

## CASE REPORT

# Bisphosphonate-related atypical insufficiency fracture of the tibial plateau : A case report

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**Abstract : Objective :** Only a few cases of insufficiency fractures of the tibial plateau following bisphosphonate use have been reported. The authors report a case with bisphosphonate (BP) -related atypical insufficiency fracture of tibial plateau, which developed delayed union. **Patient :** A 65-year-old Japanese woman presented with left knee pain without any trauma. She had a 5-year history of risedronate use for primary osteoporosis. Initial X-rays were unremarkable, but magnetic resonance imaging (MRI) confirmed an insufficiency fracture at the left tibial plateau at 3 weeks after the initial visit. Risedronate treatment was stopped because we diagnosed her with a BP-related atypical insufficiency fracture of the tibial plateau. She was treated with rest, a lateral wedge insole and protective weight-bearing with a T-cane for 3 months. **Result :** At 3-month follow-up, the patient still had a pain and a delayed healing on radiographs. Six months later, X-rays showed that the fracture site had a sclerotic change, but MRI revealed delayed union. At 8-month follow-up, the fracture was healed without any symptoms. **Conclusion :** All clinicians need to be aware of the delayed healing of atypical insufficiency fracture related with prolonged BP use. *J. Med. Invest.* 68 : 186-188, February, 2021

**Keywords :** Atypical fracture, Bisphosphonate, Insufficiency fracture, Osteoporosis, Tibial plateau

## INTRODUCTION

Osteoporosis is characterized by lower bone mass and deterioration of the microarchitecture of bone tissue, leading to bone fragility and a consequent increase in fracture risk (1). An association between long-term use of the anti-bone resorptive agent bisphosphonate (BP) and atypical subtrochanteric or diaphyseal insufficiency fractures of the femur has been well documented (2, 3). BP-related atypical insufficiency fractures usually have a delayed healing. Here, we report a case with a delayed healing of insufficiency tibial plateau fracture associated with 5-year risedronate use. The patient gave consent for data concerning this case to be submitted for publication.

## CASE PRESENTATION

A 65-year-old Japanese female presented with a sudden onset of pain in the left knee without any trauma. Her knee pain worsened on standing from sitting and walking. The patient visited our clinic the day after onset. Her body weight, height and body mass index was 47.5 kg, 150.5 cm and 20.8, respectively. She had no history of metabolic disease except primary osteoporosis. She had been treated with oral weekly risedronate (17.5 mg) for five years for osteoporosis. Dual-energy X-ray absorptiometry (DXA) was performed at lumbar vertebrae before BP treatment was started and again at three and five years after initiating treatment. T scores at the lumbar vertebrae (L2-4) improved from -4.0 at the beginning of treatment to -3.4 at three years and -2.9 at five years after treatment. Physical examination revealed mild

tenderness over the medial proximal tibia. Range of motion of the left knee was limited from 0° extension to 100° flexion. Antero-posterior radiographs of the left knee demonstrated an almost normal appearance (Fig. 1A). She was prescribed analgesics (celecoxib 200 mg/day) and a lateral wedge insole for the medial knee pain. However, two weeks after the initial visit the pain worsened and she had difficulty walking. Magnetic resonance imaging (MRI) was performed a week later and demonstrated extra-articular, proximal metaphyseal linear signal changes on T1- and T2- weighted images and surrounding marrow edema and reactive changes on short-tau inversion recovery (STIR) images (Figs. 2A and 2B). Blood tests performed at the initial visit with knee pain revealed a  $\beta$ -CTx concentration of 0.195 pg/L and total P1NP of 32.5  $\mu$ g/L, suggesting low bone turnover. Finally, the patient was diagnosed with a BP-related atypical insufficiency fracture of the tibial plateau. Risedronate treatment was stopped after this diagnosis, and the patient started on daily vitamin K 45 mg and injection of elcatonin 10mg biweekly for 3 months, followed by eldcalcitol 0.75  $\mu$ g daily. In addition, rest, lateral wedge insole and protective weight-bearing with a T-cane, were continued for 3 months. One month after the initial visit, her left knee had a pain and mild swelling. X-rays demonstrated a sclerotic change over the proximal medial metaphyseal region of the tibia, as well as a breach in continuity of the lateral cortex of proximal tibia with no comminution and minimal overlap (Fig. 1B). At 3 months follow-up, knee pain was decreased but tenderness was over the lateral tibial plateau. She could walk without any support. X-rays demonstrated discontinuity of the lateral cortex, indicating delayed healing (Fig. 1C). At 6 months follow-up, the patient complaint a slight medial knee pain. Follow-up radiographs performed after six months showed healing of the fracture with sclerotic changes extending throughout the metaphyseal region from medial to lateral cortex (Fig. 1D), but MRI still revealed fracture lines and surrounding edema (Figs. 2C and 2D). At 8 months follow-up, radiographs demonstrated bone healing, and the patient had no pain or limitation in activities of daily living.

