Bilateral atypical femoral subtrochanteric fractures in a premenopausal patient receiving prolonged bisphosphonate therapy: evidence of severely suppressed bone turnover

Naoki Kondo
Takuya Yoda
Junichi Fujisawa
Katsumitsu Arai
Mayumi Sakuma
Hiroshi Ninomiya
Hiroshige Sano
Naoto Endo

Division of Orthopaedic Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Address for correspondence:
Naoki Kondo, MD, PhD
Division of Orthopaedic Surgery
Niigata University Graduate School of Medical and Dental Sciences
1-757, Asahimachi-dori, Chuo Ku, Niigata, 951-8510, Japan
E-mail: uin42727@nifty.com

Summary
We report a case of bilateral atypical femoral fractures that occurred in a patient who had been taking bisphosphonate long-term. A 36-year-old premenopausal female diagnosed with systemic lupus erythematosus and dermatomyositis had been treated with glucocorticoid and alendronate (5 mg/day) to prevent glucocorticoid-induced osteoporosis. She was admitted to our hospital because she could not walk immediately after falling down from the standing position. Plain radiograph showed a subtrochanteric fracture of the left femur. Four months later, she fell again and sustained a contralateral subtrochanteric fracture. For each fracture, a femoral intramedullary nail was inserted. Delayed union was detected in both sides, and revision surgery with an iliac bone graft was required for implant breakage in the right side. Histomorphometric findings for the ilium revealed remarkably decreased osteoid volume with no osteoclasts and a minimally eroded surface, suggesting that bone turnover was severely suppressed. However, histology of the delayed union site revealed callus formation and some osteoclast appearance, suggesting that fracture healing was occurring. In total, it took 29 months (left) and 24 months (right) until fracture healing was achieved, showing delayed union.

This case is extremely rare in that patient who presented with atypical femoral fractures in spite of her premenopausal status. The bone histomorphometric findings from this case suggest that severely suppressed bone turnover is associated with atypical femoral subtrochanteric fracture and can cause delayed union in patients treated with alendronate long-term.

KEY WORDS: glucocorticoid-induced osteoporosis; femoral subtrochanteric fracture; alendronate; severely suppressed bone turnover; bone histomorphometry.

Introduction
Alendronate, one of the bisphosphonates, is a potent inhibitor of bone resorption and is one of main agents for the treatment of postmenopausal osteoporosis (1). In addition, glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis, and alendronate is the first-choice drug for patients taking glucocorticoids in order to prevent fragility fractures. For premenopausal fertile women, alendronate use is also recommended when patients are treated with prednisolone >7.5 mg/day for more than 3 months (2).

Alendronate was shown to reduce the incidence of vertebral, wrist, and hip fracture by approximately half in women with prevalent vertebral fractures (3). On the other hand, high-dose and long-term use of this reagent was shown to cause microdamage and decrease bone toughness by inhibiting bone remodeling in the dog rib (4). Recently, “atypical” femoral fractures of the diaphyseal part of the femur (subtrochanteric or shaft) have been reported in patients taking bisphosphonates for a prolonged period of time (5, 6). Odvina et al. described 9 patients who developed spontaneous non-spinal fractures after 1-8 years of alendronate therapy. They demonstrated a bone labeling deficiency using histomorphometric analysis of the bone biopsy and defined these conditions as severely suppressed bone turnover (SSBT) (7). Here, we present the case of a premenopausal woman with atypical subtrochanteric fractures of the bilateral femora related to SSBT after long-term use of alendronate therapy for preventing glucocorticoid-induced osteoporosis. She required revision surgery since non-union was detected in one side. We also present pathological findings, such as bone histomorphometry and sites of non-union in the fractures.

Case report
A Japanese female was diagnosed with systemic lupus erythematosus (SLE) and dermatomyositis (DM) at 32 years of age. She began treatment with oral prednisolone at a dose of 40 mg/day. Her lumbar spine bone mineral density (BMD) as measured by dual X-ray absorptiometry (Discovery; Hologic, Inc., Bedford, MA, USA) was 1.016 g/cm², which was equivalent to 98% of the mean value for the young Japanese adult female population (YAM, young adult mean), and her T-score was 0. Her serum calcium (Ca) was 9.6 mg/dL, serum phosphorous (P) was 3.9 mg/dL, which were within normal limits (Ca: 8.7-10 mg/mL; P: 2.5-4.6 mg/mL) and serum bone-specific alkaline phosphatase (BAP) was 16.0 U/L, which was upper than normal limits (BAP: 8.1-10.5 U/L).
The patient was treated with alendronate at a dose of 5 mg/day and calcium lactate at a dose of 3 g/day to prevent glucocorticoid-induced osteoporosis. She was diagnosed with deep vein thrombosis when she was 34 years old, and she was treated with warfarin at a dose of 3.5 mg/day. Because her disease activity was well controlled, prednisolone was gradually tapered to 14 mg/day.

