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CASE REPORT

Different surgical outcomes in a patient with bilateral atypical femoral fracture related to bisphosphonate use with or without teriparatide treatment

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Abstract

Bisphosphonates (BPs) are first-line drugs for the treatment of osteoporotic fractures, but long-term use of BP reduces bone turnover and is associated with atypical femur fractures (AFFs). Additionally, BP treatment may cause delayed fracture healing or nonunion, which makes AFF treatment difficult. The incidence of AFF is generally low. In fact, there are only a few clinical reports of AFF and there is no controlled study on AFF treatment. Herein, we report a case of multiple osteoporotic fractures. After 5 years of BP treatment, left and right AFFs occurred within 2 years. The fracture types and surgical operations were the same, but the level of bone metabolism and drug treatment were different. The right AFF healed well following teriparatide initiation compared with non-healed left AFF with BP continuation; thus, our case can be considered a self-controlled study. Furthermore, we have reviewed the diagnosis and treatment of this case in detail and analyzed and investigated the potential causes of the different outcomes of AFFs between the two sides to inform the clinical treatment of atypical fractures. **Mini Abstract** We report a case of bilateral AFFs. The surgical treatments were the same, but the final treatment outcomes were different with or without teriparatide treatment. We investigated the potential causes of the different outcomes of AFFs between the two sides to inform the clinical treatment of AFFs.

Keywords Atypical fracture · Bisphosphonate · Fracture nonunion · Osteoporotic bone fracture · Teriparatide

Introduction

Bisphosphonates (BPs) are the most commonly used first-line drugs for the treatment of osteoporosis and osteoporotic fractures (OPF). Clinical trials have shown that patients with osteoporosis treated with BPs have a significantly lower risk of OPF owing to decreased bone turnover rate and increased bone density [1, 2]. Nevertheless, some clinical reports have shown that long-term BP use might lead to atypical femur fractures (AFFs) [3, 4]. Bisphosphonates reduce physiological bone remodeling due to weakened osteoclast activity, leading to the continuous accumulation of microinjuries in bone tissue, resulting in AFF occurrence [5, 6]. Herein, we report a case of multiple osteoporotic vertebral compression fractures in a patient who subsequently developed bilateral subtrochanteric atypical fractures. The surgical treatments were the same, but the final treatment outcomes were different with or without teriparatide treatment.

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Case

Informed consent was obtained from the participant of this case study.

Early stage vertebral compression fracture

A 71-year-old woman was first admitted to Peking Union Medical College Hospital in February 2007 for lower back pain for 1 week after moving a heavy object. Her visual analog

score (VAS) was 5–6 points. The body mass index (BMI) was 29 kg/m^2. The patient had a history of hypertension for 5 years and took controlled-release nifedipine (30 mg daily) for blood pressure. Comorbidities such as diabetes mellitus, thyroid disease, and gynecologic cancer were absent. She had not received glucocorticoid therapy previously. X-ray examinations of the lumbar spine showed wedge deformation of the L1 vertebral body. The serum 25-hydroxyvitamin D level [25(OH)D] was 14.4 ng/mL. She was prescribed bed rest and administered symptomatic analgesics, calcium carbonate (500 mg twice daily), and calcitriol (0.25 μg twice daily) anti-osteoporosis treatment.

After 4 months (June 2007), she again developed lower back pain, limiting mobility without an obvious cause. X-ray examination revealed new vertebral compression fractures in L2 and L3. Additionally, the bone density examination results showed that the L1-L4 bone mineral density (BMD) was 0.536 g/cm^2 and the T-score was − 4.64 (L1 BMD, 0.432 g/cm^2 and T-score, − 4.88; L4 BMD, 0.586 g/cm^2 and T-score, − 4.82), the left hip BMD was 0.686 g/cm^2 and the T-score was − 2.41 (neck BMD, 0.686 g/cm^2 and T-score, − 2.09). Given that the patient had severe back pain, with a VAS score of 8 points, which seriously affected rest and sleep, she was admitted to the hospital. Subsequently, L2 and L3 percutaneous kyphoplasty (PKP) was performed. After discharge, oral calcium carbonate and calcitriol were continued with alendronate (70 mg weekly) anti-osteoporosis treatment.

After 2 years (March 2009), the patient developed lower back pain after a fall and the X-ray examinations showed a new T12 vertebral compression fracture. She was hospitalized and treated with T12 PKP. The serum 25(OH)D was 17.2 ng/mL during hospitalization. Treatment with calcium carbonate, calcitriol, and alendronate anti-osteoporosis treatments was continued.

