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## CLINICAL VIGNETTE

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# Atypical Femur Fracture after Biophosphonate Use

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An eighty-three-year-old woman who had recently moved to Southern California to live with her daughter, presented to the emergency department with a several week history of left hip pain. She was followed by an orthopedist as an outpatient. During a prior office visit, she had received a steroid injection after a diagnosis of left trochanter bursitis. The lateral hip pain improved but a few days prior to the ED visit she developed worsening pain in the left groin region radiating distally. Outpatient MRI of the left hip two days prior reported a stress fracture. In the process of getting into the car to follow up with the orthopedic surgeon, the pain intensified to such a degree that she momentarily lost consciousness, prompting her daughter to bring her into the emergency room. In the ED the pain was so severe that she required several intravenous opioid analgesic doses before radiological imaging could be tolerated. She did not have prior falls or trauma preceding her hip pain. She suffered from osteoporosis and was taking alendronate for the past four years. She was obese with a body mass index of 42 kg/m<sup>2</sup>. Her other major past medical history was long-standing pulmonary fibrosis with chronic hypoxemic respiratory failure on home oxygen and perfenidone therapy. Left hip x-ray and a subsequent CT of the right hip were significant for an incomplete fracture in the lateral cortex of the sub-trochanteric region with periosteal reaction. Her syncope was also investigated and was believed to be situational from extreme pain.

### Discussion

Osteoporosis is characterized by loss of bone mass, reduction of bone density and deterioration of bone architecture leading to increased bone fragility.<sup>1</sup> It is estimated that about 10.3 million Americans suffer from osteoporosis.<sup>2</sup> Ageing and post menopausal hormonal changes play causal roles. Secondary causes include hypercortisolism, hyperthyroidism, hyperparathyroidism, alcohol abuse and immobilization. In addition to calcium and Vitamin D, bisphosphonates are a mainstay in the treatment of osteoporosis and have been shown to reduce osteoporotic fractures in post-menopausal women. Bisphosphonates bind to the bone mineral surface and inhibit osteoclast mediated bone resorption.<sup>1</sup>

Our patient developed an atypical femur fracture as a complication of bisphosphonate use. Atypical femur fractures constitute about 4-10% of all femur fractures. They are unique for several reasons; they may occur with minimal or no injury; can be bilateral and imaging the contralateral extremity is important; and surgical treatment options can be challenging

with prolonged fracture healing and recovery. Plain x-rays, MRI and bone scan are recommended for diagnosis. Bone scan has the advantage of bilateral femur imaging.

American Society of Bone and Mineral Research defined atypical femur fracture as having all of the following major features (i) Located along the femur distal to the lesser trochanter and proximal to supra condylar flare (ii) associated with no trauma or minimal trauma (iii) transverse or short oblique configuration (iv) non-comminuted; and (v) complete fractures extend through both cortices and may be associated with a medial spike, incomplete fractures extend only through the lateral cortex.

Minor features may or may not present in individual cases and include (i) localized periosteal reaction of the lateral cortex commonly referred to as beaking or flaring (ii) generalized increase in cortical thickness of the diaphysis (iii) prodromal symptoms such as full or aching pain in the groin or thigh (iv) bilateral fractures and symptoms (v) delayed healing (vi) comorbid conditions (eg. vitamin D deficiency, rheumatoid arthritis, diabetes, hypophosphatasia) (vii) use of pharmaceutical agents (eg. Bisphosphonates, glucocorticoids, proton pump inhibitors).<sup>3</sup>

Several mechanisms have been proposed in the pathogenesis of bisphosphonate associated atypical fracture. Reducing bone turnover increases pentosidine levels, a marker of advanced glycation end products (AGP) that make bones brittle and associated with increased risk of fracture. Increased bone mineralization with reduced bone mineral heterogeneity is also proposed to play a role. Bisphosphonates prevent hip fractures by increasing proximal femur strength and perhaps transfer stress and strain to the sub-trochanteric region which experiences less or no increase in strength from bisphosphonate treatment. Affinity and retention of bisphosphonates in the bone results in prolonged effects even after the drug is discontinued.<sup>3,4</sup> Since atypical femur fractures affect only certain individuals, the role of genetic mutations is being studied. Based on whole-exome sequencing, GGPS1 mutation was found to be related to susceptibility to bisphosphonate related atypical femur fracture.<sup>5</sup>

The FDA released the safety communication on bisphosphonate associated atypical femur fractures in October 2010. Its impact on bisphosphonate utilization was specifically studied in the Medicaid fee for service population in terms of total daily

defined doses (DDD). Bisphosphonate use dropped from 866 DDD per 1000 beneficiaries in 2010 to 73 DDD per 1000 beneficiaries in 2014.<sup>6</sup>

Current recommendations are to review the need for continued bisphosphonate therapy after five years of oral drugs or three years of intravenous drugs. Women with high risk use including prior major osteoporotic fracture, hip T score -2.5 or lower, age seventy or more years, other strong risk factors such as smoking, alcohol use, corticosteroid use, rheumatoid arthritis; and WHO FRAX fracture risk score above the country-specific threshold should be continued on therapy for up to ten years on oral therapy or six years on intravenous therapy with periodic reassessment. For women not at a high fracture risk, a three to five year holiday from bisphosphonate treatment should be considered with periodic reassessment.<sup>4,7</sup>

Medical treatment includes stopping the bisphosphonate, or other resorptive agent such as estrogen, calcitonin, or RANK ligand inhibitor, assessment and correction of calcium and Vitamin D. Teriperatide, a recombinant form of parathyroid hormone may have a potential role in its treatment but more research is needed prior to recommendation for routine use. Surgical treatment includes cephalo-medullary nail fixation of complete fractures. More than a quarter of impending fractures progress to complete fractures in six months and sub-trochanteric location, functional pain and translucent line in more than 50% of lateral cortex are risk factors. These should be surgically treated with cephalomedullary nail fixation. Higher BMI, subtrochanteric location and failure to restore the normal neck shaft angle during restoration and fixation of the atypical femur fracture are risk factors for delayed healing. In comparison to typical femur fractures, surgical treatments are more complex leaving little margin for error and healing time is prolonged.<sup>7</sup>

Our patient's incomplete sub-trochanteric atypical femur fracture was promptly treated with cephalomedullary nail fixation with normal alignment in post-surgical imaging. Obesity and sub-trochanteric location were risk factors and she required 2 months of nursing home rehabilitation before improving enough to be discharged home.

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