Low-Energy Femoral Fractures Associated With Long-Term Bisphosphonate Use in a Rehabilitation Setting: A Case Series

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INTRODUCTION

Bisphosphonate therapy for the treatment of postmenopausal osteoporosis is common, with more than 22 million prescriptions for alendronate (Merck) alone in 2005. The safety of this class of medications has been supported by long-term trials [1,2]. However, during the last several years multiple small case series link the long-term use of bisphosphonates to unusual complications such as avascular necrosis of the jaw and low-energy nonvertebral fractures that in some cases surprisingly demonstrate severely suppressed bone turnover [3]. It may be that the suppressed turnover prevents effective repair of stress fractures. Recently reported cases of nonvertebral fractures include multiple small series describing an unusual fracture of the femur, either subtrochanteric or diaphyseal, in patients taking long-term alendronate [4-7]. This fracture may be preceded by vague complaints of pain in the thigh in the setting of "low or no trauma." There may be local cortical thickening and a fracture pattern that is simple and horizontally situated [4]. Biopsies in some of these patients have demonstrated a frozen bone pattern [3]. This pattern reveals depression of bone formation.

At the authors' freestanding rehabilitation hospital in the last 7 years, 1 male and 3 postmenopausal female patients with 5 atypical low-impact or no-impact femoral fractures were identified. One was subtrochanteric and 4 were diaphyseal. Two of these patients were receiving extended alendronate therapy; one had received zoledronic acid infusions as an adjunctive therapy for multiple myeloma. One patient was found to be hypogonadal and osteopenic. These cases add to the data that suggest the long-term use of bisphosphonates is associated with a risk of low-energy femoral fractures.

CASE 1

A 53-year-old white man with a history of osteoporosis, hypertension, coronary artery disease, gastroesophageal reflux, asthma, psoriatic arthritis, and obsessive-compulsive disorder complained of right-sided hip and knee pain. While walking, he felt a sudden pain in his right leg and fell to the floor. He was taken for immediate plain radiographs, which revealed a right transverse mid-femur fracture. He underwent an intramedullary nailing. He was transferred to acute inpatient rehabilitation and then discharged home without an assistive device. Endocrine consultation revealed a testosterone level of less than 50 ng/dL (normal 212-755 ng/dL) and a luteinizing hormone level of less than 0.1 mIU/mL (normal 20-140 U/mL). He was diagnosed with hypogonadism, which was thought to contribute to his insufficiency fracture. He was treated with topical androgen (Solvay) for his hypogonadism and alendronate for his osteopenia. A DEXA scan obtained at the time of the fracture had a T score of the spine of −0.98, and the hip T score was −0.3 (the lower limit of normal). This fracture did not achieve a primary union, and required a reoperation to achieve a union.

CASE 2

A 49-year-old black woman with a history of osteoporosis and multiple myeloma, status post bone marrow transplant, with chemotherapy, degenerative joint disease, and distant tobacco use had experienced aching left hip pain for approximately 1 month. She was

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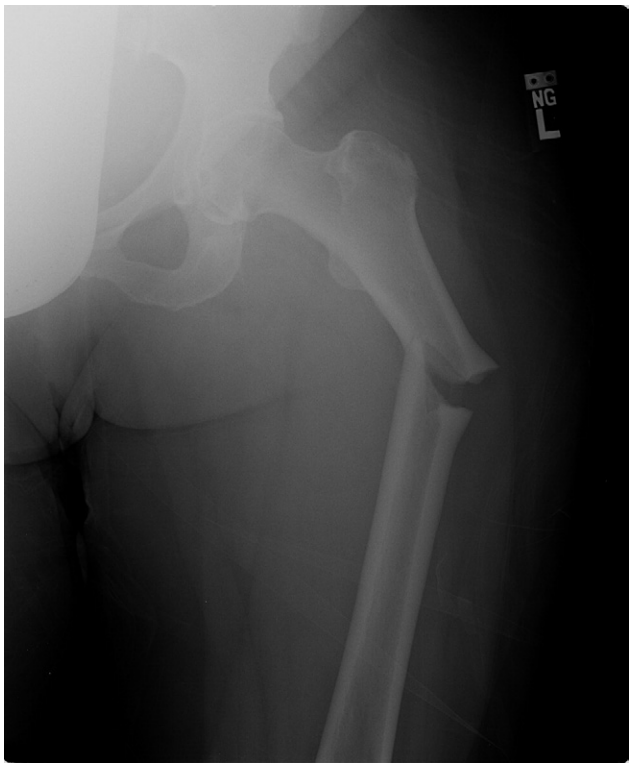

