete	Thigh pain	6 y (INC), 5 y (ZOL)	90 (70 INC, 20 ZOL)	IM	Bone union (4 mo)
Chen et al. (2018) [18]	F	54	Left	Incomplete	N/A	10 y (ALD), 0.6 y (RSN)	N/A	Conservative treatment	No progression (3 y)
Chiu et al. (2020) [19]	F	73	Bilateral						
			Right	Incomplete	Thigh pain	5 y (ZOL)	N/A	Prophylactic IM	N/A
			Left	Incomplete	Thigh pain	5 y (ZOL)	N/A	Prophylactic IM	N/A
Our case	F	75	Right	Complete	Thigh pain	4.2 y (Dmab)	25 (Dmab)	IM	Bone union (7 mo)

M, male; F, female; y, year; N/A, not available; ZOL, zoledronate; PMD, pamidronate; INC, incadronate; ALD, alendronate; RSN, risedronate; BPs, bisphosphonate; Dmab, denosumab; THA, total hip arthroplasty; BHP, bipolar hemiarthroplasty; IM, intramedullary nailing; mo, month.

the legs may form microcracks in cortical bone with bone remodeling reduced by denosumab, eventually leading to fracture. In bone metabolism, the RANK/RANKL pathway is a primary signaling cascade regulating osteoclast maturation and activation [4]. Osteoprotegerin (OPG) secreted by osteoblasts, bone marrow stromal cells, and osteocytes antagonizes the interaction between RANK and RANKL. Myeloma cells degrade OPG, but denosumab mimics the effect of endogenous OPG and inhibits bone resorption. In basic research, the combination of dexamethasone and zoledronic acid was shown to nearly abolish intracortical remodeling but not to suppress the toughness [20], and long-term administration of cyclophosphamide induced bone loss by inhibiting the differentiation of pre-osteoblasts and reducing bone formation [21]. On the other hand, proteasome inhibitor did enhance fracture repair by increasing the number and proliferation of mesenchymal progenitor/stem cells to osteoblasts [22]. Thus, any potential interactions between denosumab and other agents are fairly complicated

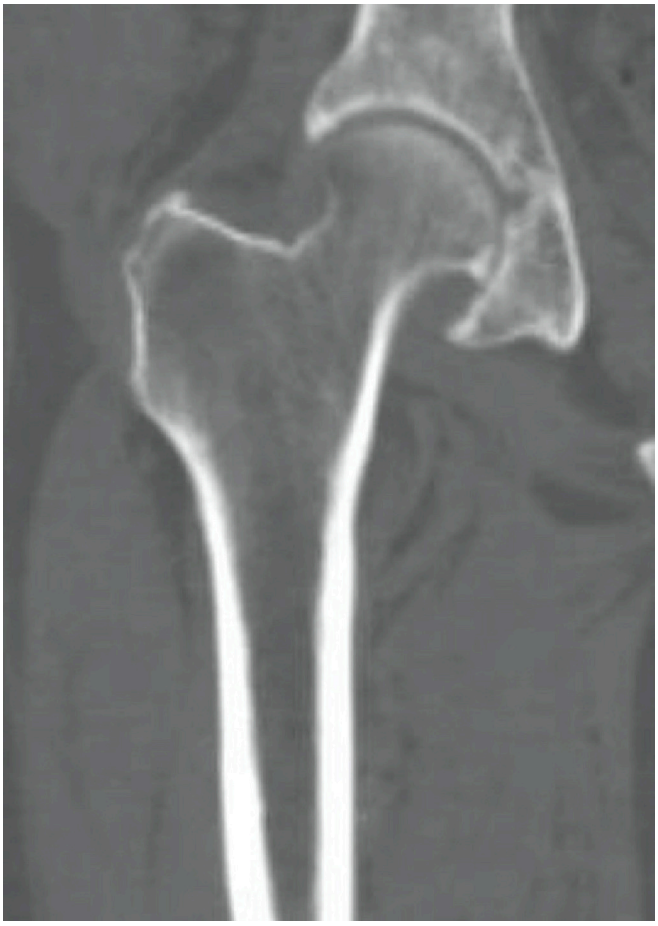

Fig. 3. Computed tomography images of the right femur during denosumab withdrawal indicating no findings of localized thickening of the lateral cortex.

in this case.

