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Case Report

A large amount of microdamages in the cortical bone around fracture site in a patient of atypical femoral fracture after long-term bisphosphonate therapy

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ABSTRACT

A breast cancer patient developed an atypical femoral fracture after 9 years of bisphosphonate therapy for the treatment of multiple bone metastases. We histopathologically analyzed the femoral cortical bone at the fracture site and the iliac cancellous bone. Four months prior to the fracture, the patient had experienced pain in the right femur and underwent plain radiography and bone scintigraphy which revealed cortical thickening and radioisotope accumulation at each site, respectively. The patient had also experienced a non-traumatic fracture at the same site on the contralateral side 2 years earlier. Based on these findings, atypical femoral fracture was diagnosed and intramedullary nailing performed. A cortical bone specimen taken from near the fracture site during surgery showed marked microdamages, and analysis of the iliac cancellous bone specimen revealed severely suppressed bone turnover. These findings suggest that microdamage and severely suppressed bone turnover are associated with atypical femoral fracture reported in this patient with long-term bisphosphonate therapy.

Introduction

Bisphosphonates are widely used in the treatment of bone disease with increased bone resorption, including bone metastasis of breast cancer, because of their potent suppressive effects on bone resorption [1–3]. However, many studies in recent years have reported atypical femoral fracture in patients receiving long-term bisphosphonate therapy [4–9]. We recently treated a breast cancer patient with multiple bone metastases who developed an atypical femoral fracture after undergoing long-term bisphosphonate therapy. We report here the histopathological findings of the fracture.

Case

A 56-year-old woman with a history of mastectomy for breast cancer at 35 years of age had been undergoing chemotherapy at the Department of Breast Surgery at our hospital. At age 47, after radiotherapy for multiple bone metastases, she was started on incadronic acid (10 mg) once every 2 weeks after radiotherapy. The drug was switched to monthly pamidronic acid (90 mg) at age 50 and subsequently to monthly zoledronic acid (4 mg) at age 51. She experienced a non-traumatic subtrochanteric fracture of the left femur at age 54 and underwent osteosynthesis because of a suspected pathological fracture due to metastatic bone tumor. Despite no intraoperative macroscopic or pathological findings of malignancy, zoledronic acid was continued after surgery for around 2 years.

The patient was recently transported to our hospital because of intense pain in the right femur after stepping up a small step into the house and immediately being unable to bear weight. Plain radiography revealed a transverse femoral subtrochanteric fracture with cortical bone thickening of the lateral cortices (Fig. 1). Four months earlier, the patient had undergone plain radiography and then bone scintigraphy for pain in the right femur, which had revealed lateral cortical thickening (Fig. 2) and accumulation of radioactive materials (Fig. 3), respectively, in the subtrochanteric region of the right femur. However, no specific treatment had been initiated. Five days after the fracture, the levels of bone metabolism markers tartrate-resistant acid phosphatase 5b (TRAP-5b) and osteocalcin were 237 mU/dL (normal range, 120–420 mU/dL) and 2.3 ng/ml (normal range, 2.5–13 ng/ml), respectively, indicating no elevation of bone turnover despite sustaining the fracture.

Taking into account her medical history and image findings, we diagnosed atypical femoral fracture and performed intramedullary nailing on day 7 after fracture (Fig. 4a). During surgery, a coaxial bone and vertebral bone biopsy needle (Zimmer Inc., Warsaw, IN) was used

Abbreviations: TRAP-5b, tartrate-resistant acid phosphatase 5b.

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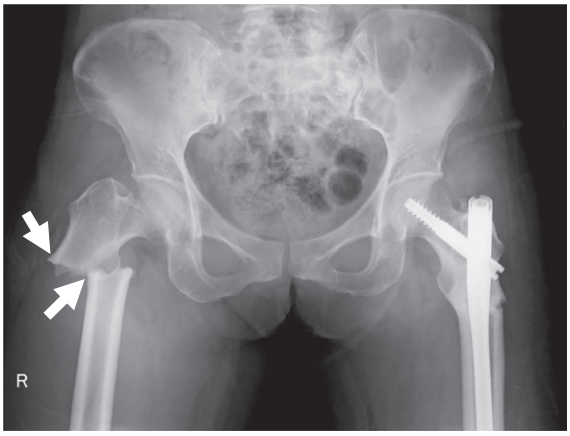

Fig. 1. Plain radiograph taken immediately after fracture. The right femur shows a transverse subtrochanteric fracture and lateral cortical thickening (arrows).