Left AFF

In June 2012, the patient developed left hip pain, limiting mobility after a fall. X-ray examinations at our hospital revealed a left femoral subtrochanteric transverse fracture (Fig. 1(A)). The patient had taken alendronate for 5 years now. According to the American Society for Bone and Mineral Research (ASBMR) diagnostic criteria for AFFs [7], her medical history, and imaging characteristics of the fracture, the left femoral subtrochanteric fracture was diagnosed as an AFF. Preoperative X-ray (Fig. 1(A)) showed thickened lateral cortical bone at the corresponding femoral fracture site. After completing preoperative examination, she underwent closed reduction and intramedullary nailing (proximal femoral nail antirotation-II, PFNA-II, 170 mm; DePuy Synthes, West Chester, PA, USA) (Fig. 1(B)). Treatment with calcium carbonate, calcitriol, and alendronate anti-osteoporosis was continued postoperatively. The 2-month follow-up examination in the outpatient clinic revealed significantly unchanged position of the internal fixation of the left hip, unhealed fracture, and well-aligned fracture ends. She was gradually encouraged to perform partial weight-bearing exercises on the lower limbs.

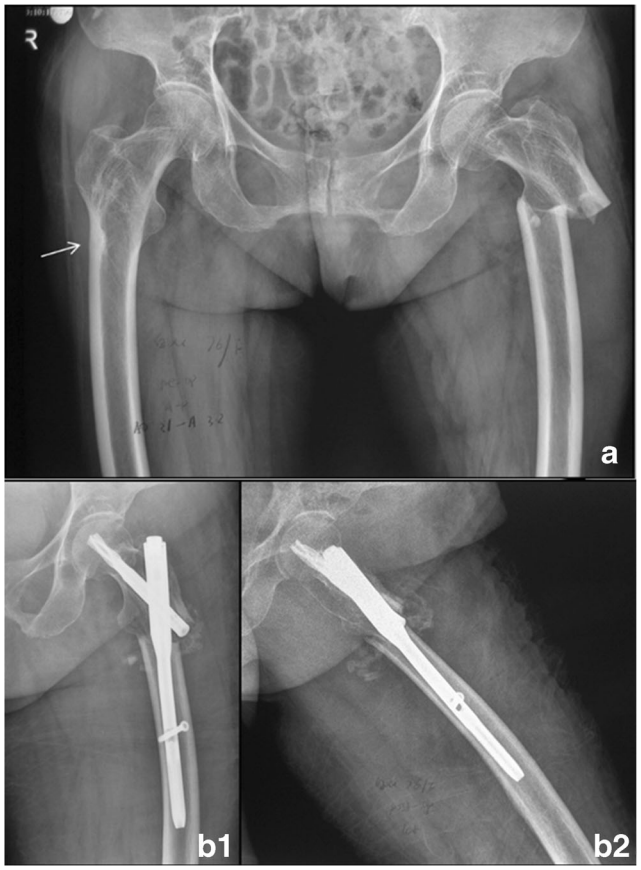

Fig. 1 Preoperative X-ray of the bilateral hip joints (A). Signs of atypical fracture can be observed in the left pelvic region: short oblique, non-comminuted subtrochanteric fracture caused by low force. Significant thickening of lateral cortical bone can be observed in the corresponding site on the opposite femur (arrow); frontal (B1) and lateral (B2) X-ray of the hip joint after intramedullary nailing (PFNA-II) fixation of the left femoral subtrochanteric fracture

Vertebral compression fracture following long-term BP treatment

In March 2013, the patient again suffered a T8 vertebral compression fracture after an accidental fall. At this time, she had taken alendronate for 5 years 9 months. She underwent T8 vertebral PKP treatment in a local hospital to relieve her pain. Before discharge, a single intravenous dose of zoledronic acid 5 mg was administered to the patient instead of alendronate and another 5 mg was administered approximately 1 year later (April 2014). Treatment with calcium carbonate and calcitriol anti-osteoporosis was administered postoperatively.

