Case Report of Spontaneous, Nonspinal Fractures in a Multiple Myeloma Patient on Long-term Pamidronate and Zoledronic Acid

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Abstract Pamidronate and zoledronic acid are two potent intravenous bisphosphonates used in the treatment of multiple myeloma as well as osteoporosis. While the concern for heightened fracture risk in a patient on long-term bisphosphonate treatment for malignancy has been previously noted, we present the first case of spontaneous, nonspinal fractures in a patient undergoing treatment for multiple myeloma. The patient had a positive 9-year history of bisphosphonate treatment and presented with sequential subtrochanteric stress fractures of the left and right femurs. Pathological reports of fracture site biopsies demonstrate signs consistent with ametabolic bone and no malignancy. These findings point to extreme inhibition of bone turnover by bisphosphonates as the cause of this patient's morbidity. This is a single retrospective case study (level IV evidence).

Keywords long-term bisphosphonate therapy · stress fracture · multiple myeloma · osteoporosis

Introduction

Multiple myeloma, a malignant plasma cell disease, results in heightened osteoclastic activity and in turn osteoporosis, lytic bone disease, and skeletal fractures. Bisphosphonates have become a standard part of treatment for the cancer-induced hypercalcemia and osteoporosis. By inhibiting the

action of osteoclasts and preventing bone resorption, bisphosphonates have been shown to reduce bony complications and fractures in patients with multiple myeloma [1–7]. In addition, by limiting endosteal resorption, bone marrow expansion of myeloma cells may be inhibited. Zoledronic acid is a nitrogen-containing bisphosphonate that inhibits enzymes of the mevalonate pathway and consequently inhibits prenylation of small guanosine triphosphate-binding proteins, which eventually leads to secondary osteoclast apoptosis [8–11]. Due to its high potency, this bisphosphonate has become the first option in the treatment of malignancy-induced hypercalcemia and osteoporosis. Its efficacy and safety have been demonstrated in randomized clinical trials using breast cancer, multiple myeloma [12–13], lung cancer, and prostate cancer patients [14].

While oral bisphosphonates have a long history of successful use in the treatment of nonmalignancy-associated osteoporosis, recent concern has arisen regarding the potential side effects of long-term use. Sustained inhibition of bone turnover leads to brittle bone due to increased mineralization and progressive microdamage that is not repaired or remodeled [15–22]. These studies have led to a concern that sustained inhibition of osteoclasts may lead to insufficient bone repair and therefore an increase in microdamage accumulation and reduction of bone quality.

There currently exists no long-term (>5-year) study that has examined the intrinsic skeletal effects of bisphosphonates in multiple myeloma patients where the bisphosphonate dosage is more than ten times the dose used in the treatment of osteoporosis. We present the first case of unusual, spontaneous bilateral subtrochanteric fractures in a multiple myeloma patient on long-time pamidronate and zoledronic acid while under complete remission.

Case

A 72-year-old woman with a 9-year history of multiple myeloma treated with melphalan for 4 years, zoledronic

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Fig. 1. AP radiograph of left hip at time of presentation. There is a transverse, valgus-impacted, subtrochanteric fracture with visible thickening of the lateral cortex

acid (4 mg IV q 3–4 weeks) for 6 years, and pamidronate (30–60 mg IV q monthly) for 5 years presented with spontaneous pain in her left thigh. The patient denied any specific trauma but had considerable pain with even partial weight bearing. She denied any fevers or chills and had never received any glucocorticoid or hormone replacement therapy. Of note, her previous dual-energy X-ray absorptiometry (DEXA) scan demonstrated osteopenia (T score -2.0 at L1–L4 and -2.2 at right femoral head). On examination, she was neurovascularly intact and had pain at extremes of all ranges of motion. Her sensation was grossly intact. Plain radiographs of the left hip demonstrated a subtrochanteric fracture arising from a stress fracture (Fig. 1). Her laboratory general chemical analysis was normal at this time including a calcium level of 9.1 mg/dL (Table 1). Markers of bone metabolism such as N -telopeptide were not completed at this time.

