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Case Report

Atypical femoral fracture in a metastatic bone disease patient six months after discontinuation of denosumab received sequentially to previous bisphosphonate therapy - A case report

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Abstract

Although, both bisphosphonates and denosumab are effective in reducing the risk of skeletal-related events in patients with metastatic bone disease, many concerns were being raised about the possible association between their use and atypical femoral fractures. A case of an atypical femoral fracture in a metastatic bone disease patient, six months after discontinuation of long-term zoledronic acid therapy and sequential treatment with denosumab is reported. After extensive laboratory and imaging examination, the fracture was classified as atypical and it was finally treated with discontinuation of denosumab, long cephalomedullary interlocking nailing and vitamin D administration. Sequential treatment with bisphosphonates and denosumab in patients with metastatic bone disease, may lead to an overlapping treatment effect, increasing bone suppression and the risk of atypical femoral fracture. In addition, discontinuation of denosumab may activate bone remodeling units in an area with microdamage accumulation in cortical bone caused by the previous bone suppression from the antiresorptive treatment. The activation of bone remodeling units may accelerate the occurrence of the atypical femoral fractures.

Keywords: Atypical Femoral Fracture, Bisphosphonates, Denosumab, Metastatic Bone Disease, Zoledronic Acid

Introduction

Bisphosphonates (BPs) and denosumab are commonly used in patients with metastatic bone disease (MBD) to reduce the risk of skeletal-related events (SRE) like pathological fractures, spinal cord compression, and hypercalcemia of malignancy[1,2]. However, many concerns were being raised about the possible association between prolonged and high-dose of both BPs and denosumab for MBD and atypical femoral fractures (AFFs)[3-7]. We present a case of an AFF in a MBD patient six months after discontinuation of an eleven-months oncologic dose denosumab administration which was received sequentially to a long-term zoledronic acid therapy.

Case presentation

In March 2020, a 76-year-old woman with a past medical history of MBD from breast cancer presented to the

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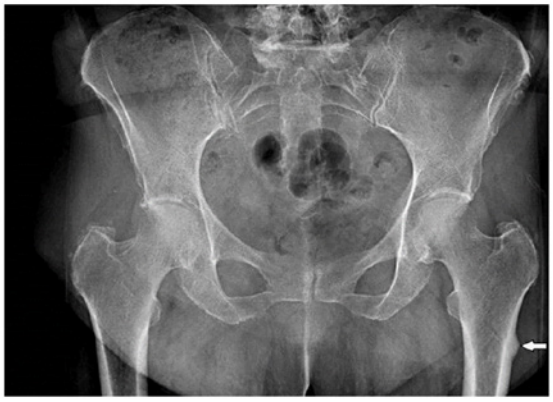


Figure 1. Anteroposterior radiograph of both femurs performed one month before the occurrence of the complete AFF showing a localized periosteal thickening in the lateral cortex of the left femur (arrow).

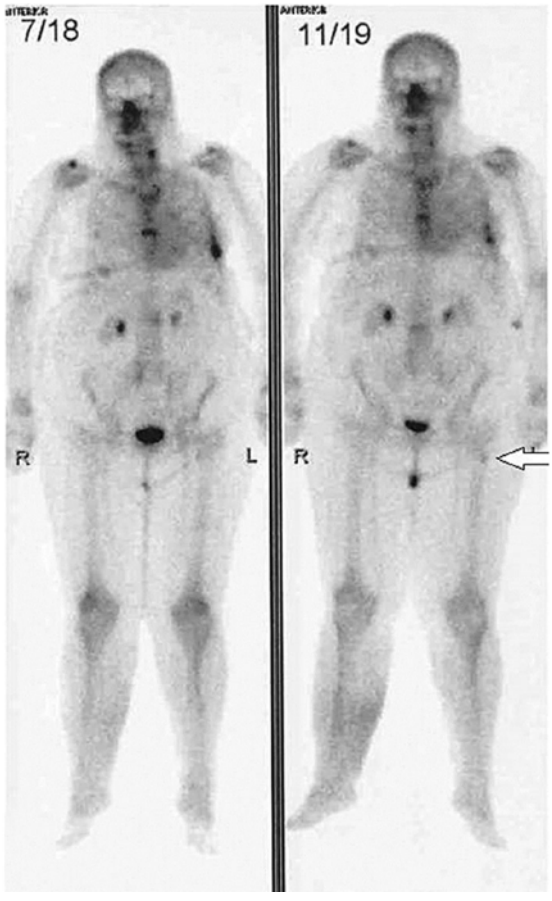


Figure 2. The three-phase bone scintigraphy obtained after eleven doses of denosumab showing increased tracer uptake in the lateral aspect of the proximal femur (arrow), while the three-phase bone scintigraphy obtained before the initiation of denosumab was negative.