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Figure 1. Serial antero-posterior plain radiographs of the left knee at the initial visit (A), 1 month (B), 3 months (C), 6 months (D), and 8 months (E) after the initial visit.



Figure 2. T1 and short-tau inversion recovery (STIR)-weighted MRI coronal views of the left knee at 3 weeks (A and B) and 6 months (C and D) after the initial visit.

## DISCUSSION

Recently, several case series reported an association between long-term BP therapy and atypical proximal metaphyseal and diaphyseal femoral insufficiency fractures (2, 3). However, atypical fracture of the tibial plateau associated with long-term BP use is uncommon, with most cases reported to date being fractures of the tibial diaphysis (4, 5). Imbuldeniya reported on a Caucasian woman with bilateral atypical insufficiency fractures of the tibial plateau and a unilateral distal femoral fracture associated with long-term BP therapy (oral alendronate for 3 years and intravenous pamidronate for the following 6 years) (6). Although they did not mention delayed healing, they showed patient's symptoms lasting more than 6 months and image abnormalities for more than one year, suggesting a delayed union as same as in our case.

The first report of atypical femoral fractures (AFFs) was published in 2005 and described 9 cases of non-spinal fractures (7). BPs, a class of antiresorptive agents, are an analogue of

naturally occurring pyrophosphates. These nitrogen-containing compounds reduce the rate of bone resorption, increase bone mineral density, and improve trabecular connectivity by binding to bone surface. The resultant effect is improved bone strength and reduced risk of fracture (8). However, concerns have been raised over the past decade regarding the potential to over suppress bone turnover with long-term BP use, leading to atypical skeletal fragility (7, 9). Prolonged BP use has been suggested to cause accumulation of microdamage in bone, reduced heterogeneity of the organic matrix and mineral properties (10), increased levels of advanced glycation end products (11), and thereby promoting the deterioration of bone quality. Thus, AFFs have been considered as stress fractures caused by the suppression of remodeling, resulting from long term BP treatment (3).

Stress fractures of the medial tibial plateau are well known to be caused by repetitive mechanical stress in runners and in military personnel (12, 13). Other factors such as surgery for anterior cruciate ligament reconstruction (14) and unicompartmental knee arthroplasty (15, 16), drug-induced osteoporosis (17, 18), and even primary and postpartum osteoporosis without BP use (19, 20) can also cause these fractures. Generally, medial tibial plateau stress fractures can be managed conservatively simply by the cessation of sports activity, and symptoms usually resolve within two months (12, 13, 21). We treated this patient with a lateral wedge insole and protective weight-bearing with a T-cane, but this case had a concomitant lateral tibial plateau fracture, and further resulted in a delayed healing. In previous case report, they have prescribed knee supports even though it has been seven months after the initial symptoms. In such a BP-related atypical insufficiency fracture, early short-term casting and/or knee supporter might be considered to prevent delayed union and deformity of the fracture site. In addition, MRI-STIR images are the most useful investigative tool when the index of suspicion is high (21, 22). Since X-ray changes are quite subtle during the period of prodromal pain, we recommend using MRI to investigate patients treated long-term with BP.

In conclusion, the involvement of a non-femoral fracture site also suggests high risk for other weight-bearing bones following long-term BP therapy. Insufficiency fractures of the tibial plateau can occur in osteoporosis alone, but if it occurs during BP therapy, the risk of delayed union should be considered.

## CONFLICT OF INTEREST

All authors state that they have no conflicts of interest.