Her past X-ray (before alendronate therapy) showed neither beaking in the lateral cortex nor focal cortical thickening in the subtrochanteric region (Figure 1a). After 42 months (3.5 years) of medication, when she was 36 years old, she was unable to walk after falling and was taken to our hospital by ambulance. Plain radiography showed a left femoral subtrochanteric fracture of the reverse oblique type (Figure 1b).

Figure 1 - Time course of radiography findings. a) Hip joint and femur radiograph before alendronate treatment. Neither beaking nor cortical thickening was observed in bilateral femora. b) Left femoral subtrochanteric fracture was detected. Fracture type was two-part and reverse oblique. Focal lateral cortical thickening was observed in the fracture site. c) One week after surgery, beaking was detected in the right lateral subtrochanteric cortex (white arrow). d) Right femoral subtrochanteric fracture was detected, and the fracture site was in agreement with the “beaking” portion. Fracture type was two-part and reverse oblique. e) Open reduction and internal fixation was performed with a proximal femoral nail to the right femoral subtrochanteric fracture. f) Right proximal femoral nail showed implant failure just adjacent to (above) the distal locking screw 5 months after surgery (white arrow head). The fracture site remained in a state of delayed union on the left side 9 months after surgery. g) Revision surgery was performed using an LCP-DF plate. The iliac bone was grafted to the non-union site after curettage. h) Radiography showed delayed union 8 months after revision surgery on the right subtrochanteric femoral fracture. i) Computed tomography finding showed that the grafted iliac bone was partially adapted to the host bone 8 months after revision surgery on the right subtrochanteric femoral fracture. j) Fracture site was healed at 24 months after revision surgery. k) On computed tomography, the fracture site was united compared to (i). l) In the final follow-up radiography at 36 months after revision surgery, union was preserved in the bilateral femoral subtrochanteric fractures.
Bilateral atypical femoral subtrochanteric fractures in a premenopausal patient receiving prolonged bisphosphonate therapy: evidence of severely suppressed bone turnover

She had no vertebral body fractures. She felt no prodromal pain in either thigh around the hip joints. Closed intramedullary nailing was performed for the fracture. After callus formation was detected on plain radiography, walking exercises were begun with the patient bearing her full weight with a support. One week after surgery, plain radiography demonstrated beaking in the right lateral cortex of the subtrochanteric region (Figure 1c). However, she felt neither prodromal pain nor tenderness in this location. Four months after the primary surgery, she fell again from a standing position and felt right hip pain; she was transported to our hospital by ambulance. Plain radiography demonstrated a right femoral subtrochanteric fracture of the reverse oblique type, which was exactly the same presentation as that on the left side four months previously (Figure 1d). Closed intramedullary nailing using Japanese proximal femoral nail A (SYNTHES, Tokyo, Japan) was performed for the fracture (Figure 1e).

After this surgery, ultrasound low-intensity pulse therapy was begun in order to promote fracture healing for the fractures on both sides with 1.5 MHz frequency pulses at a pulse width of 200 μs, repeated at 1.0 kHz at an intensity of 30 mW/cm² for 20 minutes/day. Three months following her right-side surgery, plain radiography showed delayed union, but she was still permitted to walk bearing her full weight. Five months after the right-side surgery, plain radiography showed that the intramedullary nail on her right side was broken, although she had felt no pain on walking (Figure 1f). She underwent revision surgery using the LCP-DF plate (SYNTHES, Tokyo, Japan) with an autologous iliac bone graft (Figure 1g).

Intraoperative findings exhibited that the vascular supply seemed poor at the non-union site, and curettage was required until bleeding was confirmed. At that point, laboratory tests showed that her serum Ca was 9.9 mg/dL, serum 25-hydroxyvitamin D (25(OH) D) was 17.1 ng/mL, serum alkaline phosphatase (ALP) was 236 U/L, and urinary N-telopeptide crosslinks (NTx) was 52.7 nmol BCE/mmol Cr; all were within normal limits (ALP; 106 - 322 U/L and NTx; 9.3 - 54.3 nmol BCE/mmol Cr), with the exception of 25(OH) D. Her BMD was 1.014 g/cm² (100% of the YAM). Her serum 25(OH) D concentration was in a deficient state (<20 ng/mL). Alendronate treatment was ceased after the revision surgery, and 0.50 μg/day of oral alfacalcidol was begun 2 months after revision surgery. Walking exercises were initiated with the patient bearing 1/3 of her weight with support 5 weeks after surgery and 2/3 of her weight 8 months after surgery. She reported no pain on walking with partial weight-bearing on the right side. The fracture was healed on her left side but not on her right side, as revealed by the non-union site remaining on plain radiography 8 months after the revision surgery (Figure 1h).