emergency department of our hospital with a spontaneous left femur fracture. The breast cancer was diagnosed in 1985 and treated with partial mastectomy, chemotherapy and hormonotherapy with Tamoxifen for five years. In 1997 the patient underwent total mastectomy due to local recurrence of the cancer and she was administered chemotherapy and hormonotherapy with Tamoxifen for another five years. Bone metastases were found in January 2012 and she received zoledronic acid (4 mg monthly) until April 2015 when she presented acute renal failure. She continued receiving zoledronic acid in lower dose (5 mg every two months) until October 2018 when BPs were switched to denosumab in oncologic dose (120 mg monthly) due to MBD recurrence. She received eleven doses of denosumab until September 2019 when she underwent hysterectomy with the suspicion of endometrial cancer. Although the histopathology was negative, she presented serious wound infection. Additionally, the patient was suffered from diabetes mellitus and psoriatic arthritis.

Upon her arrival at the emergency department, she reported that was experienced continuous pain in her left thigh, for a period of eight months. Although an initial frontal radiograph of the left hip showed localized thickening of the lateral cortex in the subtrochanteric region of the left femur, the examination was misinterpreted as normal (Figure 1). Moreover, bone scan obtained in November 2019, two months since the patient discontinued denosumab, showed increased tracer uptake at the subtrochanteric area, while the previous bone scan obtained in July 2018 was negative (Figure 2).

The recent serial hip radiographs revealed a complete non-comminuted transverse subtrochanteric fracture at the left femur with focal lateral cortical thickening and a small medial spike (Figure 3), while radiographs at the contralateral femur were negative. At the time of fracture, the following blood test results were found: urine (47mg/dl, normal range 10-50 mg/dl), creatinine (0,9 mg/dl, normal range 0,5-1,5 mg/dl), alkaline phosphatase (52 U/L normal range 25-130 U/L), blood calcium (8,2 mg/dl, normal range 8,2-10,4 mg/dl), blood phosphate (2,5 mg/dl, normal range 2,5-4,5 md/dl) and parathyroid hormone (69 pg/ml, normal range 15-69 pg/ml) were in normal ranges, while 25-hydroxy-vitamin D level was low (12,6 ng/ml, normal range 20-40 ng/ml). No bone turnover markers obtained at the time of fracture or at any point during the course of the patient. Patient underwent DXA scan only twice in her life, the first one five years before and the second one nine months after AFF, with normal BMD values.

Multidetector computed tomography (MDCT) of pelvis and femurs was performed for exclusion of a MBD fracture. The MDCT scan demonstrated imaging features suggesting stress fracture such as complete transverse fracture line at the subtrochanteric region of left femur with focal lateral cortical thickening of the shaft, no aggressive periosteal reaction, no endosteal scalloping or soft tissue mass (Figures 4a-b).

Long cephalomedullary interlocking nailing was performed and histopathology showed no evidence of malignancy. The

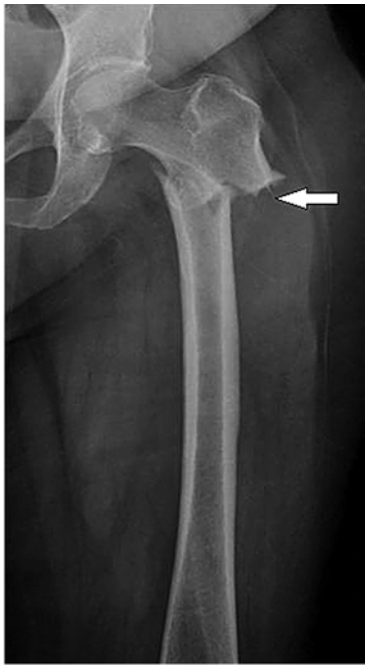
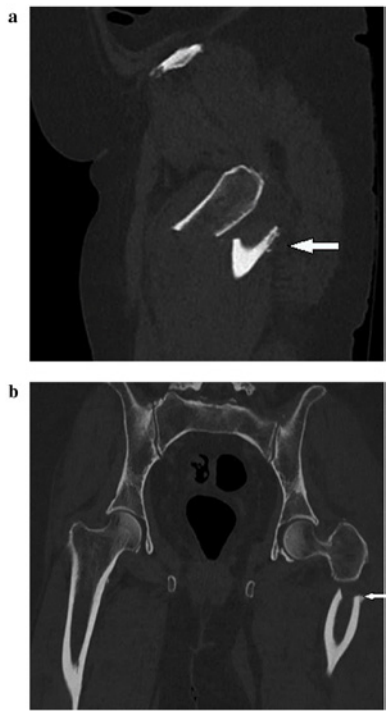


