Histological finding of atypical subtrochanteric fracture after long-term alendronate therapy

J Orthop Sci (2012) 17:313–318
DOI 10.1007/s00776-011-0085-8

CASE REPORT

Histological finding of atypical subtrochanteric fracture after long-term alendronate therapy

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Received: 24 November 2010 / Accepted: 23 March 2011 / Published online: 21 May 2011

Introduction

Drug therapy for osteoporosis is widely accepted. Bisphosphonates in particular significantly inhibit bone resorption by suppressing osteoclast activity and increasing bone density [1–3]. Alendronate is one of these bisphosphonates; it was approved in the United States in the 1990s and is commonly prescribed worldwide [1, 4, 5]. Clinical trials have shown its effectiveness in the treatment of fractures related to postmenopausal osteoporosis [6]. However, some recent reports have described unusual subtrochanteric or femoral shaft fractures following long-term alendronate therapy [4, 7–13]. Although no causal relationship between long-term alendronate treatment and these atypical stress fractures has been established, some reports suggest that the severe suppression of bone turnover by alendronate may lead to accumulated microdamage to the bone that subsequently results in complete fracture [4, 12].

In this report, we describe a patient who experienced prodromal pain and 14 months later sustained an atraumatic subtrochanteric fracture after 3 years of alendronate therapy. We include a detailed histological analysis of bone from the unusual fracture site.

Informed consent for this report was obtained from the patient, and the research protocol was approved by the hospital investigational review board.

Case report

A 62-year-old woman (154 cm, 49 kg, BMI 20.7 kg/m^2) had been hospitalized for the treatment of asthma attacks. Her medical history showed Churg-Strauss syndrome, sinusitis, goiter, diabetes mellitus, and cerebral infarction. She was given an oral glucocorticoid (7 mg/day) for asthma. Oral alendronate (5 mg/day) was prescribed to prevent glucocorticoid-induced osteoporosis; 6 months later this was converted to one weekly tablet (35 mg/week).

About 26 months after initiation of the therapy, the patient experienced prodromal pain in her left thigh without any trauma and consulted the orthopaedics department as an outpatient. A radiograph at that time showed diffuse cortical thickening on the bilateral femora and an external cortical bone reaction on the left femur, but no fracture (Fig. 1a). MR imaging showed cortical thickening and atypical signaling on both the endosteum and periosteum surfaces in the same region of the left femur (Fig. 1b). We recommended partial weight bearing and restricted activities, and the pain soon decreased. Bone mineral density (BMD) of the L2–L4 vertebrae measured by dual-energy X-ray absorptiometry (DEXA) 1 month before the fracture was a T-score of −0.5, which is not in the osteoporotic range defined by the World Health Organization [14]. Laboratory investigations made 3 months before the injury and biochemical markers of bone turnover taken just after

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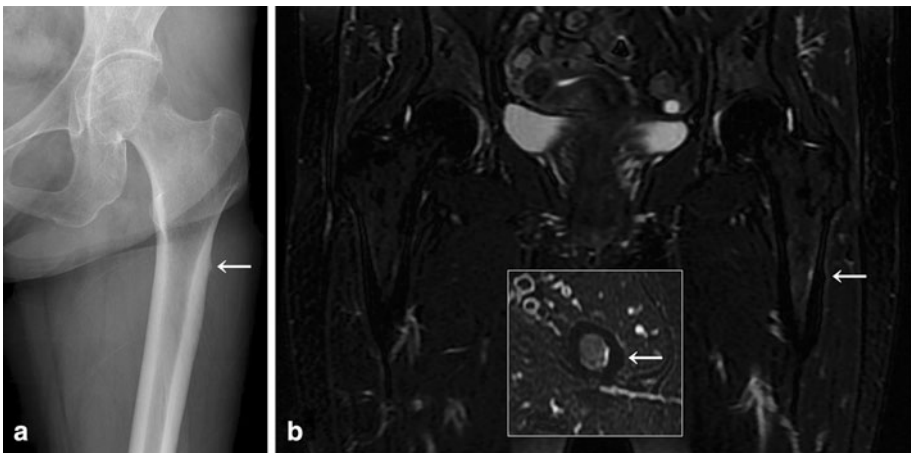


Fig. 1 **a** Plain radiograph taken at the first presentation of thigh pain (14 months before the fracture). There is a cortical reaction (*arrow*) on the lateral side of the subtrochanteric region with diffuse cortical thickening. **b** MR imaging (coronal and axial view) shows atypical signaling on both the endosteum and periosteum surfaces in the same region of the left femur