However, the grafted bone seemed partially adapted to the surrounding host bone on computed tomography 8 months after her revision surgery (Figure 1i). Full weight-bearing was permitted 12 months after the revision surgery. Finally, fracture healing was achieved in her right femur after 24 months (Figures 1j and 1k).

At the last follow-up, plain radiography demonstrated that fracture healing had persisted 36 months after her revision surgery (Figure 1j). Her serum 25(OH) D level gradually elevated to 18.8 ng/mL 1.5 years after induction of alfacalcidol and reached 25.9 ng/mL after 2.3 years. At that time, BAP level decreased to 9.5 U/L.

With her informed consent, a part of the patient’s iliac bone was removed and subjected to bone histomorphometry to clarify whether this case was related to SSBT. No tetracycline labeling was performed. Villanuevea bone staining showed little osteoid (Figure 2a). Histomorphometric findings revealed that bone volume parameters such as bone volume/tissue volume (BV/TV), trabecular thickness (Tb.Th), and wall thickness (W.Th) were within normal limits. However, the level of each osteoid parameter such as osteoid volume/tissue volume (OV/TV), osteoid surface/bone surface (OS/BS), and osteoid thickness (O.Th) was extremely low compared to age-matched control data (8). In addition, the bone resorption parameter (ES/BS) was also extremely low. Notably, no osteoclast was detected (Table 1). These data suggest that both bone formation and resorption were severely suppressed. Finally, at the time of revision surgery, the fracture site was

Table 1 - Bone histomorphometric findings from the ilium.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abbreviation</th>
<th>Value</th>
<th>Normative Value [31-40F]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Volume</td>
<td>BV/TV %</td>
<td>16.77</td>
<td>18.5±6.7</td>
</tr>
<tr>
<td></td>
<td>Tb.Th μm</td>
<td>124.48</td>
<td>126.1±7.9</td>
</tr>
<tr>
<td></td>
<td>W.Th μm</td>
<td>38.01</td>
<td>39.2±2.5</td>
</tr>
<tr>
<td>Osteoid</td>
<td>OV/TV %</td>
<td>0.002</td>
<td>0.1-1.0</td>
</tr>
<tr>
<td></td>
<td>OV/BV %</td>
<td>0.01</td>
<td>2.8±0.5</td>
</tr>
<tr>
<td></td>
<td>OS/BS %</td>
<td>0.17</td>
<td>17.4±3.0</td>
</tr>
<tr>
<td></td>
<td>O.Th μm</td>
<td>3.38</td>
<td>9.9±1.3</td>
</tr>
<tr>
<td>Bone Resorption</td>
<td>ES/BS %</td>
<td>0.69</td>
<td>3.5±1.1</td>
</tr>
<tr>
<td></td>
<td>N.Oc/BS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fb.V/TV %</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Compared to age- and sex-matched normative data, each osteoid parameter was remarkably decreased. Each bone volume parameter was normal. No osteoclast was detected, and the eroded surface was severely low. Abbreviations are as follows: BV/TV, Bone volume/Tissue volume; Tb.Th, Trabecular thickness; OV/TV, Osteoid volume/Tissue volume; OV/BV, Osteoid volume/Bone volume; OS/BS, Osteoid surface/Bone surface; O.Th, Osteoid thickness; ES/BS, Eroded surface; Ob.S, Osteoblast surface; N.Oc/BS, Osteoclast number; Fb.V/TV, Fibrosis volume.

Clinical Cases in Mineral and Bone Metabolism 2015; 12(3): 273-277

275
subjected to a pathological evaluation. Callus formation, osteoclasts (Figures 2b, 2c, and 2d), and angiogenesis (Figure 2e) were detected in the fracture site, suggesting that fracture healing had progressed to some extent.

Discussion

Odvina et al. reported 9 cases of non-traumatic and non-vertebral fracture under long-term bisphosphonate therapy. They presented iliac bone histomorphometric findings in all cases (7). Cells were barely observed in the bone surface, and osteoid volume and bone formation rate were severely suppressed. In addition, the resorbing surface of the bone was also intensively inhibited in most cases, and no double tetracycline labeling was detected. As noted above, they defined the condition in which both bone formation and resorption are extremely hampered as SSBT. In clinical settings, this condition indicates that atypical and non-traumatic fracture has occurred in cortical bone-rich areas, such as the pubis, ischium, or femoral diaphysis.

Shane et al. reported the clinical features of atypical femoral fractures divided into major and minor characteristics (9). In our case, radiography findings demonstrated the short (or reverse) oblique fracture type without comminution, and the patient was injured after simply falling from a standing posture, demonstrating major characteristics. In addition, our case had most of the minor features as well, including lateral focal cortical thickening (beaking) and bilateral fracture, delayed union confirmed by follow-up radiography, long-term glucocorticoid and bisphosphonate use (3.6 years), and vitamin D deficiency [25(OH)D; 17.1 ng/mL].