Figure 3. Anteroposterior radiograph of left femur shows a non-comminuted transverse subtrochanteric fracture with lateral cortical hypertrophy and medial spiking. Note the generalized increase in lateral cortical thickness (arrow).



Figures 4. Sagittal and coronal MDCT scan of the left femur revealed a non-comminuted transverse subtrochanteric fracture with localized periosteal thickening in the lateral cortex (arrow).

fracture healed in a normal time period of 5 months with callus formation (Figure 5). Postoperatively, vitamin D was commenced. Denosumab was given again in oncologic dose 120 mg monthly, six months after the fracture occurrence in order to prevent SRE and since there was no evidence of AFF in the contralateral femur.

Discussion

BPs given in high doses, usually at frequent of monthly interval, intravenously or orally, seemed to delay the time of first SRE and to decrease the incidence of SRE[1]. Oncologic dosing of denosumab comparing with BPs in MBD patients was proved to reduce the risk and to delay the time of the first SRE even more[2]. Despite the proven efficacy of both BPs and denosumab in preventing SRE, their use in long-term, high-doses and sequential manner in MBD patients is reported to be associated with increased risk for AFFs[3-7].

The American Society for Bone and Mineral Research (ASBMR) task force described major and minor defining features of AFF[8]. Our case had all of the major features: the location was the subtrochanteric region, the fracture was transverse with a small medial spike, there was no trauma, there was no comminution, and there was a focal periosteal reaction of the lateral cortex. Regarding the minor features, there was generalized lateral cortical thickening and

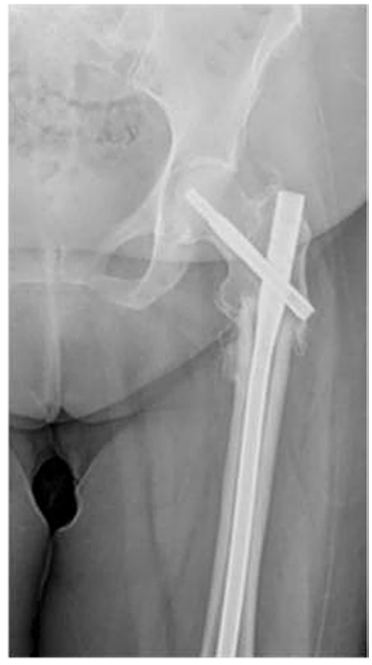


Figure 5. Anteroposterior radiograph of left femur 5 months after the operation, showing healing of the fracture with callus formation.

prodromal pain, but not bilaterality.

Pathological fractures are excluded from ASBMR definition for AFF[8]. In the setting of complicated patients with advanced cancer, AFF may be confused with a pathological fracture. First of all, it should be noted that cortical bone metastases are very rare. Secondary, additional cross-sectional imaging with MDCT or MRI should be used for the distinction of pathological fractures from the insufficiency fractures like AFF[9]. MDCT scan in our case revealed features such as focal callus formation and endosteal thickening around a fracture site which are suggestive of a stress fracture. It didn't reveal features like aggressive periosteal reaction, bone marrow pattern of destruction, endosteal scalloping, mineralized matrix and a large soft tissue mass which are present in pathological fractures. Additionally, histopathology of tissues obtained during surgery showed no evidence of malignancy.

The current consensus is that AFFs are stress or insufficiency fractures that develop over time[8]. Since, antiresorptive agents like BPs and denosumab inhibit osteoclast function[10,11], (osteoclast inhibitors) and cause a reduction of bone turnover, long-term use or high doses are associated with an altered bone structure and biomechanics. Microcracks within femoral lateral cortex are not adequately repaired due to severely bone suppression, accumulate and over the time these can precipitate a fracture. Moreover, BPs and denosumab inhibit osteoclast function through different pharmacological pathways and BPs are retained in bone for several months to years[10,11]. Sequential treatment with BPs and denosumab might lead to an overlapping treatment effect and increased bone suspension, due to the addition of the effect of denosumab on the residual BPs effect. A multi-center retrospective study found that the incidence rate of AFF was 1.8% among 277 cancer patients who had received monthly denosumab treatment[7]. In the same study long-term denosumab treatment and prior zoledronic acid treatment were identified as risk factors for the development of AFF. Our patient was treated sequentially with zoledronic acid and denosumab in high doses for more than 8 years. Major limitations in the supporting of the overlapping effect in the present patient are the lack of BMD values, bone turnover markers and histological indexes of bone turnover at the end of both zoledronic and denosumab treatments.