Figure 1. Myeloma patient receiving zoledronic acid with a left diaphyseal fracture. Left diaphyseal fracture, 9 cm below the lesser trochanter, shows severe valgus deformity lesion present. Note slight cortical thickening of the bone at this level.

negotiating a set of stairs and tripped over a step, causing a fall to the ground. She was taken to a local hospital, and radiographs revealed a left transverse femoral fracture (Figure 1). Also noted was a 6-mm moderate medial cortical thickening on the right femur films (Figure 2). The patient was taken to the operating room and underwent open reduction, internal fixation (ORIF) surgery of the left femur with intramedullary rod placement. Several days after this procedure the patient was taken for ORIF of the right femur to prevent fracture. The cortical thickening was believed to represent a stress fracture at risk for progressing. A bone biopsy was done with her surgical fixation and showed no plasmacytic infiltrate. Her multiple myeloma was judged to be in remission. At 2-year follow-up there is still no myeloma recurrence. Endocrine service consultation identified no cause of secondary osteoporosis. The patient had received intravenous bisphosphonate therapy for more than 5 years as an adjunctive treatment for her multiple myeloma. She started with 4 monthly infusions of pamidronate, followed by monthly infusions of zoledronic acid for 3 years, followed by every other month infusions until the time of fracture. After her acute care the patient was sent to inpatient rehabilitation. She was discharged from rehabilitation independent with all activities of daily living and ambulating without assistive device.

CASE 3

A 59-year-old white woman with a history of osteoporosis, left hip stress fracture 3 years earlier, experienced a 2- to 3-month history of right-sided hip pain. She had seen her physician, who ordered hip radiographs that were interpreted as normal. She was sent to physical therapy for treatment of these symptoms. A few days later the patient returned home from grocery shopping and as she entered her back door she felt a sudden sharp pain in the right hip and fell to the floor. At a local hospital radiographs showed a left subtrochanteric transverse femur fracture and a right midiaphyseal transverse femur fracture. She underwent bilateral intramedullary rod fixation (Figure 3). Endocrine service consultation found no cause for these pathologic fractures. The patient was transferred to inpatient rehabilitation after her acute care stay and was discharged home with a single-point cane after her stay. This patient had been treated with

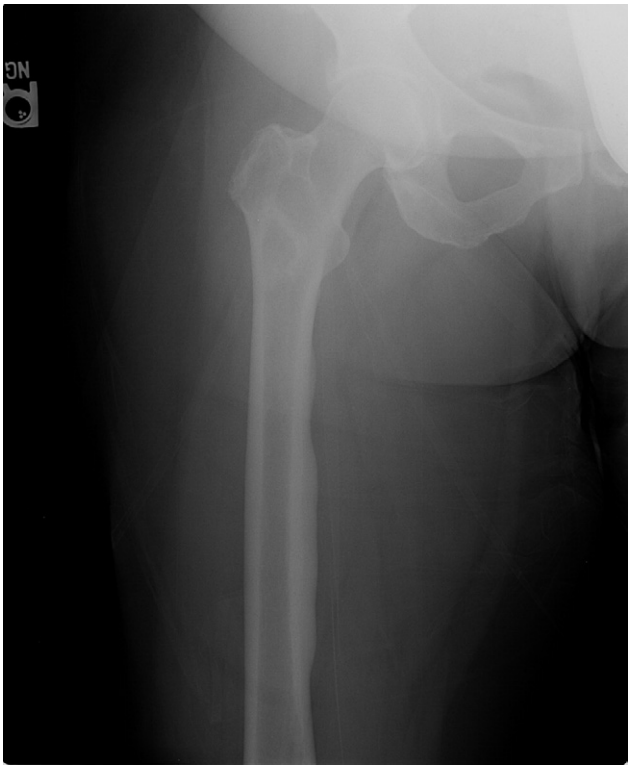

Figure 2. Same myeloma patient as in Figure 1 the left diaphyseal fracture. The contralateral (right) femur shows diffuse cortical thickening present along the medial cortex of the femoral diaphysis. Although cortical thickening is typically thought to represent a strengthened cortical bone, this may in fact represent a failure of active bony remodeling with limited osteoblastic and osteoclastic activity.