Table 1 Laboratory investigations and biochemical markers of bone turnover

		Reference range
Serum calcium (mg/dl)[a]	10.0	8.0–10.5
Serum phosphate (mg/dl)[a]	3.5	2.5–4.5
Serum ALP (IU/l)[a]	161	115–359
Serum albumin (g/dl)[a]	4.2	4.0–5.0
TRAP-5b (mU/dl)[b]	188	120–420
Urine DPD/Cr (nM)[b]	6.4	2.8–7.6
Serum ucOC (ng/ml)[b]	0.46	<4.5

ALP alkaline phosphatase, *TRAP-5b* serum tertrate-resistant acid phosphatase type 5b, *DPD* deoxypyridinoline, *Cr* creatinine, *ucOC* undercarboxylated osteocalcin

[a] Data 3 months before the injury

[b] Data just after the fracture

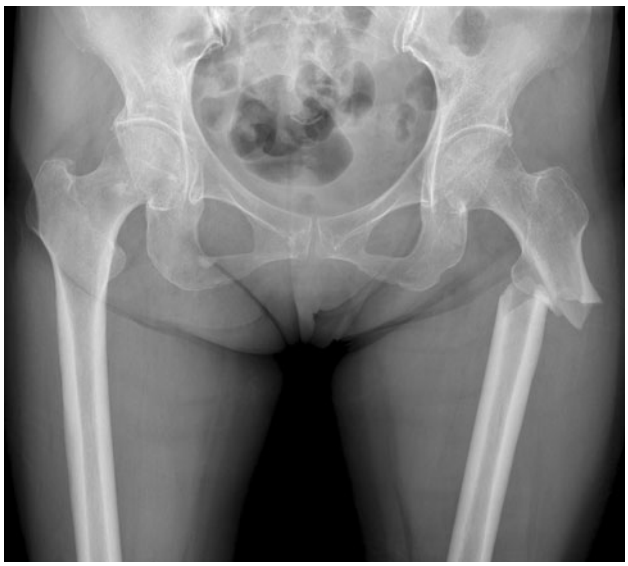


Fig. 2 A plain radiograph reveals a displaced subtrochanteric fracture of the left femur with diffuse cortical thickening and a unilateral cortical spike

the fracture are summarized in Table 1. These results were all within reference ranges.

Fourteen months after prodromal pain, she experienced acute pain on her left thigh while walking and turning around in the hospital ward, and then fell down. Radiography showed a subtrochanteric fracture of the left femur classified as AO type 31-A3 accompanied by diffuse cortical thickening, external cortical bone reaction, and a cortical spike (Fig. 2). The fracture occurred in the same region where atypical findings had been observed in the radiograph and MR images at her first visit.

Operation and histological examination

Surgery was performed 8 days after the injury. Alendronate treatment was discontinued before the operation. The fracture was treated with internal fixation using a plate (NCB® distal femur, Zimmer Trauma, Warsaw, IN) on the tension side of the femur because the medullary canal had been distinctly narrowed by the diffuse cortical thickening, making it impossible to insert any intramedullary nailing. We did not perform bone grafting to the fracture site because bony contact was completely achieved between fragments. A bone biopsy of the unusual hypertrophied external "beak-shaped" cortex was performed intraoperatively for histological analysis. The fractured cortex was extremely hard and sclerotic, like osteopetrosis (Fig. 3). A histological examination stained by hematoxylin and eosin showed immature new bone formation added on the existing cortex, which included some chondroid tissues; this was presumed to be a response to the past microfracture (Fig. 4a, b). Tertrate-resistant acid phosphatase (TRAP) staining showed almost no TRAP-positive multinucleated osteoclasts in either the existing cortex or the newly formed bone (Fig. 4c).

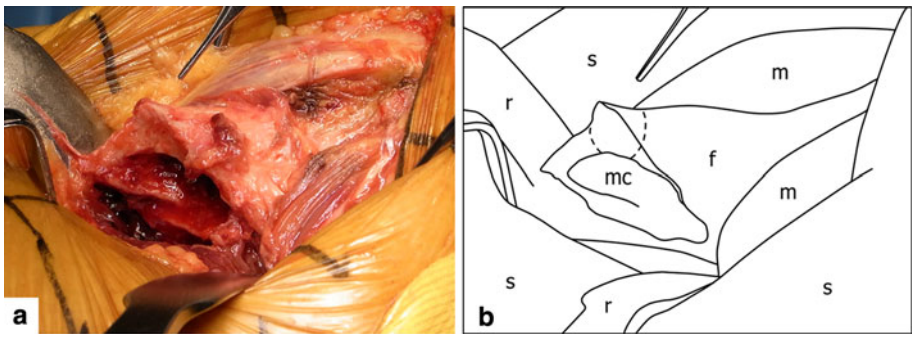


Fig. 3 **a** Intraoperative photo of the unusual beak-shaped fracture end (proximal side). The fractured cortex was extremely hard and sclerotic, as in osteopetrosis. **b** Schema of the fracture site. The unusual hypertrophied external "beak-shaped" cortex (circled by *dashed line*) was excised for histological analysis. *f* femur, *mc* medullary cavity, *s* skin, *m* muscle, *r* retractor