Postoperative nonunion of left AFF

In April 2015 (2 years 10 months after the left femoral subtrochanteric fracture operation), she was admitted to the outpatient clinic of our hospital for pain in the left hip when walking. X-ray examination of the left hip (Fig. 2(B)) showed fracture nonunion. Compared with those in X-rays immediately after surgery (Fig. 2(A)), the main PFNA-II nail had loosened, but the spiral blade fixation was still stable. The bone density was as follows: L1 0.758 g/cm^2 T (−2.1) and L4 0.783 g/cm^2 T(−2.5). The bone turnover indices were as follows: bone gla protein (BGP) 3.85 ng/mL (15–46 ng/mL), ß-crosslaps (ß-CTx) 0.010 ng/mL (0.21–0.44 ng/mL), and total procollagen type 1 amino-terminal propeptide (T-P1NP) 29.88 ng/mL (20.25–76.31 ng/mL). Considering that an internal fixation device had been implanted for a long time and there was a risk of fracture, surgical treatment was recommended. Given that she could still tolerate the pain when walking, she did not consent to surgical treatment; However, considering that the bone turnover rate was very low, we administered teriparatide treatment (20 μg daily) to the patient, discontinued zoledronic acid treatment, and maintained the previous doses of oral calcium carbonate and calcitriol, expecting the osteogenic effects of teriparatide to promote fracture-end healing. It was 6 years 10 months from the initiation of alendronate therapy to the last zoledronic acid treatment.

Right AFF

In June 2015, the patient suffered from right hip pain, limiting mobility after an accidental fall. This time, teriparatide had been used for approximately 2 months. The time between the fracture and the last time zoledronic acid was used was 15 months. She was monitored in a local hospital emergency department, and X-ray examinations showed right femoral subtrochanteric transverse fracture (Suppl Figure 1A). Fracture imaging showed obvious characteristics of AFF. Intramedullary nailing (gamma nail) was performed and the teriparatide treatment (20 μg daily) was continued as before, during, and after hospitalization. Outpatient X-ray examination at 4 months postoperatively (Suppl Figure 1B) showed fracture healing.

Revision of postoperative nonunion of left AFF

In May 2017 (4 years 11 months after left femoral subtrochanteric fracture treatment), the patient visited the outpatient clinic of our hospital 2 years after teriparatide treatment. The bone density was as follows: L1 0.802 g/cm^2 T(−1.7) and L4 0.835 g/cm^2 T(−2.1). The bone turnover indices were as follows: osteocalcin 11.76 ng/mL (15–46 ng/mL), ß-CTx 0.139 ng/mL (0.21–0.44 ng/mL), and T-P1NP 53.29 ng/mL (20.25–76.31 ng/mL). X-ray re-examination of the left hip (Fig. 2(C)) showed unhealed fracture. Owing to long-term weight-bearing walking, the spiral blade also exhibited nail