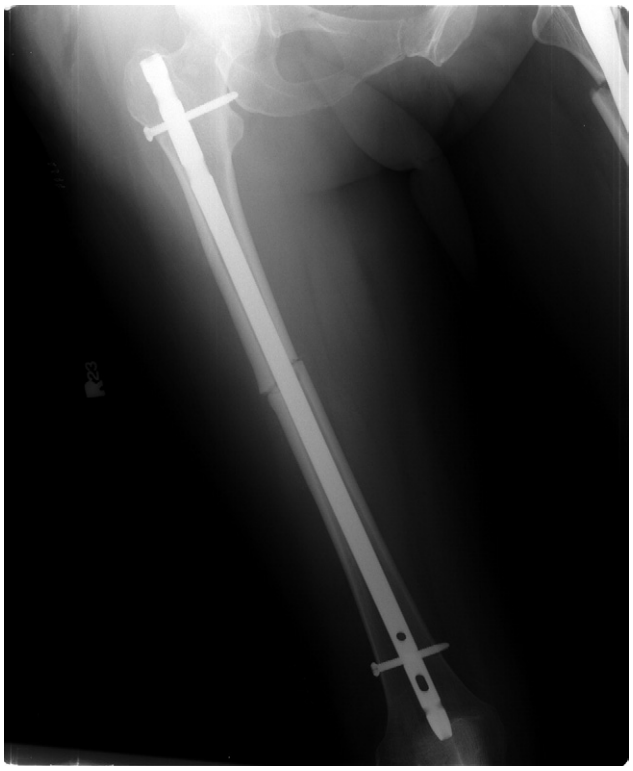

Figure 3. Patient with a right mid-shaft diaphyseal transverse femur fracture; radiograph partially demonstrates her left subtrochanteric fracture.

alendronate therapy for 5 years before these fractures. Her DEXA scan T scores were as follows: 5 years before fracture, femoral neck −2.3, spine −1.8 (osteopenic range); 3 years before fracture, femoral neck −1.6, spine −1.2 (osteopenic range but improved). Her bisphosphonate was discontinued after her acute bilateral fractures. The endocrine service recommended starting the patient on teriparatide (Eli Lilly) injections, and oral calcium and vitamin D for continued treatment of her osteopenia.

CASE 4

A 58-year-old black woman with a history of type 2 diabetes (controlled by diet) and osteoporosis had been having pain and stiffness in her right hip for 2 months. She was walking across a vacant lot and tripped over a short tree stump. She fell to the ground and was unable to rise. She was taken to a local hospital and found to have a right midshaft diaphyseal transverse femoral fracture just proximal to the isthmus (Figure 4). She was taken to the operating room and underwent interlocking intramedullary rod fixation. During her inpatient stay endocrine service consultation found no secondary cause for this pathologic fracture. This patient had been treated with alendronate therapy for 6 years at the time of her fracture. She was transferred to inpatient rehabilitation and subsequently was discharged home without an assistive device. Her bisphosphonate therapy was discontinued, and endocrine service recommended the patient start teriparatide injections, calcium, and vitamin D. The patient was discharged home from rehabilitation independent with activities of daily living and ambulation. Her DEXA scores 3 years earlier showed T scores of spine −2.2, femoral neck −1.5, and hip −1.4 (osteopenic range); 1 year earlier the T scores were spine −1.9, femoral neck −1.6, and hip −1.9 (osteopenic range without overall change).

DISCUSSION

Recent journal case reports and series of cases [4-11] describe atypical fractures of the femoral diaphysis in conjunction with prolonged bisphosphonate therapy. One study of low-energy femoral shaft fractures reported 25 patients taking alendronate for an average of 6.9 years; 19 of these patients had a fracture described as simple, transverse, and with a unicortical break [6]. Many of these reported patients, as did all 4 of our patients, had a prodrome of pain in the affected hip or groin area weeks to months before fracture.

In another series of 17 patients with subtrochanteric stress fracture while taking alendronate, 64% of the patients had

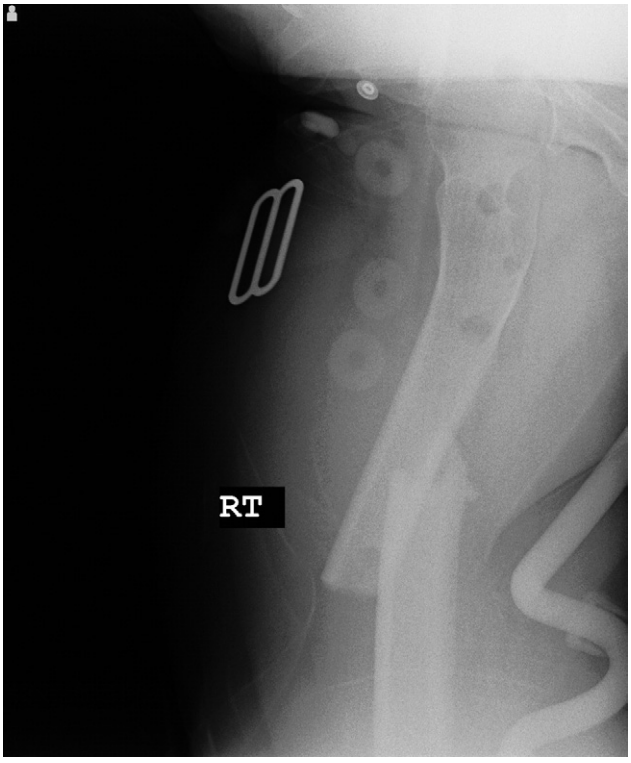

Figure 4. Patient taking alendronate with low-impact femoral fracture. Note the fracture shows a straight transverse plane with no underlying bony lesion found approximately 19 cm below the lesser trochanter. Significant anterior angulation at the apex of the fracture site is present.

documented prodromal symptoms of thigh pain, vague discomfort, or subjective weakness. These symptoms were often dismissed or treated as symptoms of spinal stenosis [9].