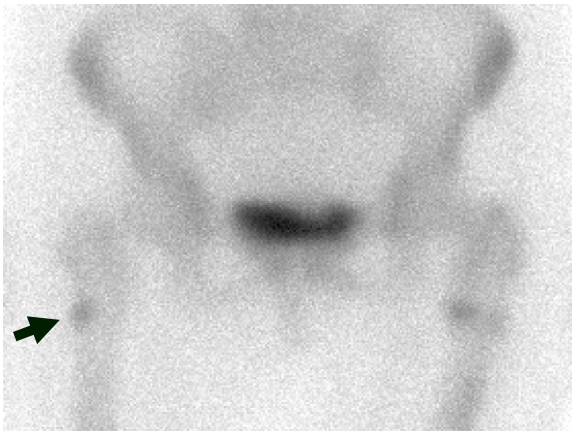

Fig. 3. Bone scintigraphy taken 4 months before fracture. Radioactive materials are evident below the trochanter in the right femur (arrow).

to take a biopsy specimen from the lateral thickened cortical bone adjacent to the fracture cite before intramedullary nailing (Fig. 5a). This was followed by transiliac bone biopsy for bone morphometry. In the femoral cortical bone, the area was measured at least 1.5 mm from the edge of the collected bone to avoid the biopsy needle infringing on the resection margin (Fig. 5a). Histopathological findings revealed no malignancy but did reveal many microcracks (Fig. 5b) in the cortical bone adjacent to the fracture site and few osteoid surfaces in the iliac cancellous bone (Fig. 6). We therefore assessed bone microdamage by the method proposed by Burr [10]. The results revealed a microcrack density of 5.8/mm^2, mean microcrack length of 91.6 μm, and microcrack surface density of 553.4/μm/mm^2. Microdamage accumulation was notably more extensive than that reported by Norman and Wang [11], who evaluated microdamage in normal human cortical bone of the femur (Table 1). Furthermore, the iliac cancellous bone specimen showed that the suppression of bone turnover was notably more extensive than that observed in postmenopausal women [12], even in those who had received alendronate (10 mg) therapy for 3 years for the treatment of osteoporosis [13] (Table 2).

After confirming the disappearance of metastatic foci for an extended period, we stopped the zoledronic acid and switched to teriparatide and concurrent physical therapy. Bony union became apparent at 3 months after surgery and was complete by 6 months after surgery (Figs. 4b, c).

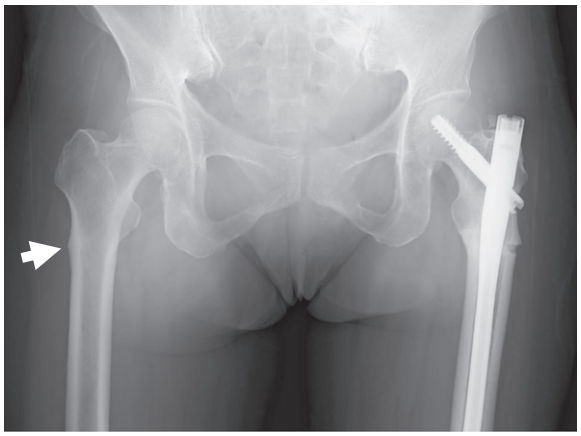

Fig. 2. Plain radiography image taken 4 months before fracture. Subtrochanteric cortical thickening is evident on the lateral right femur (arrow).

Discussion

The increasing number of patients with atypical femoral fracture after long-term bisphosphonate therapy led to the American Society for Bone and Mineral Research organizing a taskforce to investigate the situation surrounding bisphosphonate therapy [9]. A typical femoral fracture was defined as a transverse or short oblique non-comminuted fracture occurring between the subtrochanteric and supracondylar regions with no or only minor traumatic injury. In addition, complete fracture was defined as a fracture with a medial cortex spike and incomplete fracture as a fracture of the lateral cortical bone only. The fracture may be caused by modification of collagen cross-linking, accumulation of bone microdamage, increased mineralization or reduced heterogeneity of mineralization, change in bone metabolism, or reduced angiogenesis [9,14–21]. The factors underlying the above conditions are osteomalacia, rheumatoid arthritis, impaired phosphorylation, and the use of bisphosphonates, steroids, and proton pump inhibitors [9, 22–25]. We classified the femoral fracture in the present case as an atypical fracture because it was caused by only a small movement after long-term bisphosphonate therapy and it showed characteristic morphological findings of atypical femoral fracture. According to Ivaska et al., the blood levels of TRAP-5b and osteocalcin seldom change immediately after fracture, but increase over time due to the post-fracture reaction [26]. In the present case, although 5 days had passed since the fracture, TRAP-5b was within the normal range while osteocalcin was abnormally low, indicating that bone remodeling had been suppressed before the fracture occurred.