On the other hand it is well documented that discontinuation of denosumab therapy may be followed by rebound-associated vertebral fractures in a period of 3 to 12 months due to the synergy of rapid bone resorption and accelerated microdamage accumulation in trabecular bone[12]. In the same way, the activation of bone remodeling units at the time of loss of denosumab effect, in an area with microdamage accumulation due to failure of microdamage repair in cortical bone caused by the previous bone suppression from the antiresorptive treatment, may accelerate the occurrence of the AFFs. Again, major limitations in the supporting of this hypothesis in the present patient are the lack of bone turnover markers values as well as the lack of histological indexes of bone turnover and microdamage accumulation. In our case, denosumab was given monthly for eleven doses sequentially after a long-term BPs therapy and it was discontinued for six months before complete AFF occurred due to serious wound infection after hysterectomy although wound infection is not an indication for denosumab discontinuation. The rebound phenomenon six months after denosumab discontinuation was not mitigated from zoledronic acid retained to bones because its effect was decreased seventeen months after its discontinuation. Moreover, in a period of eight months before AFF occurrence, patient continued to walk bearing full weight although she experienced pain in the left thigh.

In addition, stress concentration on the lateral cortex of the femur especially in curved femur is considered to be possible contributing factor[13-16]. Multiple other factors associated with deterioration of bone quality such as certain medications use (glucocorticoids, proton pump inhibitors)[17,18], certain comorbid conditions (diabetes, rheumatoid arthritis and other autoimmune diseases)[16,18], and conditions with impaired mineralization caused by osteomalacia or vitamin D deficiency[8], are considered as risk factors for AFF. Our patient presented diabetes mellitus, psoriatic arthritis and vitamin D deficiency.

The presence of prodromic symptoms and subclinical imaging changes in the lateral femoral cortex should be assessed among patients with MBD treated with BPs or denosumab[4,7]. In our case, the incomplete AFF went unrecognized despite the thigh pain lasting for eight months and the focal cortical thickening along the lateral cortex of the proximal femur until it proceeded to a complete AFF.

Static intramedullary nailing is the first-line treatment for AFF in patients with MBD. Although, stopping of denosumab or BPs therapy, as well as the prescribing of calcium and vitamin D are mandatory in order to avoid AFF bilaterally and to improve the fracture healing, they must be accurately weighted in patients with MBD. Moreover, teriparatide treatment although found to reduce the time to union of AFFs treated with intramedullary nails[9], is unsuitable for patients with MBD.

Conclusions

In conclusion, sequential treatment with zoledronic acid and denosumab in patients with MBD leads to an overlapping treatment effect and increases bone suspension, due to the addition of the effect of denosumab on the residual bisphosphonates effect, increasing the risk of AFF. Additionally, discontinuation of denosumab may activate bone remodeling units at the time of loss of its effect in an area with microdamage accumulation, due to failure of microdamage repair in cortical bone caused by the previous bone suppression from the antiresorptive treatment and may accelerate the occurrence of the AFF.

Ethics approval and consent to participate

Institutional Review Board of Asclepieion Voulas General Hospital approved the case report presentation.

Consent for publication

Informed consent was given by the patient.

Authors' contributions

George F. Georgiadis was responsible for the design, collection of data and writing of the manuscript, Alexia P. Balanika evaluated the radiological findings, Alexandros E. Vasilakis operated and followed the patient, Dimitrios G. Begkas collected clinical data and participated in the design and revision of the manuscript, Christos S. Baltas participated in radiological data analysis, and Alexandros P. Pastroudis coordinated the manuscript.