The current consensus is that AFF should be treated by surgical fixation, cessation of bisphosphonate and denosumab, and administration of calcium, vitamin D, and teriparatide, which is often not available in MM [23]. Minor features of AFF include a focal periosteal reaction in the lateral cortex and prodromal symptoms such as pain in the groin or thigh [23]. Bone scintigraphy should be effective for detecting incomplete AFF, and this was also true in our case. The most frequently reported complications in patients with AFF are non-union, delayed union, and implant failure [12]. It is important to recognize the imaging findings and prodromal symptoms of AFF and detect incomplete AFF early before the onset of a complete fracture.

The duration of denosumab for MM is controversial. Based on osteoporosis research, the European Calcified Tissue Society reported that discontinuation of denosumab was associated with rapid bone loss and increased risk of vertebral fractures and that bisphosphonate therapy should be considered to reduce or prevent a rebound increase in bone turnover after discontinuation of denosumab. However, there are currently no data on patients with MM who have discontinued denosumab [4]. In our patient, pathological examination revealed some viable myeloma cells in the tissue reamed at the fracture site. The MM was controlled by anticancer agents but it was not clear whether it would be safe to discontinue denosumab in view of the increased risk of SREs and rebound in bone turnover. Therefore, discontinuation of denosumab was a very difficult decision. Among patients with denosumab-induced AFF in the literature, 4 discontinued and 2 resumed denosumab administration. One randomized clinical trial showed a low occurrence rate of the AFF (<0.1 %) in patients treated with the monoclonal anti-sclerostin antibody romosozumab [24]. There is controversy regarding how to choose and utilize bone-modifying agents after diagnosis and surgical procedure of AFF, and this is a limitation of this paper. The IMWG advises that discontinuation of denosumab can be considered after 24 months of treatment only if the patient achieves a partial response or better with antimyeloma treatment (grade D recommendation) [6]. The IMWG also suggests that a single intravenous dose of zoledronic acid should be administered within 6 months if discontinuation of denosumab is necessary [6]. Further research on discontinuation of denosumab in patients with MM is needed.

4. Conclusion

This is the first report of denosumab-induced AFF in MM that was successfully treated by surgery and switching to an oral bisphosphonate 7 months after cessation of denosumab. However, it is important for physicians involved in the treatment of patients with MM to intervene before a complete fracture occurs. If typical symptoms or radiological findings appear, irrespective of the disease for which short-term denosumab was prescribed, atypical femoral fracture should be suspected.

Abbreviations

AFF	atypical femoral fracture
BCd	Bortezomib and cyclophosphamide and dexamethasone
IMWG	International Myeloma Working Group
MM	multiple myeloma
OPG	osteoprotegerin
RANKL	receptor activator of nuclear factor-kappa B ligand
SREs	skeletal-related events

CRediT authorship contribution statement

YO contributed to data curation, formal analysis, writing – original graft. ST contributed to conceptualization, supervision, writing – review and editing. MA, TH, TN interpreted the clinical data and revised the manuscript critically for important content. KS contributed to supervision. All authors have reviewed and approved the final manuscript.

Registration of research studies

1. Name of the registry: No
2. Unique identifying number or registration ID: No
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): No

Guarantor

Shunichi Toki.

Ethics approval and consent to participate

Informed consent was obtained from the patient according to the protocol approved by The Ethics Committee of Tokushima University Hospital (11000161), Tokushima, Japan on 25th January 2021.

Consent for publication

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

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Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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