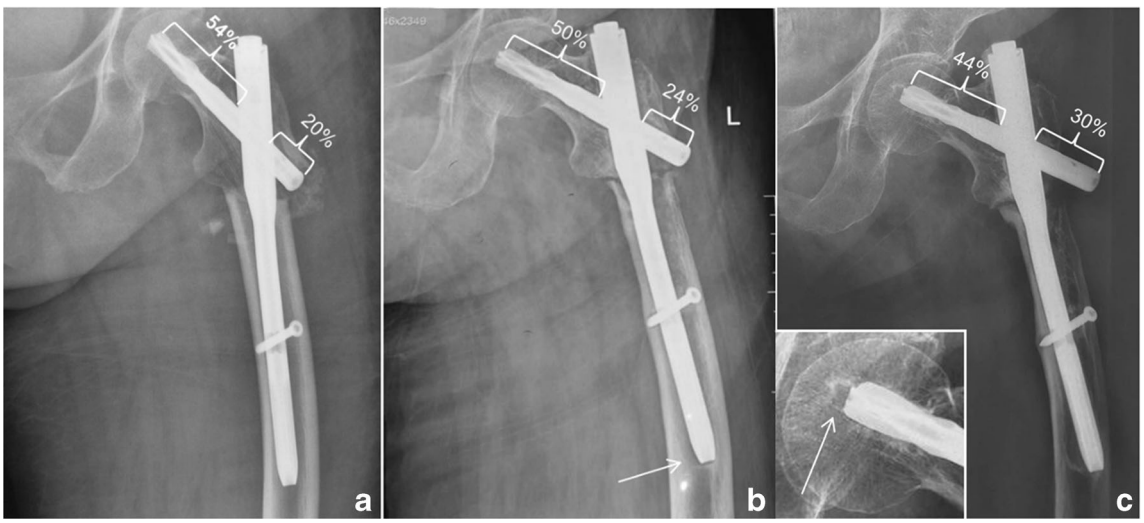

Fig. 2 X-rays of the left femoral subtrochanteric fracture 2 years 10 months after operation (B) showing fracture nonunion. Compared with those in the X-rays immediately after surgery (A), the main PFNA-II nail is close to the medial cortex of the femur and the distal end is displaced to the lateral side. It was considered that the main nail was loosened, because it was loose in the femoral medullary cavity. A bone-hardening band (arrow) with a wider diameter than the main nail was present. The length of the spiral blade was measured, and the relative position of the main nail was displaced outward by approximately 4%; as the PFNA-II itself was designed with a spiral blade, the sliding force of the main nail was applied, and the distance from the tip of the blade to the edge of the femoral head was not increased. It was considered that the screw blade was still stable. X-ray of the left hip joint after 2 years of teriparatide treatment (C). The fracture had not healed, and the spiral blade had slid outward by approximately 10% the length of the position of the main nail. More importantly, the distance from the tip of the blade to the edge of the femoral head was significantly increased and the tip of the blade exhibited a characteristic "radiolucent shadow" appearance (arrow)

loosening (Fig. 2(C)). Considering that the internal fixation device had been implanted for nearly 5 years and the affected limb was often subject to weight-bearing when walking, the possibility of fatigue fracture of the internal fixation device was extremely high; hence, surgical treatment was recommended; however, the patient still refused surgery.

In April 2018 (5 years 10 months after the left femoral subtrochanteric fracture operation), the patient self-reported that left hip pain was significantly aggravated when walking. She requested surgical treatment at our hospital. At this time, she had stopped taking BPs for 3 years. The proposed operation plan was to replace the full-length intramedullary nail and use autogenous iliac grafts as implants for the bone fracture ends. Intraoperatively, owing to the large angle of the anterior curvature of the femur, a full-length intramedullary nail could not be placed. The standard 240-mm PFNA-II was replaced, and the placement of the main nail was uneventful. To strengthen the grip force and antirotation effect of the replacement PFNA-II spiral blade, a small amount of bone cement was injected into the femoral head and neck after the removal of the original blade; thereafter, the new spiral blade was inserted and finally the fracture ends were cleaned. After applying the autogenous iliac bone grafts, the operation was completed. X-ray re-examination of the right hip joint at 3 months postoperatively (Suppl Figure 2) showed good internal fixation, fracture healing, and no pain or discomfort on weight bearing.

Discussion

Osteoporotic fracture has become one of the main problems seriously affecting the quality of life and health of the elderly patients. To reduce fracture incidence, anti-osteoporosis treatment is particularly important. Currently, BPs are widely used owing to their safety and effectiveness; they have helped to significantly reduce osteoporotic fracture incidence in postmenopausal women [1, 8]; however, their long-term use might be an important cause of AFFs [3, 4]. The ASBMR report clearly states that long-term BP use might lead to a higher risk of AFF [7, 9]. Although its incidence has gradually increased with the widespread use of BPs, there are currently no diagnostic and therapeutic guidelines.

In recent years, long-term BP use has caused excessive bone remodeling inhibition, and AFFs have gradually attracted the attention of clinicians [7, 9, 10]. However, some studies have shown that the absolute AFF risk in patients taking BP is low, with only 3.2–50 cases/100,000 patients/year [5, 7, 11]; thus, BPs will continue to be the first-line anti-osteoporosis treatment until better alternative drugs are available [12]. However, it is now recognized there might be ethnic differences in the risk of AFF, and Asians have a greater propensity to suffer an AFF while taking BP therapy [13]. With the wider use of BPs, AFF incidence will gradually increase [12]. Given its severe bone remodeling inhibition, patients with AFFs often have delayed fracture healing [9]. Conservative treatment of AFFs with incomplete fracture also has poor outcomes [14, 15] and thus promoting AFF healing is a difficult aspect of treatment. Herein, we present a case of bilateral atypical fracture of the femurs. Although roughly the same surgical treatment was given to both the fractures, the outcomes of the two sides were completely different. The left AFF occurred 5 years after taking alendronate. Given the surgical approach was closed reduction and intramedullary nailing, the operation had less effect on the blood supply and soft tissue of the fracture ends, and early postoperative X-ray re-examination showed good fixation of the fracture, ruling out fracture nonunion caused by the operation. At this time, the bone turnover rate of the patient was low, which might have been the main cause of postoperative fracture nonunion.