To our knowledge, this is the first study to assess microdamage by histopathologically examining the fracture site of an atypical femoral fracture, and therefore direct comparisons with other studies cannot be made. However it could be compared with previous reported microdamaged values in other relevant references. Norman and Wang reported microdamage of the femoral cortical bone in 27 cadavers to have a microcrack density of 0.21/mm^2, microcrack length of 90.9 μm, and microcrack surface density of 19.5/μm/mm^2 [11] (Table 1), which means the level of microcracks in the present case was approximately 28-fold that of Norman and Wang, which is an extremely high level of microdamage accumulation for a normal femur. On the other hand, Vashishth et al. reported that microcrack density in the cortical bone of human fractured tibia under mechanical loading was 11.1/mm^2 [27]. This indicates that microdamage level seen in our patient was below the levels caused by the fracture itself. It is therefore more likely that levels seen in this patient reflect in vivo accumulation of microdamage before fracture.

The histomorphometric findings of the iliac bone indicated severely suppressed bone turnover in the present patient compared with a

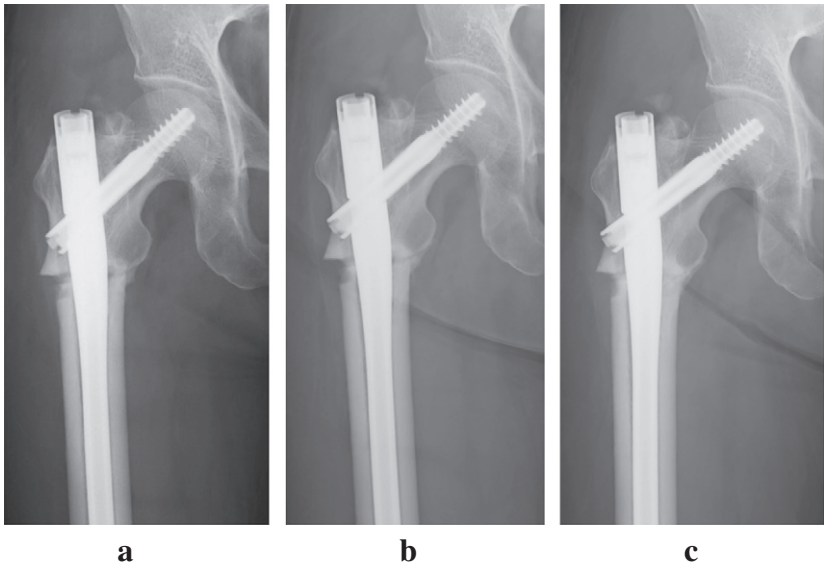

Fig. 4. Postoperative plain radiographs of (a) the fracture site immediately after surgery for intramedullary nailing, (b) the filled postoperative cortical bone defect with a callus 3 months after surgery, and (c) complete bone union 6 months after surgery.

similar study on postmenopausal women [12], even those treated with 10 mg alendronate for 3 years [13]. Therefore, the bone in the present patient was in the same severely suppressed bone turnover state reported by Odvina et al. [4], in which no double fluorescent label surfaces were observed in the iliac cancellous bone of all spontaneous fracture patients under long-term alendronate therapy.

High-dose bisphosphonate therapy has been shown to inhibit bone remodeling and elevate microdamage accumulation in dogs and monkeys, which have similar bone metabolism systems to humans [19–21]. Suppression of bone turnover was associated with increased production of advanced glycation end products, with a reduction in the toughness of bone [14–18,27]. Moreover, increased AGEs are associated with increased formation of linear microcracks that were found in our patient. It is possible that long-term bisphosphonate therapy at higher dose than those for osteoporosis treatment in this patient caused severe suppression of bone remodeling, which might accumulate microdamage due to suppressed repair and may lead to occurrence of atypical femoral fracture.

The microdamage accumulation observed in the biopsy specimen taken during surgery does not necessarily imply the accumulation of bone microdamage before the fracture because bone sampling itself can cause microdamage. Using a hollow needle for drilling bone, we took biopsy specimens of 8 mm diameter from the fracture site that enabled us to assess microdamage at least 1.5 mm from the edge of the collected bone to avoid artifacts caused by the biopsy needle infringing on the resection margin. Although this uncertainty about the cause of microdamage may be regarded as a limitation of this study, the present findings are still valuable because there are no other reports of microdamage accumulation at the site of an atypical femoral fracture.

