Bilateral Subtrochanteric Femur Fractures in a Patient with Polymyalgia Rheumatica and Ibandronate Use

Shawn P. Mountain, DO; Elisha A. Chance, BSAS; James E. Boniface, MD

Abstract
We report on a 62-year-old woman with polymyalgia rheumatica who sustained simultaneous, bilateral, low-energy femoral fractures (AO/OTA classification 32-A3) while on methotrexate, prednisone, PPI, and ibandronate sodium therapy. Due to the rarity of atypical fractures, specific diagnosis and procedural codes for atypical fractures should be created and based on the major and minor criteria delineated by the ASBMR to facilitate large sample analyses from national databases.

Keywords
Atypical fracture; Bilateral femur fractures; Bisphosphonate related fracture; Femur

Abbreviations
PPIs: Proton Pump Inhibitors; HIPAA: Health Insurance Portability and Accountability Act; AO/OTA: Association for Osteosynthesis-Orthopaedic Trauma Association; mg/dL: milligram per deciliter; DEXA: Dual-energy X-ray absorptiometry; ASBMR: American Society for Bone and Mineral Research.

Introduction
There is no dispute that bisphosphonates have prevented innumerable osteoporotic fractures in the population. Case reports, retrospective analyses, and systematic literature reviews evaluating the relationship between bisphosphonates and atypical femoral fractures have been reported and show mixed evidence suggesting that long-term bisphosphonate use increases atypical fracture risk [1-18]. The absolute risk of an atypical fracture while on bisphosphonate therapy is extremely low at 5 cases per 10,000 patient years[16], making atypical fractures the exception and not the rule. Notably, atypical fractures have been reported in patients who do not take bisphosphonates [1,2,16]. Additionally, concomitant use of proton pump inhibitors (PPIs) and glucocorticoids, and multiple comorbid conditions have been identified as compounding risk factors for atypical fractures in patients on bisphosphonate therapy [2,5,8,11,12,17-19].

Bisphosphonates are a class of drugs that have been used to prevent or treat osteoporosis caused by many different factors such as long-term corticosteroid use and in elderly females with estrogen...
depletion. These drugs work by decreasing osteoclastic resorption of bone thereby inhibiting bone turnover [20]. More specifically, ibandronate sodium is a nitrogen-containing bisphosphonate that acts through the inhibition of the mevalonate pathway; this in turn disrupts regulatory protein signaling in the osteoclast leading to apoptosis [20]. Many previous examples of bisphosphonates had a poor compliance due to required daily regimens for effectiveness. Next generation bisphosphonates had better adherence because of weekly dosing, however this was still not perfect. Ibandronate was developed to improve usage by offering monthly dosing.

This article presents a case of a 62-year-old woman who sustained bilateral simultaneous subtrochanteric fractures while on methotrexate, prednisone, PPI, and ibandronatesodium therapy. She was informed that data concerning the case would be submitted for publication in accordance with HIPAA regulation, and she provided her written informed consent.

Case Report

A 62-year-old Caucasian female presented to a level I trauma center after a low-energy fall at home. The patient reported that while attempting to dress herself, she felt her left leg give way, lost balance, and started to fall. In attempting to break her fall, she felt her other leg give out. She had immediate pain bilaterally and was unable to bear weight. Upon further questioning, she reported a history of experiencing several weeks of bilateral thigh pain, but she did not have this investigated by a physician. Hip radiographs revealed complete, displaced, angulated fractures (AO/OTA classification 32-A3) throughout the proximal femurs just inferior to the lesser troCHANTERS, bilaterally (Figures 1 and 2). The fractures were both transverse in nature with bilateral cortical thickening and medial spikes present.

Her medical history included a body mass index of 33.2 kg/m², hypertension, hyperlipidemia, polymyalgia rheumatica, arthritis, hypothyroidism, and a left 5th metatarsal stress fracture 2 years prior. Her extensive surgical history included but was not limited to a complete thyroidectomy, left breast lumpectomy, complete hysterectomy, and hemangiopericytoma removal with skin grafting. Her home medications were levothyroxine, bisoprolol fumarate, clonidine, nabumetone, ibandronate sodium, pantoprazole, simvastatin, prednisone, methotrexate, and tramadol. Her additional supplements were folic acid, vitamins C and E, and calcium with vitamin D₃. Notably, she had been taking prednisone 10 mg daily for over 6 years and oral ibandronate sodium therapy 150 mg monthly for less than 1 year for glucocorticoid-induced osteoporosis.

At admission, her calcium level was 8.5 mg/dL (range 8.6-10.5 mg/dL), creatinine 1.1 mg/dL (range 0.5-1.1 mg/dL), and vitamin D 25-hydroxy was 46 mg/dL (range 30-80 mg/dL). She did not have a parathyroid hormone lab assessment performed. Four months prior to the femur fractures, dual energy x-ray absorptiometry (DEXA) bone scan T-score in her hip was -0.3 and 2.8 in her lumbar spine, indicating normal bone density. She did not have a (DEXA) scan performed at admission.