Teriparatide is a fragment of recombinant human parathyroid hormone from amino acids 1–34, which have been used to treat osteoporosis and reported to promote fracture healing [16, 17]. In the present study, the patient was treated with teriparatide to promote healing of the left AFF. The bone turnover indices before treatment (Suppl Table 1) showed that her bone turnover rate was extremely low, further confirming that one of the important reasons of left femoral subtrochanteric fracture nonunion could be the low bone metabolism level. The right AFF occurred 2 months after teriparatide use. At this time, teriparatide had reached the required course of treatment to stimulate bone formation [18], and X-ray re-examination after 4 months showed uneventful fracture healing. The different outcomes of the AFFs on the two sides suggest that bone metabolism inhibition induced by long-term BP use might be one of the causes of delayed fracture healing or fracture nonunion. For such patients, BP should be stopped immediately, and teriparatide might be considered in the early stages of fracture healing to restore normal bone metabolism and promote fracture healing. In this patient, BP was immediately discontinued after the left AFF and started teriparatide treatment. The prime time of fracture healing is the early stage after the fracture. The patient began teriparatide treatment 2 years 10 months after the left AFF, and the decreased ability of fracture healing might be a reason the fracture was not healed. More importantly, if teriparatide treatment was started earlier after the left AFF, the patient might have avoided the right AFF.

The patient's bone turnover indices 2 years after teriparatide use (Suppl Table 1) were as follows: osteocalcin increased from 3.85 ng/mL before treatment to 11.76 ng/mL (15–46 ng/mL), ß-CTx increased from 0.010 to 0.139 ng/mL (0.21–0.44 ng/mL), and T-P1NP increased from 29.88 to 53.29 ng/mL (20.25–76.31 ng/mL). Although the bone metabolism status improved overall, X-ray re-examination showed that the left hip fracture had not healed, presumably because the internal fixation device in the left subtrochanteric fracture had already loosened during teriparatide use, and the

fracture instability affected fracture healing. Additionally, ossified bone at the fracture ends (confirmed by later revision surgery) also hindered normal fracture healing.

The ASBMR report on AFFs suggests that surgical treatment of atypical fractures should be performed with full-length intramedullary nail reconstruction to protect the entire femur, but in the present case, ultra-short intramedullary nails were used in both subtrochanteric fracture operations. Particularly, BPs were used for nearly 3 years after the left subtrochanteric fracture operation, and there was no atypical fracture of other parts of the femur postoperatively. Leclerc et al. also found that the type of implant, its position, and the femoral geometry did not appear to be risk factors for atypical periprosthetic femoral fractures (APFFs) compared with periprosthetic femoral fractures (PFFs) [19]. This might be partly because the proximal one-third of the femoral shaft endured severe bending stress and more inclined to develop AFF, but most types of implants have covered this part of the femur. AFFs are relatively rare in other parts of the femur. Therefore, whether full-length intramedullary nailing is necessary in the absence of signs of significant atypical fractures in other parts of the femur is still worthy of discussion. Additionally, early postoperative follow-up X-ray examinations also confirmed that short intramedullary nails provide sufficient stability in the early postoperative period, but the different outcomes of atypical femoral fractures on the left and right sides suggest that the immediate recovery of bone metabolism level from the inhibited state may be a key to atypical fracture healing postoperatively. If bone metabolism level remains low for a long time post-surgery, fracture healing will be delayed, and the internal fixation device will gradually loosen due to weight bearing in the affected limb, eventually causing fracture nonunion.

To relieve the patient's pain symptoms and to avoid the fracture of the left hip internal fixation device, the patient underwent surgical treatment again at 5 years 10 months after the left hip operation. Fracture nonunion was confirmed intraoperatively, and hardened bone was formed at the fracture ends. The 240-mm PFNA-II was replaced and autogenous iliac bone grafting was performed. The patient's bone turnover indices were significantly increased after 2 years of teriparatide treatment (Suppl Table 1). X-rays confirmed fracture healing only at 3 months postoperatively, indicating that a specific bone metabolism level is among the basic conditions for fracture healing.

Given the low incidence of BP-related atypical fractures, a large-scale case study is relatively difficult, and there is no clear guidance or consensus on their treatment. The value of this case lies in the fact that this is a self-controlled study in the same individual. By analyzing and investigating the possible causes of the different outcomes of the two AFFs, a reference for the clinical treatment of atypical fracture is provided to improve the standard of treatment.

Compliance with ethical standards

Conflict of interest None.

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