Partial weight bearing was begun 4 weeks after the operation and full weight bearing started after 7 weeks. At an 8-month follow-up, the patient reported complete pain relief. Radiographs made at that time showed abundant callus formation on the fracture gap, and fracture healing was achieved (Fig. 5).

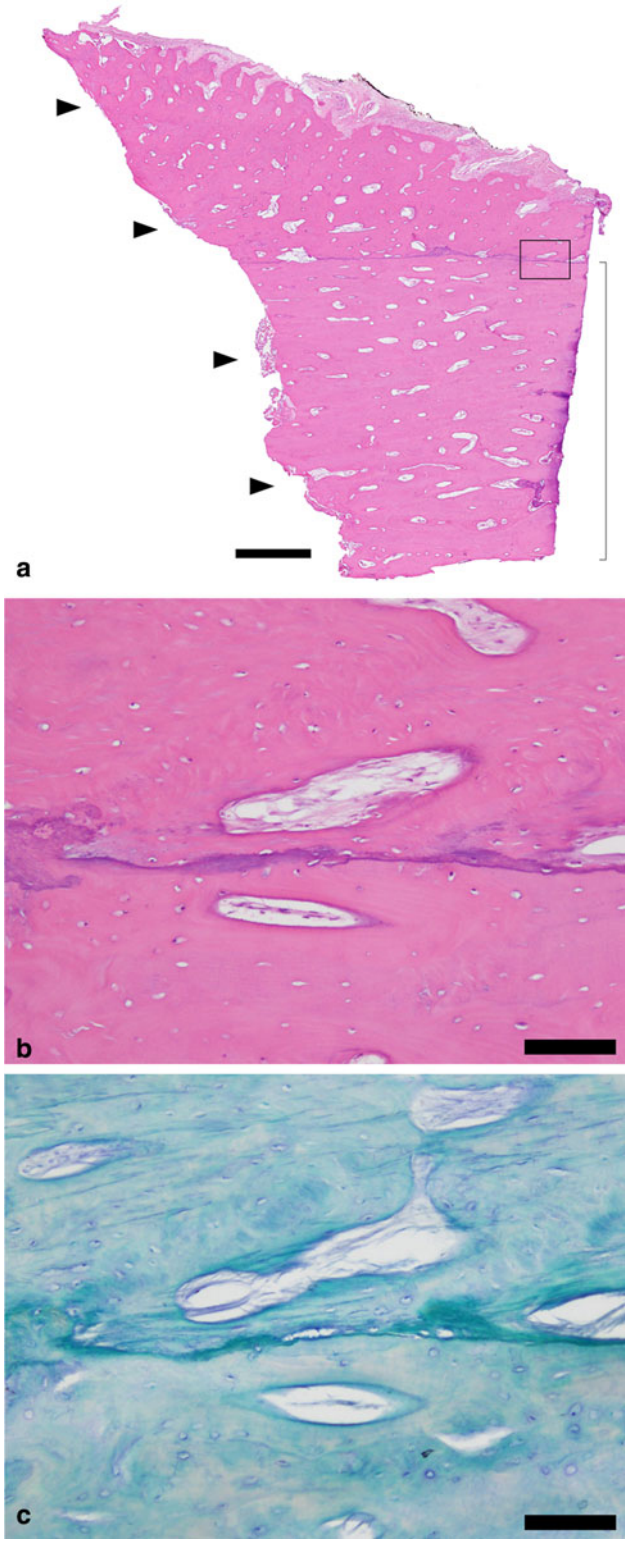
We performed no preventive surgery or treatment on the contralateral femur other than discontinuing alendronate therapy because the patient experienced no pain on that side and no inconvenience, although diffuse cortical thickening was present on the radiograph [15]. No subsequent pain and no additional fractures have occurred since the follow-up.

