Spontaneous Bilateral Femoral Fractures After High-Dose Zoledronic Acid

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The authors report a case of spontaneous bilateral diaphyseal femoral fractures believed to be caused by oversuppression of bone remodeling as a result of long-term, high-dose treatment with bisphosphonate. The patient reported pain in both thighs before the fractures. Typical pathologic changes appeared on both femoral radiograph and bone scan before the fractures. Several hours after admission to the emergency department of the authors’ institution, the patient underwent closed reduction and internal fixation with intramedullary nails for the bilateral femoral diaphyseal fractures. Treatment with zoledronic acid was immediately discontinued. In recent years, low-energy femoral diaphyseal fractures in patients undergoing long-term bisphosphonate treatment have been reported. It is believed that the prolonged treatment causes long-term suppression of bone remodeling and accumulation of microdamage. It is important to observe patients who are undergoing bisphosphonate treatment carefully. In this case study, the authors report the patient’s unique medical history. [Orthopedics. 2015; 38(11):e1051-e1054.]

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Osteoporosis is associated with increased morbidity and mortality. Approximately 50% of women older than 50 years will have an osteoporosis-related fracture during their lifetime. Treatment with bisphosphonates reduces the risk of vertebral and nonvertebral fractures in more than 50% of cases. High affinity with hydroxyapatite and inhibition of protein prenylation in osteoclasts lead to osteoclast apoptosis and potent inhibition of bone resorption. Intravenous zoledronic acid is the longest-acting bisphosphonate available and has been approved for use in patients with osteoporosis at a once-yearly dose of 4 mg. Much higher doses are used in several malignant diseases to prevent pathologic fractures as a result of bone metastases.

Recently, there has been growing concern about risk factors for atypical subtrochanteric and midshaft femoral fractures associated with long-term bisphosphonate treatment.

Recently, the authors treated a 68-year-old woman who had spontaneous nontraumatic pathologic bilateral midshaft femoral fractures as a result of prolonged intravenous bisphosphonate treatment.

**CASE REPORT**

A 68-year-old postmenopausal woman was admitted to the emergency department at the authors’ institution with nontraumatic spontaneous bilateral femoral fractures. On arrival, the patient was treated with traction with Thomas splints on both extremities (Figure 1). The medical history included hepatic cholangiocarcinoma that was diagnosed 14 years earlier and was treated with left hepatic lobectomy. One year postoperatively, the patient was diagnosed with a local recurrence of a 4×3.5×3-cm nodule in segment 1, in close proximity to the inferior vena cava, the right inferior hepatic vein, and the right portal branch. The patient was treated with 3 cycles of chemoembolization and 5 cycles of chemotherapy with 5-fluorouracil, cisplatin, and folic acid. Then the patient underwent hepatic segmentectomy, with implantation of a Gore-Tex (W L Gore & Associates, Inc, Newark, Delaware) caval prosthesis. Follow-up showed no intrahepatic recurrence and normal tumor markers. Three years later, the patient had back pain. Computed tomography scan of the lumbar spine showed osteoporotic fractures that were mistaken for metastases to the lumbar spine. Treatment was started with zoledronic acid (4 mg/mo), a regimen given for bone metastases. The same high-dose treatment with zoledronic acid was continued for 10 years. Several months before the femoral fractures, the patient had bilateral thigh pain, especially with weight bearing. Radiographs of the thighs showed thickening of the lateral cortex in each femoral diaphysis (Figure 2A). Bone scintigraphy obtained 2 months before the femoral shaft fractures showed radionuclide accumulation at the fracture sites (Figure 2B).

While walking in her garden, the patient felt a sudden, sharp pain in both thighs and collapsed on the ground. On admission to the emergency department, she was diagnosed with spontaneous nontraumatic bilateral femoral shaft fractures. Deformities were detected in both thighs. She underwent surgery on the same day, with an intramedullary nail placed in each femur. Results of laboratory studies that included kidney function, liver function, and white blood cell count were normal. The vitamin D level was also normal. Intraoperative bone biopsy specimens obtained from both femurs showed no evidence of metastatic disease. Therefore, the pathologic fractures were most likely caused by prolonged treatment with bisphosphonate. After surgery, the patient began physiotherapy with full weight bearing on both extremities. Bisphosphonate treatment was immediately discontinued, and the patient was followed on an outpatient basis. At 1-year follow-up, she was walking unassisted and was free of pain at the fracture sites. Follow-up radiographs showed that the fractures were healed.

One specimen from each femur was evaluated pathologically. Specimen sizes were 1×0.3×0.4 cm and 1.5×0.7×0.5 cm. Macroscopically, the specimens were irregular, brown, and partially covered by a membrane. Microscopically, hematoxylin and eosin staining showed wide osteons, with many osteocytes but no osteoclasts or osteoblasts at the fracture site. Between osteons there was a marked appearance of fibrotic tissue. Leukocytes appeared at the fracture site as a result of bone trauma (Figure 3). Mason staining showed marked fibrosis of the soft tissue surrounding the fracture site (Figure 3).