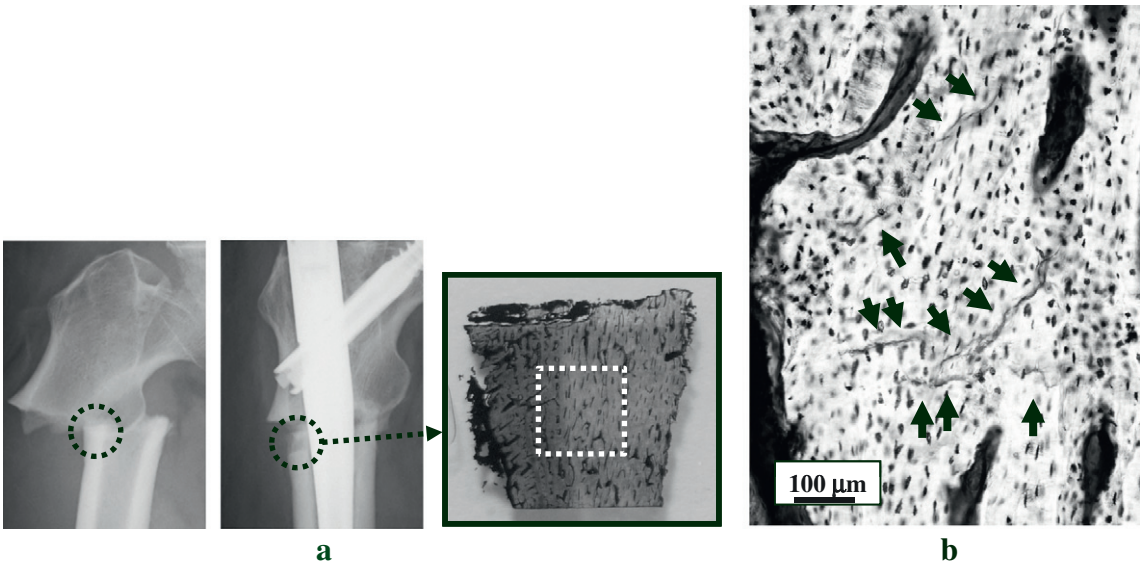

Fig. 5. A cortical bone specimen was taken from thickened lateral cortical bone adjacent to the fracture site (a). Assessment of bone microdamage (a) at the specimen site from where two 3 × 3-mm sections were taken at least 1.5 mm from the resection margin, and (b) a large number of microcracks (arrows) as revealed by light microscopy.

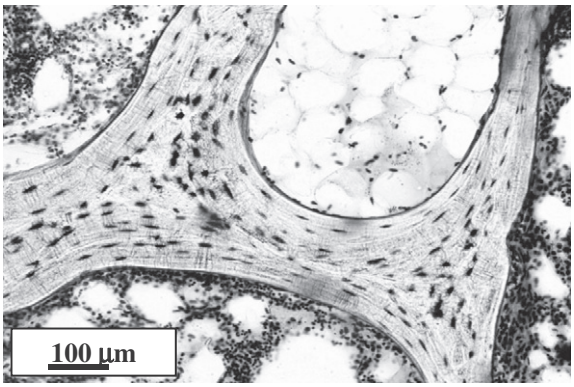

Fig. 6. Transiliac bone biopsy. Few osteoid or resorption surfaces are visible on the trabecular surfaces, indicating highly suppressed bone turnover.

Conclusions

In a breast cancer patient with atypical femoral fracture after long-term bisphosphonate therapy for the treatment of multiple bone metastases, transiliac bone histomorphometry revealed severely suppressed bone turnover, and bone histomorphometry of the fracture site revealed pronounced microdamage accumulation. Careful attention should be paid not only to bone turnover, but also to the occurrence of an atypical femoral fracture, especially in cancer patients receiving long-term bisphosphonate treatment.

Conflict of interest

None of the authors have any conflicts of interest associated with this study.

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Table 1
Results of microdamage assessment.

Microdamage parameter	Present case	Norman and Wang
Density (/mm^2)	5.8	0.21
Length (μm)	91.6	–
Surface density (μm/mm^2)	553.4	19.5

Severe microdamage accumulation was observed in the present case compared with the 27 cadavers assessed by Norman and Wang [11].