Table 1 Useful laboratory values available from 2001 to present demonstrating course of low to moderate calcium levels and suppressed bone metabolic activity (NTX and bone-specific alkaline phosphatase)

Date	Calcium	NTX	Bone alkaline phosphatase
9/24/2001	9.1		
10/31/2001	8.9		
6/7/2005	9.9		
6/17/2005	8.5		
6/18/2005	8.1		
8/24/2005	9.2		11.4
11/29/2005		22	13.5
2/24/2006		18	13.7
8/17/2006	9.6	23	
13/5/2006	9.4	29	

Reference ranges: Ca (8.5–10.2 mg/dL), NTX (21–83 BCE/mM), bone alk phos (6.6–20.1 μ g/L)

Fig. 2. Postoperative anteroposterior pelvic X-ray of left hip bipolar hemiarthroplasty well situated through fracture site

She was treated with a long stem cemented, bipolar hemiarthroplasty (Fig. 2). Gross examination in the operating room did not reveal destructive bone lesions at the femoral head or near the fracture site that would suggest a pathologic fracture secondary to multiple myeloma. Microscopic evaluation of the femoral head, neck, and bone marrow from the left femoral canal demonstrated mature plasma cells, present in normal numbers, scattered throughout the marrow. Immunoperoxidase staining demonstrated hypocellular bone marrow, polyclonal plasma cells according to cytoplasmic immunoglobulin expression, and thus no evidence of multiple myeloma. She had a full, uncomplicated postsurgical recovery and maintained complete control over her multiple myeloma and continued on her program of zoledronic acid therapy.

Fig. 3. Enlarged view of the anteroposterior radiograph of right proximal femoral diaphysis demonstrating lateral cortical thickening as well as incomplete fracture extending through approximately 50% of the cortex

Seven months later, she presented with pain in her right thigh and groin. Again, there was no history of trauma or changes in her general health. While she was neurovascularly intact, her physical exam was significant for discomfort in all planes of movement. Radiographs of the right hip demonstrated a stress fracture in the subtrochanteric area of the lateral aspect of the right proximal femoral cortex (Fig. 3). The medial and posterior aspects of the femoral cortex appeared to be intact. A magnetic resonance imaging (MRI) of the right hip demonstrated a possible fracture 8 cm below the lesser trochanter as evidenced by transverse images (Fig. 4). A DEXA scan at this time revealed an improvement of her bone density *T* score (−1.1 and −1.8 in the L1–L4 and right femoral neck, respectively). She was treated operatively with a right, cemented total hip arthroplasty due to arthritic changes in her acetabulum. At the time of surgery, a biopsy was taken from the fracture site. The microscopic evaluation of the bone biopsy showed thin, sclerotic trabeculae and an almost complete absence of osteoclastic and osteoblastic activity (Fig. 5a); this is in contrast to normal healthy bone (Fig. 5b). There was no evidence of osteomalacia.

X-rays taken at 3 months postoperatively from her right total hip arthroplasty demonstrated impaired healing at both fracture sites (Figs. 6a, b). In light of her profound bone inactivity (frozen bone), the patient was started on teriparatide, and at 1-year follow-up, plain radiographs demonstrated partial healing of both right and left subtrochanteric fractures (Fig. 6c). At this point, her DEXA scores revealed marked improvement (−0.7 and −0.6 in L1–L4 vertebrae and right forearm, respectively), and her laboratory values had begun to normalize from previous measurements (Table 1).