She was taken to the operating room where her fractures were fixed bilaterally with T2™ Recon nails (Stryker, Kalamazoo, Michigan, USA), both 9 mm x 340 mm x 125°, and 80-mm proximal lag screws and 75-mm proximal lag screws with distal locking screws (Stryker, Kalamazoo, Michigan, USA). Specimens for bone histomorphometry were not obtained. She went on to physical and occupational therapy at 6 days post-fixation. She resumed her home medications including prednisone and
methotrexate at 6 days post-operatively and resumed ibandronate sodium at 34 days post-op. At 2 months follow-up, the fracture showed healing. At 6 months follow-up, both fractures healed, and the patient was ambulating with the use of one cane only, and radiographs were obtained a final time at 15 months follow-up (Figures 3-4).

**Discussion**

The task force of the American Society for Bone and Mineral Research (ASBMR) classified common features of atypical femur fractures as either major or minor [17]. Major features include fractures located anywhere from just distal to the lesser trochanter to just proximal to the supracondylar flare, those occurring after minimal or no trauma, transverse or short oblique, noncomminuted, complete fractures extending through both cortices with or without a medial spike, and incomplete fractures involving only the lateral cortex [17]. Minor features include prodromal thigh pain, local periosteal reaction of the lateral cortex, increase in cortical thickness of the diaphysis, delayed healing, comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, and hypophosphatasia), and use of other pharmaceuticals (e.g., bisphosphonates, glucocorticoids, and PPIs) [17]. Our case included all of the major features, and all of the minor features except delayed healing.

The direct causation between bisphosphonate usage and atypical femoral fractures has been studied and no direct link has been clearly demonstrated. Black et al. evaluated the effects of bisphosphonates on femoral shaft fractures from three large randomized controlled trials of bisphosphonates with more than 14,000 patients and 10 years of follow-up [2]. They identified 12 atypical femoral fractures in 10 women with 3 of the 12 patients receiving placebo [2]. The authors concluded that the risk of atypical fracture with bisphosphonate use alone is very low, specifically, an annual rate of 2.3 subtrochanteric fractures per 10,000 patient years [2]. However, they recognized that there may be a subgroup of especially high-risk patients—those taking corticosteroids, PPIs, or antiretroviral medications [2].

Simultaneous bilateral atypical femur fractures while on bisphosphonate therapy is rare, and to our knowledge, none have been reported on ibandronate sodium. However, there have been a few reports of simultaneous bilateral atypical subtrochanteric femur fractures in patients taking other bisphosphonates (i.e., alendronate sodium, risedronate sodium, and pamidronate disodium) [3,5]. Capeci et al. in 2009 reported on low-energy diaphyseal femur fractures [3]. In the sample, 7 patients sustained bilateral femur fractures while on alendronate sodium therapy, and 1 sustained simultaneous bilateral femur fractures [3]. They concluded that if a low-energy fracture occurs unilaterally in patients on bisphosphonates, the contralateral femur should be fixed prophylactically [3]. A review of all bisphosphonate-related fracture case reports by Giusti et al. in 2010 revealed that 19/120 patients had simultaneous bilateral femur fractures, and 53/120 patients had subsequent contralateral femur fractures [5]. The authors went on to report that 23% of the patients had 3 or more comorbid conditions, and 10.3% of the patients reported rheumatoid arthritis. More than 25% of the cases were on long-term glucocorticoid treatment. PPIs were the most common co-medication prescribed 39% of the time [3].

The causes of atypical fractures in patients on bisphosphonate therapy, while unknown, have been discussed by several investigators [21-23], and the following different theories have emerged: (1) microdamage accumulation and impaired stress healing, (2) reduced heterogeneity of organic matrix
and mineral properties, and (3) increased advanced glycation end-products [21-23]. Moreover, it has been observed that patients on long-term steroids are at higher risk for fracture, regardless of bisphosphonate use [5,11,17-19,24-25].

This case report was a perfect storm for the development of an atypical femur fracture. First, the patient’s thyroidectomy and hysterectomy placed her at a higher risk for fracture. Second, the patient was on long-term corticosteroids and methotrexate for her polymyalgia rheumatica. Third, she had more than three comorbidities, a known history of a stress fracture, and she was taking a PPI. Due to these risks, she was prescribed ibandronate sodium for induced osteoporosis. Despite a normal DEXA bone scan months prior, the patient had prodromal thigh pain and sustained simultaneous bilateral femoral fractures.

Ideally, more randomized controlled trials studying the development of atypical femoral fractures in patients taking multiple medications, especially corticosteroids and PPIs, in combination with bisphosphonates are warranted. Given the rarity of atypical fractures, randomized, controlled trials may not be feasible or ethical. Therefore, specific diagnosis and procedural codes for atypical fractures should be created and based on the major and minor criteria delineated by the ASBMR to facilitate large sample analyses from national databases.

**Figures**

**Figure 1:** Hip radiograph of the left femur showing a complete, displaced, angulated fracture that is transverse in nature.

**Figure 2:** Hip radiograph of the right femur showing a complete, displaced, angulated fracture that is transverse in nature.
References