Giusti et al. suggested the possible contribution of glucocorticoid therapy to the risk of atypical femoral fractures, showing that 30% of all patients with atypical fractures were using glucocorticoids for a much longer period of time compared to only 7.5% of those with ordinary subtrochanteric/femoral shaft fractures (10). Glucocorticoids were used in our case. The patient's BAP was 16.0 U/L, which was higher than normal range, but histomorphologic finding of the ilium showed low bone formation (Figure 2a). The cause of this discrepancy is unknown. However, the patient never complained of prodromal thigh pain before the incidence of fracture, although beaking was detected in her right lateral femoral cortex 2 months after surgery for the left subtrochanteric fracture.

Although tetracycline labeling was not performed, her bone staining findings and histomorphometric findings suggest a diagnosis of SSBT, especially since both osteoid and bone resorbing parameters were extremely low. Histological findings from the non-union site showed callus formation and os bone staining findings and histomorphometric findings suggest a diagnosis of SSBT, especially since both osteoid and bone resorbing parameters were extremely low. Histological findings from the non-union site showed callus formation and os

Figure 2 - Histological findings from the iliac bone and histological findings of the fracture non-union site.

In the revision surgery, the non-union fracture site was removed and subjected to histological findings after decalcification with EDTA. The bone was embedded in paraffin, cut on a microtome, mounted on a glass slide, and stained with hematoxylin and eosin. a) Villanueva bone staining showed no osteoid formation around the trabecular bone. b) Callus formation was observed in the squared areas surrounded with solid and dotted lines. c) It shows an enlarged area of the solid squared line in (b). The enlarged area clearly demonstrates multinucleated giant cells (osteoclasts) (black arrows) gathered and surrounded with callus (d). In the enlarged area of the dotted squared line (b), fibroblast-like cells (osteoid) (asterisks) and vessel formations were detected (e).
Bilateral atypical femoral subtrochanteric fractures in a premenopausal patient receiving prolonged bisphosphonate therapy: evidence of severely suppressed bone turnover

Neoclast appearance and angiogenesis (Figure 2b-e), suggesting that fracture healing progressed to some extent in this case. Long-term use of bisphosphonate may prevent fracture healing by hampering osteoclast function. In this case, beaking was detected in the right lateral subtrochanteric cortex 1 week after open reduction and internal fixation to the left femoral subtrochanteric fracture. Why this beaking appeared is unknown. We speculated that this phenomenon was caused by increased stress to the right subtrochanteric region because weight-bearing was temporarily more loaded after her left femoral surgery. Although there is no report to support our speculation, a bilateral fracture pattern was reported in 28% of patients in the American Society of Bone and Mineral Research (ASBMR) Task Force report (9). Therefore, continuous radiography follow-up is required. Das De et al. reported that contralateral femoral subtrochanteric fracture will be incidental after atypical femoral subtrochanteric fracture in one side; therefore, further examinations, such as magnetic resonance imaging or bone scintigraphy, are required for the diagnosis. They also reported that intramedullary fixation is recommended before complete fracture occurs (11). In this case, we performed neither these examinations nor preventable intramedullary fixation. Although the patient reported no prodromal pain, contralateral femoral subtrochanteric fracture occurred. Bisphosphonate treatment should have been ceased immediately after the left femoral subtrochanteric fracture.

When beaking is detected in the contralateral side, the recent ASBMR Task Force guidelines recommend ceasing bisphosphonate, the evaluation of calcium and vitamin D with supplementation in the case of insufficiency (deficiency), and intramedullary nailing if pain persists in the beaking site (12). Some Authors have indicated that teriparatide is effective (13, 14). In our case, bisphosphonate was ceased immediately after the contralateral subtrochanteric fracture, and vitamin D therapy was initiated for her vitamin D deficiency. After 27 months of vitamin D supplementation, her serum 25(OH)-D level was upregulated to 25.9 ng/mL. This increase may be due primarily to the effect of ceasing the bisphosphonate and due partially to active vitamin D supplementation. In either case, it is likely that the upregulation of 25(OH)-D contributed to fracture healing because this patient finally achieved union. Pathological findings showed callus formation on revision surgery, suggesting that she had the potential ability for fracture healing even though histomorphometry of the ilium showed SSBT.

In general, delayed union can sometimes occur in atypical femoral fracture. For instance, Giusti et al. reported that 39% of atypical femoral fractures associated with long-term bisphosphonate use showed delayed union (15), and Shane et al. reported delayed union in 26% of such cases (9). Delayed union or non-union should be considered when treating this type of fracture.

Ethical approval
Written informed consent was obtained for this case.

Conflict of interest
None of the Authors has any conflicts of interest associated with this study.

References