The optimal duration of bisphosphonate therapy for patients with appropriate indications for therapy is not yet precisely defined. There are some data to support the safe discontinuation of alendronate after 5 years of use when treating women for postmenopausal osteoporosis. In one study [1], patients were randomly assigned to continue alendronate for 5 more years or to stop. There was no clinical benefit to continue past 5 years as measured by symptomatic nonvertebral fractures or by radiographically defined vertebral fractures.

In 2 of 3 patients in the present study receiving bisphosphonate therapy, after multidiscipline consultation including endocrinology, teriparatide injections were started. Case series of alendronate-associated fractures reported bone biopsy data. These biopsies demonstrated signs of severely suppressed bone turnover including depression of bone formation and absence of tetracycline labeling [3]. Teriparatide may be useful to help treat patients with this type of fracture as it has a mechanism of action that increases both bone osteoblast and osteoclast activity [10].

Rehabilitation specialists will evaluate patients receiving bisphosphonates with leg, hip, and thigh pain. Focusing on length of bisphosphonate therapy as part of the relevant history is recommended. Prolonged therapy, especially therapy longer than 5 years, may indicate a need to consider stress fractures as a cause of pain. If radiographs demonstrate several millimeters of focal cortical thickening or the presence of a stress fracture, one should re-examine the indication for ongoing bisphosphonate use. Magnetic resonance imaging of the involved limb may best demonstrate a microfracture or cortical thickening. If such changes are found, orthopedic referral for possible preemptive surgical fixation may be indicated. In addition, prescribing an assistive device such as a single-point cane to widen the base of support and avoiding high-impact activity may be advised.

Almost all these reports describe patients who took alendronate alone, or in some cases, alendronate and later another bisphosphonate. However, there are a few recent reports of fractures in patients taking a bisphosphonate other than alendronate. Patient 2 was taking pamidronate briefly and then zoledronic acid. Another patient was taking pamidronate alone for 5 years [7]. Another case reported online took zoledronic acid and then pamidronate [11]. These recent cases suggest that this fracture may be related to a class effect of bisphosphonates. The current preponderance of alendronate cases could relate to a combination of factors that may include the length of time the drug has been on the market, its half-life, its potency, and its market share. Alendronate has been on the market since 1995, and is a more potent blocker of osteoclasts than risedronate, which was approved by the FDA in 2000 [12]. In 2003, ibandronate became available in oral and intravenous formulations to treat osteoporosis.

Bisphosphonate use increased after untoward cardiovascular effects of hormone replacement therapy became widely publicized in 2002. In 2008 there were more than 7 million prescriptions for risedronate, more than 4 million for ibandronate, and 15 million for alendronate.

Zoledronic acid has been on the market (as Zometa) since 2001 for indication of treatment of bony metastatic disease. In 2007 it became available as Reclast at a lower dose for the prevention of osteoporosis as a 15-minute yearly intravenous infusion. As it may be a more potent inhibitor of osteoclasts than alendronate, it will be of interest to monitor for additional cases of this atypical fracture associated with zoledronic acid with time.

This type of fracture is a rare event when considering the large number of patients on bisphosphonates. However, it is unclear at this time whether patients who sustained a fracture had a rare predisposition to fracture (for example, undiagnosed hypogonadism or a yet undefined predisposition) or whether with prolonged exposure or the passage of time more cases might occur. In some previously reported cases, the fracture occurred years after stopping alendronate [3,7].

Femoral fractures are serious injuries and require surgical fixation. Initially, patients will be partially weight-bearing in most cases but may be non-weight-bearing for up to 6 weeks depending on the orthopedic surgeon's recommendations. Physiatric evaluations in some cases can safely restore mobility and provide independence or a quick return to a home environment.

CONCLUSIONS

Physiatrists routinely see patients with hip and thigh pain and participate in the postoperative rehabilitation of hip and thigh fractures. They should consider the possibility that low-impact insufficiency femoral fractures may be related to prolonged bisphosphonate use. Patients receiving long-term bisphosphonate with thigh pain should be evaluated for cortical thickening and stress fractures.

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