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CASE REPORT

Weekly Teriparatide for Delayed Unions of Atypical Subtrochanteric Femur Fractures

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ABSTRACT

Introduction: The occurrence of atypical femur fractures (AFFs) in patients on prolonged bisphosphonate treatment has been gaining medical attention, but the use of pharmacotherapy for these fractures has not been explored in detail. The authors describe a case of AFFs successfully treated with once-weekly administration of 56.5 μg teriparatide (TPTD).

Case Presentation: The patient was a 74-year-old female patient who had been taking alendronate for approximately 6 years and who suffered with a fall while walking. X-rays revealed a subtrochanteric right femur fracture. The contralateral femur showed cortical thickening and a transverse radiolucent fracture line. Based on these specific features, the patient was diagnosed with AFF. The patient underwent osteosynthesis with intramedullary nailing for the right fracture. Alendronate treatment was discontinued. Low-intensity pulsed ultrasonography therapy did not affect the healing of the fracture with delayed union, even after 3 months of application. Prophylactic osteosynthesis was performed for the subtrochanteric left femur. Bone tissue collected from the left fracture site during surgery showed severe suppression of bone turnover. Union of bilateral femurs was achieved after 3 months of a once-weekly administration of TPTD.

Conclusion: Once-weekly TPTD treatment is shown to be beneficial for improving the healing of AFFs showing delayed union.

Keywords: Atypical femoral fractures; Bisphosphonates; Delayed union; Teriparatide

INTRODUCTION

Atypical subtrochanteric or femoral shaft fractures occasionally show delayed union, especially in osteoporosis patients undergoing long-term treatment with bisphosphonates. However, there have been few published studies on the effects of pharmacotherapy on

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these fractures. Previous studies have suggested that teriparatide (TPTD) therapy can be effective to promote healing of fractures with delayed unions [1–6]. However, it is still unknown whether a once-weekly administration of TPTD could offer an effective alternative to the daily TPTD. Herein, the authors report a patient with delayed union after surgery for an atypical femoral fracture (AFF) who was effectively treated with once-weekly administration of 56.5 μg of TPTD.

CASE REPORT

A 74-year-old female patient with osteoporosis, who had been taking alendronate and alfacalcidol for approximately 6 years, suffered femur fractures following a fall in March 2012. Radiography revealed a subtrochanteric right femur fracture (Fig. 1a). In addition, her contralateral thigh showed thickening of the lateral cortex and a transverse radiolucent fracture line in the subtrochanter (Fig. 1b). The patient was diagnosed with AFFs. The patient had normal levels of bone resorption markers, but low levels of a bone formation marker (Table 1).

Four days after admission, the authors performed minimally invasive osteosynthesis using intramedullary nails (Fig. 2). Alfacalcidol was continued but alendronate was ceased. Two weeks later, low-intensity pulsed ultrasonography (LIPUS) therapy was started for both thigh regions to promote bone healing. In June 2012, radiography and computed tomography imaging revealed signs of delayed union at the right fracture site (Fig. 3).

The patient could not walk without a crutch owing to contralateral thigh pain. After obtaining informed consent, prophylactic osteosynthesis was performed on the left subtrochanteric lesion in June 2012. Bone biopsy samples collected at the intramedullary nail insertion site revealed an absence of osteoblasts and osteoclasts on trabecular surfaces (Fig. 4), as well as low bone volume (Table 2).

LIPUS treatment was restarted after surgery. In August 2012, once-weekly TPTD (56.5 μg)