Table 2
Histomorphometric analysis of iliac cancellous bone.

	Present case	Chavassieux et al.[a]	Recker et al.[b]
Cancellous bone volume (%)	23.2	16.6	19.6
Osteoid volume (%)	0.005	–	0.36
Osteoid volume/bone volume (%)	0.023	0.12	1.2
Osteoid surface/bone surface (%)	1.15	1.5	14
Eroded surface (%)	0.47	1.3	3.66

Bone turnover was severely inhibited in the present case compared with the cases of Chavassieux et al. [13] and Recker et al. [12].

[a] Seventeen postmenopausal women with osteoporosis who received alendronate (10 mg) for 3 years.

[b] Thirty-four postmenopausal women.

References

[1] Hortobagyi GN, Theriault RL, Lipton A, Porter L, Blayney D, Sinoff C, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. J Clin Oncol 1998;16:2038–44.
[2] Rosen LS, David G, Tchekmedylan NS, Yanagihara R, Hirsh V, Krzakowski M, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613–21.
[3] Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol 2005;23:3314–21.
[4] Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CYC. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005;90:1294–301.
[5] Goh SK, Yang KY, Koh JSB, Wong MK, Chua SY, Chua DTC, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy. J Bone Joint Surg [Br] 2007;89-B:349–53.
[6] Neviaser AS, Lane MJ, Lanart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma 2008;22:346–50.
[7] Kwek EBK, Goh SK, Koh JSB, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury 2008;39:224–31.
[8] Armamento-Villareal R, Napoli N, Diemer K, Watkins M, Civitelli R, Teitelbaum S, et al. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tissue Int 2009;85:37–44.
[9] Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Mineral Res 2010;25:2267–94.
[10] Burr DB. Validity of the bulk-staining technique to separate artifactual from in vivo bone microdamage. Clin Orthop Relat Res 1990;260:305–8.
[11] Norman TL, Wang Z. Microdamage of human cortical bone: incidence and morphology in long bones. Bone 1997;20:375–9.
[12] Recker RR, Kimmel DB, Parfitt AM, Davies KM, Keshawarz N, Hinders S. Static and tetracycline-based bone histomorphometric data from 34 normal postmenopausal females. J Bone Miner Res 1988;3:133–44.
[13] Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest 1997;100:1475–80.
[14] Vashishth D, Gibson GJ, Khoury JI, Schaffler MB, Kimura J, Fyhrie DP. Influence of nonenzymatic glycation on biomechanical properties of cortical bone. Bone 2001;28:195–201.
[15] Allen MR, Gineyts E, Leeming DJ, Burr DB, Delmas PD. Bisphosphonates alter trabecular bone collagen cross-linking and isomerization in beagle dog vertebra. Osteoporos Int 2008;19:329–37.
[16] Saito M, Mori S, Mashiba T, Komatsubara S, Marumo M. Collagen maturity, glycation induced-pentosidine, and mineralization are increased following 3-year treatment with incadronate in dogs. Osteoporos Int 2008;19:1343–54.
[17] Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D. Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. Osteoporos Int 2009;20:887–94.
[18] Tang SY, Vashishth D. Non-enzymatic glycation alters microdamage formation in human cancellous bone. Bone 2010;46:148–54.
[19] 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 2000;15:613–20.
[20] Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. Bone 2001;28:524–31.
[21] Yamagami Y, Mashiba T, Iwata K, Tanaka M, Nozaki K, Yamamoto T. Effects of minodronic acid and alendronate on bone remodeling, microdamage accumulation, degree of mineralization and bone mechanical properties in ovariectomized cynomolgus monkeys. Bone 2013;54:1–7.
[22] Wood J, Bonjean K, Ruetz S, Bellahce'ne A, Devy L, Foidart JM, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002;302:1055–61.
[23] Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. N Engl J Med 2010;362:1848–9.
[24] Somford MP, Draijer FW, Thomassen BJ, Chavassieux PM, Boivin G, Papapoulos SE. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to the mechanism of increased bone fragility. J Bone Miner Res 2009;24:1736–40.
[25] Guisti A, Hamdy NAT, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. Bone 2010;24:1736–40.
[26] Ivaska KK, Gerdhem P, Åkesson K, Garnero P, Obrant KJ. Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. J Bone Miner Res 2007;22:1155–64.
[27] Vashishth D, Behiri JC, Bonfield W. Crack growth resistance in cortical bone: concept of microcrack toughening. J Biomech 1997;30:763–9.