Fig. 4. Transverse cut of T2-weighted, FSEIR (fat suppressed) MRI of the right thigh. There is decreased signal on the lateral cortical border of the femur approximately three times as wide as the medial cortex representing significant cortical thickening. Furthermore, there is increased signal within the adjacent marrow cavity representing edema

Fig. 5. **a** This photomicrograph is of the cancellous bone from the excised femoral head at time of arthroplasty. This is one of the only fields that showed any indication of remodeling activity—a small region of osteoblastic activity at the bone surface near the *asterisk*—while the majority of trabecular surfaces are stagnant or “frozen” (hematoxylin and eosin, $\times 10$). **b** This photomicrograph is of the cancellous bone from a typical hip arthroplasty specimen presented for comparison. Most of the surfaces show some degree of remodeling activity either with surface osteoblasts or osteoclasts (hematoxylin and eosin, $\times 10$)

Discussion

Multiple clinical trials show the efficacy and safety of bisphosphonates in improving bone mass density and reducing fracture risk in multiple myeloma and osteoporotic patients. However, there are no studies beyond 10 years of treatment and no studies that show continued reduction in fracture risk after 5 years of treatment. The possibility of heightened fracture risk in patients on long-term bisphosphonates has been considered in the past [23–25]. Another possibility is the adverse effect of other anticancer agents on bone turnover. However, there are some reports in the literature of fracture and delayed healing in otherwise healthy patients not receiving chemotherapy. Odvina et al. reported on nine patients who sustained spontaneous,

Fig. 6. **a** Anteroposterior radiograph 3 months postoperation from right total hip arthroplasty showing clear fracture line and no healing. **b** AP radiograph 1 year postoperation from left bipolar hemiarthroplasty demonstrating hypertrophic nonunion of proximal

diaphyseal fracture. **c** Anteroposterior pelvic radiograph 1 and 2 years postoperation (*right* and *left*, respectively) showing fracture healing with callus development

nonspinal fractures while on alendronate therapy [26]. Six of these patients displayed delayed or absent fracture healing. Iliac crest bone biopsies in all nine patients revealed severe depression of bone formation with absence of double-tetracycline labeling. Schneider et al. reported a case of a previously healthy woman who experienced two nontraumatic stress fractures, 4 years apart, while on alendronate therapy for approximately 7 years [27]. This patient went on to suffer a delayed union of a spiral femoral fracture that resulted from the stress fracture. Both fractures healed after several months of stopping bisphosphonate treatment.

The therapeutic goal in medical treatment of multiple myeloma with bisphosphonates has been both to target osteoclast-mediated bone disease, including hypercalcemia of malignancy, bone metastases, and osteoporosis, and to gain additional antitumor effects. However, this class of drugs does not go without side effects including hypocalcemia, injection site reaction, flu-like syndrome, renal toxicity, ocular complications, and recently, numerous reports of osteonecrosis of the jaw [28–29]. Based on these risks and uncertainties, the Mayo Clinic Consensus Statement for Bisphosphonates in Multiple Myeloma recommends the cessation of bisphosphonate use if the patient has achieved response and is in a stable plateau phase of treatment [30].

Conclusion

Pamidronate and zoledronic acid are two potent intravenous bisphosphonates used in the treatment of multiple myeloma as well as osteoporosis. While the concern for heightened fracture risk in a patient on long-term bisphosphonate treatment for malignancy has been previously noted, we present the first case of spontaneous, nonspinal fractures in a patient undergoing treatment for multiple myeloma. Though it is possible for these fractures to have been pathologic due to our patient's underlying disease, we have imaging studies as well as gross and micropathological bone biopsies from the fracture sites showing complete remission from her multiple myeloma. These fractures could also be osteoporotic insufficiency fractures; however, their unusual locations and the patient's improved bone mass density and normal laboratory values indicate a different type of pathology. The pathology in this patient demonstrated decreased cellular activity on the cancellous bone surfaces, indicating decreased bone metabolism. This decrease in cellular activity renders the bone incapable of responding to normal microdamage, eventually leading to stress fractures. The delays in the healing of both fractures, extending well beyond the cessation of bisphosphonate treatment, are likely a repercussion of both the potency and

highly absorptive nature of zoledronic acid in the bone. This case raises concerns about the long-term suppression of bone turnover with large doses of intravenous bisphosphonates.

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