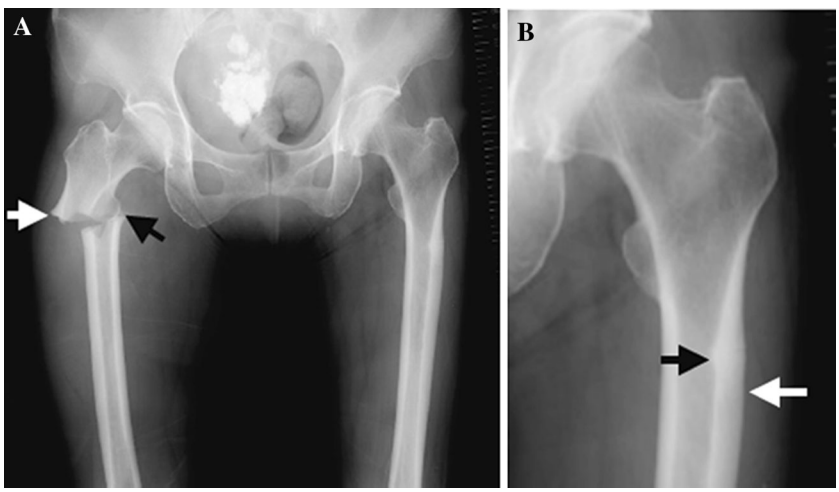

Fig. 1 Radiograph imaging at the time of admission. **a** Radiograph imaging at the time of admission shows the right subtrochanteric fracture with breaking of the lateral cortex (*white arrow*) and spiking of the medial cortex (*black arrow*). **b** Zoomed image of the left thigh shows thickening of the lateral cortex (*white arrow*) and a transverse radiolucent fracture line (*black arrow*)

Table 1 Biochemical markers at the time of admission

Parameters	Results	Reference range
Serum calcium (mg/dL)	8.9	8.7–10.3
Serum phosphorous (mg/dL)	2.7	2.5–4.7
Serum alkaline phosphatase (U/L)	163	115–369
Urine NTX (nmol BCE/mmol·Cre)	17.1	14.3–89.0
Serum TRACP-5b (mU/dL)	257	120–420
Serum P1NP (μg/L)	6.4	17.0–64.7[a]
Serum ucOC (ng/mL)	0.39	<4.50
Serum homocysteine (nmol/mL)	8.2	5.1–11.7
Serum pentosidine (pg/mL)	20.3	9.2–43.1

NTX N-telopeptide of type I collagen, *P1NP* procollagen type 1*N*-terminal propeptide, *TRACP-5b* tartrate-resistant acid phosphatase type 5b, *ucOC* uncarboxylated osteocalcin

[a] Postmenopausal

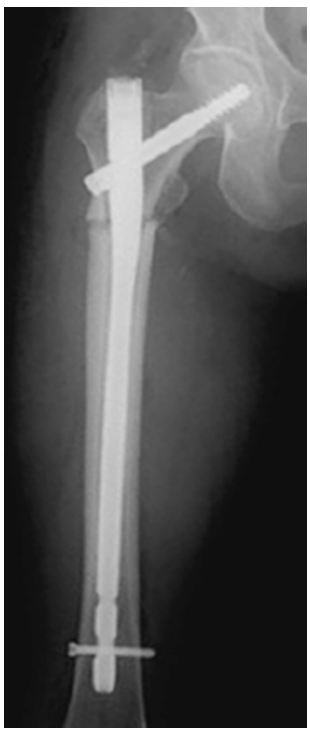

Fig. 2 Radiograph imaging of the right thigh at the time of surgery

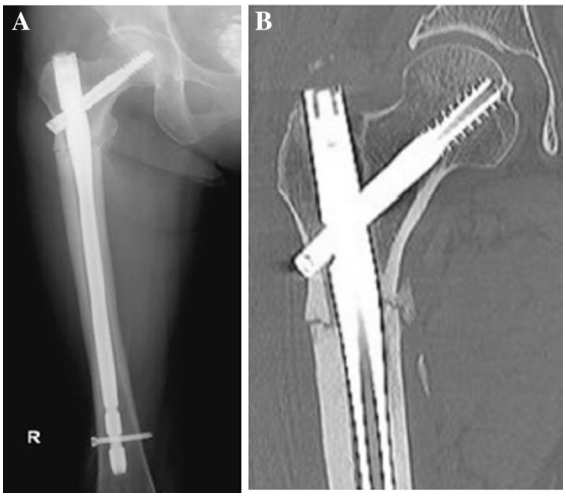

Fig. 3 Radiograph and CT imaging after 3 months of LIPUS therapy. **a** Radiograph imaging after 3 months of LIPUS therapy shows delayed union at the fracture site. **b** CT imaging after 3 months of LIPUS therapy shows delayed union at the fracture site. *CT* computerized tomography, *LIPUS* low-intensity pulsed ultrasonography

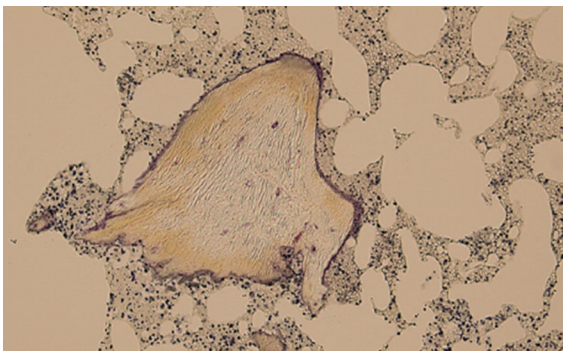

Fig. 4 Trabecular surfaces (×200 magnification, Villanueva bone stain) show a total absence of osteoblasts and osteoclasts (photomicrographs were taken at the Niigata Bone Science Institute, Niigata, Japan)

was added, and the patient's tartrate-resistant acid phosphatase type 5b (TRACP-5b) and procollagen type 1*N*-terminal propeptide (P1NP) levels increased transiently, as did their lumbar bone mineral density (Table 3). After 3 months of TPTD treatment, the patient's fractures had improved (Fig. 5). Administration of TPTD was terminated in February 2013 and