## REFERENCES

1. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser 843 : 1-129, 1996
2. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, 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* 29(1) : 1-23, 2014
3. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster D, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Koval K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Sen HT, van der Meulen MC, Weinstein RS, Whyte M : 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(11) : 2267-2294, 2010
4. Breglia MD, Carter JD : Atypical insufficiency fracture of the tibia associated with long-term bisphosphonate therapy. *J Clin Rheumatol* 16(2) : 76-78, 2010
5. Odvina CV, Levy S, Rao S, Zerwekh JE, Rao DS : Unusual mid-shaft fractures during long-term bisphosphonate therapy. *Clin Endocrinol (Oxf)* 72(2) : 161-168, 2010
6. Imbuldeniya AM, Jiwa N, Murphy JP : Bilateral atypical insufficiency fractures of the proximal tibia and a unilateral distal femoral fracture associated with long-term intravenous bisphosphonate therapy : a case report. *J Med Case Rep* 6 : 50, 2012
7. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY : Severely suppressed bone turnover : a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 90(3) : 1294-1301, 2005
8. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE : Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 348(9041) : 1535-41, 1996
9. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB : Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. *J Bone Miner Res* 15(4) : 613-620, 2000
10. Donnelly E, Meredith DS, Nguyen JT, Gladnick BP, Rebolledo BJ, Shaffer AD, Lorich DG, Lane JM, Boskey AL : Reduced cortical bone compositional heterogeneity with bisphosphonate treatment in postmenopausal women with intertrochanteric and subtrochanteric fractures. *J Bone Miner Res* 27(3) : 672-678, 2012
11. Saito M, Mori S, Mashiba T, Komatsubara S, Marumo K : Collagen maturity, glycation induced-pentosidine, and mineralization are increased following 3-year treatment with incadronate in dogs. *Osteoporos Int* 19(9) : 1343-54, 2008
12. Engber WD : Stress fractures of the medial tibial plateau. *J Bone Joint Surg Am* 59(6) : 767-769, 1977
13. Harolds JA : Fatigue fractures of the medial tibial plateau. *South Med J* 74(5) : 578-581, 1981
14. Delcogliano A, Chiossi S, Caporaso A, Franzese S, Menghi A : Tibial plateau fracture after arthroscopic anterior cruciate ligament reconstruction. *Arthroscopy* 17(4) : E16, 2001
15. Brumby SA, Carrington R, Zayontz S, Reish T, Scott RD : Tibial plateau stress fracture : a complication of unicompartmental knee arthroplasty using 4 guide pinholes. *J Arthroplasty* 18(6) : 809-812, 2003
16. Yang KY, Yeo SJ, Lo NN : Stress fracture of the medial tibial plateau after minimally invasive unicompartmental knee arthroplasty : a report of 2 cases. *J Arthroplasty* 18(6) : 801-803, 2003
17. Ishimaru D, Sumi H : A Case of an Insufficiency Fracture of the Medial Proximal Tibia Secondary to Osteomalacia Associated with Long-Term Saccharated Ferric Oxide Administration. *Case Rep Orthop* : 1675654, 2017
18. Meier L, van Tuyll van Sersooskerken AM, Liberton E, Kleijn L, Westgeest T, Polak M, de Nijs R : Fractures of the proximal tibia associated with longterm use of methotrexate : 3 case reports and a review of literature. *J Rheumatol* 37(11) : 2434-2438, 2010
19. Clemetson IA, Popp A, Lippuner K, Ballmer F, Anderson SE : Postpartum osteoporosis associated with proximal tibial stress fracture. *Skeletal Radiol* 33(2) : 96-8, 2004
20. Kadowaki M, Imade S, Kuwata S, Uchio Y : Sequential multiple insufficiency fractures around knee over 6 months in a patient with primary osteoporosis. *Eur J Orthop Surg Traumatol* 22 Suppl 1 : 181-4, 2012
21. Yukata K, Yamanaka I, Ueda Y, Nakai S, Ogasa H, Oishi Y, Hamawaki JI : Medial tibial plateau morphology and stress fracture location : A magnetic resonance imaging study. *World J Orthop* 8(6) : 484-490, 2017
22. Prasad N, Murray JM, Kumar D, Davies SG : Insufficiency fracture of the tibial plateau : an often missed diagnosis. *Acta Orthop Belg* 72(5) : 587-591, 2006