References

1. Van Acker HH, Anguille S, Willemen Y, Smits EL, Van Tendeloo VF. Bisphosphonates for cancer treatment: mechanisms of action and lessons from clinical trials. Pharmacol Ther 2016;158:24-40.
2. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, Richardson GE, Siena S, Maroto P, Clemens M, Bilynskyy B, Charu V, Beuzeboc P, Rader M, Viniegra M, Saad F, Ke C, Braun A, Jun S. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomized, phase 3 trials. Eur J Cancer 2012;48(16):3082-92.
3. Edwards BJ, Sun M, West DP, Guindani M, Lin YH, Lu H, Hu M, Barcenas C, Bird J, Feng C, Saraykar S, Tripathy D, Hortobagyi GN, Gagel R, Murphy WA Jr. Incidence of atypical femur fractures in cancer patients: the MD Anderson Cancer Center experience. J Bone Miner Res 2016;31(8):1569-76.
4. Puhaindran ME, Farooki A, Steensma MR, Hameed M, Healey JH, Boland PJ. Atypical subtrochanteric femoral fractures in patients with skeletal malignant involvement treated with intravenous bisphosphonates. J Bone Jt Surg Am 2011;93(13):1235-42.
5. Chang ST, Tenforde AS, Grimsrud CD, O'Ryan FS, Gonzalez JR, Baer DM, Chandra M, Lo JC. Atypical femur fractures among breast cancer and multiple myeloma patients receiving intravenous bisphosphonate therapy. Bone 2012;51(3):524-27.
6. Yang SP, Kim TWB, Boland PJ, Farooki A. Retrospective review of atypical femoral fracture in metastatic Bone disease patients receiving Denosumab therapy. Oncologist 2017;22(4):438-44.
7. Takahashi M, Ozaki Y, Kizawa R, Masuda J, Sakamaki K, Kinowaki K, Umezu T, Kondoh C, Tanabe Y, Tamura N, Miura Y, Shigekawa T, Kawabata H, Baba N, Iguchi H, Takano T. Atypical femoral fracture in patients with bone metastasis receiving denosumab therapy: a retrospective study and systematic review. BMC Cancer 2019;19(1):980-90.
8. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling PR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Howe TS, van der Meulen MC, Weinstein RS, Whyte MP. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2014;29(1):1-23.
9. Fayad LM, Kamel IR, Kawamoto S, Blumke DA, Frassica FJ, Fishman EK. Distinguishing stress fractures from pathologic fractures: A multimodality approach. Skeletal Radiol 2005;34(5):245-59.
10. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 2008;19(6):733-59.
11. Dempster DW, Lambing CL, Kostenuik PJ, Grauer A. A Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: a review of preclinical and clinical data. Clin Ther 2012;34(3):521-36.
12. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JEB, McClung M, Roux C, Torring O, Valter I, Wang AT, Brown JP. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM Trial and its extension. J Bone Miner Res 2018;33(2):190-98.
13. Yoo H, Cho Y, Park Y, Ha S. Lateral femoral bowing and the location of atypical femoral fractures. Hip Pelvis 2017;29(2):127-32.
14. Mahjoub Z, Jean S, Leclerc JT, Brown JP, Boulet D, Pelet S, Grondin C, Dumont J, Belzile EL, Michou L. Incidence and characteristics of atypical femoral fractures: clinical and geometrical data. J Bone Miner Res 2016;31(4):767-76.
15. Hagen JE, Miller AN, Ott SM, Gardner M, Morshed S, Jeray K, Alton T, Ren D, Abblit WP, Krieg JC. Association of atypical femoral fractures with bisphosphonate use by patients with varus hip geometry. J Bone Joint Surg Am 2014;96(22):1905- 9.
16. Lim SJ, Yeo I, Yoon PW, Yoo JJ, Rhyu KH, Han SB, Lee WS, Song JH, Min BW, Park YS.Incidence, risk factors, and fracture healing of atypical femoral fractures: a multicenter case-control study. Osteoporos Int 2018;29(11):2427-35.
17. Koh JH, Myong JP, Yoo J, Lim YW, Lee J, Kwok SK, Park SH, Ju JH. Predisposing factors associated with atypical femur fracture among postmenopausal Korean women receiving bisphosphonate therapy: 8 years' experience in a single center. Osteoporos Int 2017;28(11):3251-59.
18. Kim D, Sung YK, Cho SK, Han M, Kim YS. Factors associated with atypical femoral fracture. Rheumatol Int 2016;36(1):65-71.
19. Yeh WL, Su CY, Chang CW, Chen CH, Fu TS, Chen LH, Lin TY. Surgical outcome of atypical subtrochanteric and femoral fracture related to bisphosphonates use in osteoporotic patients with or without teriparatide treatment. BMC Musculoskelet Disord 2017;18(1):527.