Table 2 Results of histomorphometric assessment of bone biopsy specimens

Parameters	Abbreviations	Results	Reference data[a]
Bone volume			
Bone volume	BV/TV (%)	11.54	11.0 ± 1.8
Trabecular thickness	Tb.Th (μm)	103.09	131.3 ± 28.1
Wall thickness	W.Th (μm)	17.96	28.3 ± 3.7
Osteoid characteristics			
Osteoid volume	OV/TV (%)	0.01	0.36 ± 0.31
Osteoid volume	OV/BV (%)	0.06	1.6 ± 0.4
Osteoid surface	OS/BS (%)	1.04	12.8 ± 2.2
Osteoid thickness	O.Th (μm)	2.83	6.4 ± 0.8
Osteoblast surface	Ob.S/BS (%)	NC	
Resorption			
Eroded surface	ES/BS (%)	0.06	3.0 ± 1.0
Osteoclast surface	Oc.S/BS (%)	NC	
Fiber volume	Fb.V/TV (%)	0.00	0

NC not calculated

[a] Reference data from iliac crests of female over 71 years old

Table 3 Treatment and changes in bone turnover markers and lumbar bone mineral density

Parameters	Admission	1 month	3 months	5 months	6 months	7 months	10 months	14 months
Treatment	Alfacalcidol	Alfacalcidol + LIPUS	Alfacalcidol + LIPUS	Alfacalcidol + LIPUS + TPTD	Alfacalcidol + LIPUS + TPTD	Alfacalcidol + LIPUS + TPTD	Alfacalcidol + LIPUS + TPTD	Alfacalcidol
TRACP-5b (mU/dL)	257	380	330	460	484	400	358	261
P1NP (μg/L)	6.4	86.2	54.8	81.8	90	65	47.1	39
Lumbar bone mineral density (g/cm^2)	0.845	–	0.826	–	–	–	0.810	0.872

LIPUS low-intensity pulsed ultrasonography, *P1NP* procollagen type 1*N*-terminal propeptide, *TPTD* teriparatide, *TRACP-5b* tartrate-resistant acid phosphatase type 5b

the patient can now walk independently without crutch.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from the patient for being included in the case report.

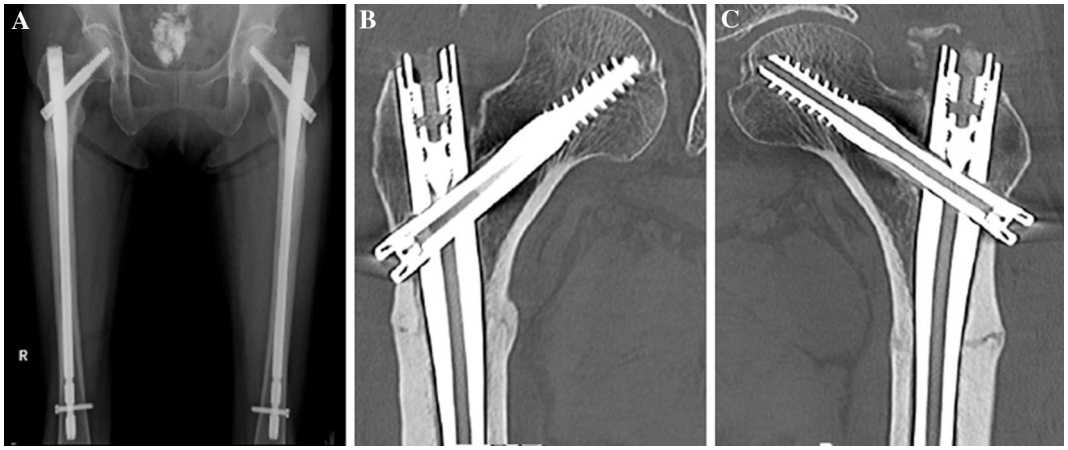

Fig. 5 Radiograph and CT imaging after 3 months of TPTD therapy. **a** Radiograph imaging after 3 months of TPTD therapy shows complete union of fractures. **b** CT imaging after 3 months of TPTD therapy shows complete union of the right thigh fracture. **c** CT imaging after 3 months of TPTD therapy shows complete union of the left thigh fracture. *CT* computerized tomography, *TPTD* teriparatide