**DISCUSSION**

The authors reported a unique case of a patient who had spontaneous bilateral midshaft femoral fractures as a result of prolonged treatment with a very high dose of bisphosphonate.

Bisphosphonates have a high affinity for hydroxyapatite in bones. After binding to the bones, they are absorbed by osteoclasts. This process inhibits functions such as bone resorption and remodeling, increases bone density and strength, and reduces the risk of fragility fractures. Bisphosphonates are used routinely to prevent bone-related events in other medi-
eral conditions in addition to osteoporosis, such as systemic corticosteroid treatment, Paget’s disease, and bone metastases. Some reports claim that zoledronic acid delays the progression of bone metastases from hepatocellular carcinoma. However, over the past few years, there has been growing concern about long-term bisphosphonate treatment and its associated risk factors for atypical subtrochanteric and midshaft femoral fractures.

The pattern of the diaphyseal femoral fracture is unique. The characteristics of this fracture were summarized by Ishizuna et al: (1) This type of fracture is often observed in patients undergoing long-term bisphosphonate therapy. (2) The fracture is transverse and has cortical spiking. (3) Cortical thickening is observed. (4) Many patients have femoral pain before the fracture. (5) Bone scintigraphy may show increased radionuclide uptake before bone fracture.

Unfortunately, the current patient had all of the characteristics described earlier. She underwent treatment for a very long period (10 years) with a very high dose of zoledronic acid (4 mg/mo). This high-dose therapy was given as a treatment for bone metastases. However, this diagnosis was proven wrong when the lumbar spine computed tomography scan was reassessed. In most reports, pathologic fractures occurred 4 years or more after the initiation of treatment. In the current case, the patient was treated for 10 years before the fractures occurred. This very high dose is usually given to patients with bone metastases from a primary tumor and to those with multiple myeloma.

Pathologic fractures as a result of prolonged bisphosphonate therapy are believed to be the result of long-term suppression of bone remodeling and accumulation of microdamage. Usually, bone mass increases but no bone remodeling occurs because of osteoclast suppression. In the current case, pathologic examination showed wide bone trabeculae with no osteoblasts or osteoclasts at the fracture site. Similar findings were noted in 2 other case reports of atypical femoral fractures. Interestingly, in the current case, the pathology report also described a marked appearance of fibrotic tissue at the surrounding soft tissue adjacent to the fracture site. The authors believe that the surrounding fibrous tissue was the result of inability of the bone to remodel and repair chronic microdamage.

Previous cohort studies showed an increased risk of subtrochanteric fractures associated with the use of bisphosphonates for osteoporosis. A large retrospective cohort study linking pharmaceutical and radiographic data found that 90% of patients with atypical femoral fractures had taken bisphosphonates. Further, longer duration of use increased the risk. Interestingly, the effect of bisphosphonate use continues after surgery. Several authors reported delayed union after surgical treatment in patients who had prolonged bisphosphonate treatment before fracture occurred. Some authors even treat patients with bisphosphonate-induced femoral fractures with teriparatide to accelerate fracture healing. The current patient refused teriparatide treatment, but eventually the fractures healed, with no additional treatment except for bilateral intramedullary nailing. Treatment with reamed intramedullary nailing for femoral fracture nonunion is considered highly successful. Reaming particles represent a strong osteoinductive substance and are important in fracture healing when vital tissue is presented at the nonunion site. In the current case, both femurs...
were reamed in preparation for nail fixation. The authors assume that the use of a reamed intramedullary nail is a good option for treating bisphosphonate-induced complete and incomplete femoral fractures and can help to avoid delayed union or nonunion.

These preliminary data appear to support a causal relationship between bisphosphonate use and atypical femoral fractures. Bisphosphonates have a key role in preventing skeletal complications caused by bone metastases. In recent years, femoral diaphyseal fractures caused by minor trauma have been reported in patients undergoing long-term bisphosphonate treatment.

**CONCLUSION**

The authors report a rare case of a low-energy atypical femoral midshaft fracture after treatment with high-dose zoledronic acid for bone protection after a mistaken diagnosis of bone metastases. This case report raises concerns about atypical femoral shaft fractures after high-dose zoledronic acid therapy. Physicians should be aware of this entity. The optimal dose of zoledronic acid for the treatment of skeletal metastases and for bone protection must be determined through clinical trials. Patients who are receiving bisphosphonates and who present with spontaneous or traumatic thigh or groin pain must be screened with radiography of the femur to exclude atypical femoral fractures. In addition, patients with a documented fracture should undergo radiographic examination of the contralateral femur.

**REFERENCES**