Discussion

Bisphosphonates significantly decrease osteoclast-mediated bone resorption and increase bone mineral density [2, 5, 8]. Thus, the administration of bisphosphonates is one of the first treatments considered for the prevention of osteoporosis-related fractures in postmenopausal patients [3, 8, 16]. Alendronate is one of these bisphosphonates. It was approved in the 1990s in the US and is commonly prescribed worldwide [1, 5]. The effectiveness of bisphosphonates in the treatment of fractures related to postmenopausal osteoporosis has been demonstrated in numerous large clinical trials, and it has been reported that their long-term use for up to 10 years is safe and effective [3, 6].

However, Odvina et al. [11] first described a series of atraumatic nonspinal fractures in patients who had been taking alendronate for a long period, noting it as a potential complication of alendronate therapy. Thereafter, an increasing number of subtrochanteric or femoral shaft fractures associated with long-term alendronate treatment have been reported [4, 7–13]. Goh et al. [8] described patients who sustained fractures in the subtrochateric region, and five of nine patients (56%) had prodromal pain in the affected hip. Kwek et al. [9] retrospectively reviewed 17 patients who had sustained low-energy subtrochanteric fractures while on alendronate therapy and reported characteristic fracture configurations that consisted of (1) cortical thickening on the lateral (tension) side of the subtrochanteric region, (2) a transverse fracture, and (3) a medial cortical spike. They reported that 9 patients (53%) had bilateral stress fractures and 13 (76%) experienced prodromal pain before the injury. Lenart et al. [10] also described a unique radiographic pattern, defined as a simple transverse or oblique (<30°) fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft. Our patient shared these same atypical radiographic patterns, with prodromal pain prior to the injury, which corresponded to the report of a task force of the American Society for Bone and Mineral Research (ASBMR) [17].

Many reports have described unusual discrete thickening (prominence) on the lateral cortex on the radiograph as well as prodromal pain [9, 18, 19]. This external cortical reaction in the lateral femoral tension side is thought to be caused by microfractures at these high stress points on the skeleton [9, 13, 18, 20, 21]. The subtrochanteric region of the femur is subject to large bending forces with compression stress on the medial cortex and tensile stress on the external cortex [4, 7, 22]. The microdamage to the bone is repaired through normal physiological remodeling processes by the action of both osteoblasts and osteoclasts [17, 23]. However, alendronate inhibits bone resorption by suppressing osteoclast activity and impairs bone turnover [8]. Mashiba et al. [23] reported that in an experimental dog model bone turnover suppression led to an accumulation of microdamage, resulting in reduced bone strength. The increased microdamage accumulation may increase the risk of insufficiency fractures [8, 23]. Odvina et al. [11] reported patients who sustained atraumatic nonspinal fractures while



◀ **Fig. 4** A histological analysis of the unusual fracture end was performed. **a** A lower magnification of H&E staining shows immature new bone formation added on the existing cortex. *Scale bar* represents 1 mm. **b** A large magnification of the H&E staining of the *box* in **a**. Upper half of the figure represents the newly formed bone, and lower half is the existing cortex. *Scale bar* represents 100 μm. **c** On the serial section of **b**, tertrate-resistant acid phosphatase (*TRAP*) staining found almost no TRAP positive multinucleated osteoclasts in either area. Methyl green was used for the counterstain

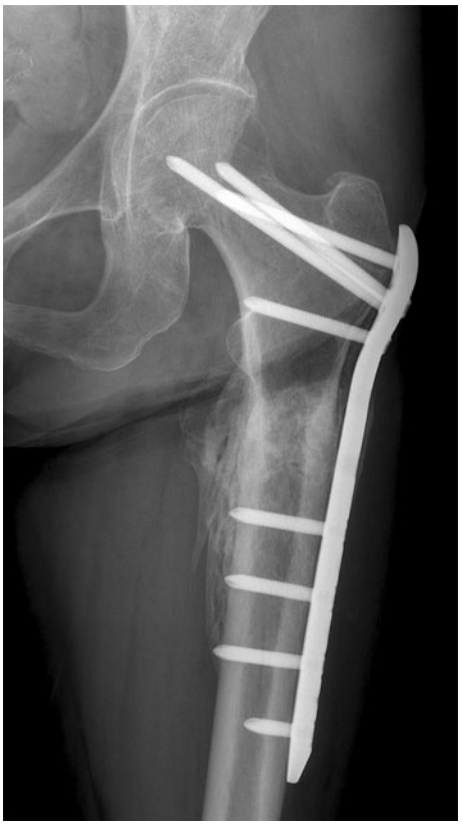


Fig. 5 Internal fixation was accomplished using a plate on the tension side of the femur without bone graft. A plain radiograph performed at follow-up, 8 months after the operation, shows abundant callus formation on the fracture gap; fracture healing was achieved