DISCUSSION

The occurrence of AFFs associated with severely suppressed bone turnover (SSBT) in osteoporotic patients receiving bisphosphonates over prolonged periods was first reported in 2005 [7]. A task force from the American Society for Bone and Mineral Research (ASBMR) defined the major and minor features of AFFs [8], recommending that all major features should be present to confirm a diagnosis of AFF. Bisphosphonates effectively reduce the risk of femoral neck fractures in elderly women, but when continued for more than 5 years, the therapy can result in excessive suppression of bone turnover, thus increasing the risk of AFFs [9].

The present case had an approximately 6-year history of alendronate therapy and subtrochanteric fractures with the major features designated by ASBMR; therefore, the case was diagnosed as having bisphosphonate-associated AFFs. Although urine *N*-telopeptide of type I collagen and serum TRACP-5b levels were normal, the patient's serum P1NP was low, suggesting reduced bone formation. Bone biopsy was performed at the intramedullary nail insertion site and undecalcified thin sections were made for trabecular bone histomorphometry. The data revealed a decrease in bone formation parameters (wall thickness, osteoid volume, osteoid surface, osteoid thickness, osteoblast surface) as well as a decrease in bone resorption parameters (eroded surface, osteoclast surface). It was speculated that the patient's bone turnover was extremely low in the proximal femur of this patient, and that SSBT attributed to alendronate use for more than 5 years led to their AFFs and delayed union. On the other hand, Zanchetta et al. [10] reported that there were no distinctive microarchitecture features in the peripheral skeleton of a female patient who had suffered AFF while receiving bisphosphonate treatment. So, other factors including patient characteristics and instability of osteosynthesis might be concerned with AFFs and delayed union.

Union of both femur fractures was confirmed after 3 months of TPTD treatment. It was

thought that TPTD stimulated the suppressed bone formation caused by long-term use of bisphosphonates. Two types of TPTD injection are available for treatment of osteoporosis in patients with a high risk of fracture in Japan: once-daily 20 μg or once-weekly 56.5 μg. It was thought that the increased bone formation owing to TPTD may have accelerated fracture healing and improved bone union. A search of the literature revealed several other similar clinical cases that were successfully treated with TPTD [1–6]. Aspenberg et al. [11] showed a shorter healing time in postmenopausal women with dorsally angulated distal radial fractures who were treated once daily with TPTD 20 μg, compared with women treated with placebo. However, no difference in fracture healing time was observed between women treated once daily with TPTD 40 μg and women treated with placebo [11]. Therefore, it appears that the dose of TPTD is important to achieve accelerated fracture repair. Although the patient in the current study received once-weekly TPTD, the overall dose received is considered closer to the once-daily 20 μg dose than to the once-daily 40 μg dose. Chiang et al. [12] showed that once-daily TPTD 20 μg improved the bone quality and healing of AFFs associated with bisphosphonate therapy, while Mitani [13] described a case in Japan showing nonunion of a femoral neck fracture who, like the patient in the current study, benefited from once-weekly treatment with TPTD 56.5 μg. Collectively, these findings [13], together with the findings in the current case, suggest that fracture repair might be accelerated by once-weekly treatment with TPTD 56.5 μg, or once-daily treatment with TPTD 20 μg. Warden et al. [14] reported in animal model that TPTD and LIPUS have contrasting additive effects during fracture healing, and the patient in the current case treated with TPTD and LIPUS, so the fracture repair might be due to the combination therapy. Based on the authors' experience, it is suggested that once-weekly TPTD treatment is beneficial for improving the healing of AFFs showing delayed union as well as other fracture treatment methods including electrical stimulation, bone graft, bone morphogenetic proteins, and LIPUS.

CONCLUSION

Suppressed bone formation caused by long-term bisphosphonate therapy can delay the union of fractures in osteoporotic patients. Although TPTD administration has been shown to accelerate the healing in such patients, it is not clear if daily or weekly treatments are required. The authors demonstrate in this report that weekly treatments are sufficient and should be considered for treating patients with AFFs with delayed union.

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Conflict of interest. F. Fukuda, N. Kurinomaru, and A. Hijioka, declare no conflict of interest.

Compliance with ethical guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the

Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from the patient for being included in the case report.

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