on alendronate therapy, with histomorphometric analysis showing severely suppressed bone turnover (SSBT). In our case, an abnormal signal was detected by MR imaging before the complete fracture, and the detection by bone scintigraphy or SPECT of increased uptake at the site of the cortical thickening has been reported by others [3, 13, 18]. Our images were consistent with a microfracture on the lateral femoral tension side. The ellipsoid thickening was a local response to the microfracture; our laboratory investigations and bone mineral density readings were all within the reference ranges and corresponded with those reported previously [4, 18, 19]. Given that reiterative tensile stress is one of the factors associated with a subtrochanteric insufficiency fracture [7], we determined that plate fixation on the femoral tension side was a more valid procedure than intramedullary nailing.

Some reports have advised discontinuance of alendronate therapy after the identification of atypical radiographic patterns on the proximal femur, thigh pain, or after an

insufficiency fracture has unfortunately occurred [13, 18, 24]. However, the skeletal half life of alendronate is very long [3, 12, 25]; when discontinued, it remains in the skeleton for years, and the physiological effect on bone resorption has been reported to remain for up to 5 years [3, 5, 26]. Somford et al. [19] reported some patients treated with intramedullary nailing who went into delayed union when alendronate therapy was not discontinued. The advantages or disadvantages of discontinuing alendronate therapy after a fracture remain unresolved.

We also performed a bone biopsy from the unusual lateral "beak-shaped" cortex, and this is one of few reports of a biopsy from the unusual fracture end. Both hematoxylin/eosin and tertrate-resistant acid phosphatase (TRAP) staining showed immature new bone formation added on the existing cortex, which included some chondroid tissues and almost no TRAP-positive osteoclasts in either the existing cortex or the newly formed bone; this might be presumed a response to the past microfracture and suppressed bone remodeling.

Many patients reported to have alendronate-associated insufficiency fractures had concurrent diseases and were receiving many types of medications other than bisphosphonates. In fact, our patients had been treated for Churg-Strauss syndrome, which was a rare diffuse vasculitis accompanied by severe asthma and was treated with glucocorticoids as first-line therapy [27]. However, there has been no report about this syndrome per se influencing bone metabolism. The patient also had a history of diabetes mellitus and goiter. These conditions might influence the occurrence of the atypical fracture; however, the influence of these concurrent diseases and medications on the fractures remains unknown [13, 19].

From the large, randomized clinical trials of bisphosphonates, it was concluded that there is no significant relationship between bisphosphonate treatment and the risk of subtrochateric or diaphyseal fracture [28, 29]. Subtrochanteric or diaphyseal fractures in postmenopausal women are relatively rare, representing 2–6% of all osteoporotic hip fractures [5, 10]. Shane claims that the study's statistical power was low and, if bisphosphonate use is causal, the benefits exceed the risk of atypical femoral fractures [5].

In June 2010, a warning about the possibility of unusual atraumatic subtrochanteric or femoral shaft fractures during long-term alendronate therapy was added to the drug information in Japan. However, atypical femoral fractures might not be characteristics attributable only to alendronate treatment. Recently, the same fracture pattern was also reported in patients who were treated with risedronate [9, 12].

As a result of an increasing number of reports about atypical femoral fracture (more than 300 cases), ASBMR published the aforementioned report of a task force [17]. They defined major and minor features of atypical femoral fracture, and our case corresponded with almost all these features. They also described some pathogenesis that might be associated with these atypical fractures, such as alterlation of collagen cross-linking, reduced heterogeneity of mineralization and reduced vascularity in addition to the microdamage accumulation we noted, and consequently concluded that the precise pathogenic mechanisms were still unknown and more information was urgently needed. Also some case reports and animal studies have been reported about the potential effects of parathyroid hormone (PTH) to the suppression of bone turnover and impaired fracture healing by bisphosphonates [30]. Further study will be needed.

Although the causal relationship between long-term alendronate therapy and atypical femoral fractures and its precise mechanisms and pathogenesis are not completely understood, awareness is needed of this potential complication. These atypical fractures could be caused by the combination of the severe suppression of bone turnover by long-term bisphosphponate treatment and the increased accumulation of microdamage at the subtrochanteric region of the femur. Clearly, additional investigations are necessary.

Acknowledgments We wish to thank Ms. Yoko Kasai for the preparation of the histological analysis and Dr. Kensaku Abe for his assistance in performing the surgery.

Conflict of interest Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with this article.

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