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2023

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Jennifer B. Bamford  
jbbamfor@uvm.edu

Jennifer Kelly  
Jennifer.Kelly@uvmhealth.org

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### Recommended Citation

Bamford, Jennifer B. and Kelly, Jennifer, "Presentation of a Peri-prosthetic Atypical Femur Fracture After Long Term Anti-Resorptive Medication Use" (2023). *Larner College of Medicine Faculty Publications*. 13. <https://scholarworks.uvm.edu/comfac/13>

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## ***Presentation of a Peri-prosthetic Atypical Femur Fracture After Long Term Anti-Resorptive Medication Use***

Jennifer Bamford, MD<sup>1</sup> and Jennifer Kelly, DO<sup>2</sup>

<sup>1</sup>Assistant Professor of Family Medicine, Larner College of Medicine, University of Vermont Medical Center

<sup>2</sup>Professor of Medicine, Director of the Metabolic Bone Program, Larner College of Medicine, University of Vermont Medical Center

### **The Case:**

The patient is a 74-year-old female with osteoporosis and bilateral hip replacements for osteoarthritis (left 8.5 years ago, right 2.5 years ago), who presented with severe atraumatic leg pain. Prior to the event she had left hip pain and weakness for two months. She had been evaluated by orthopedics, had a negative x-ray (fig 1), and received an ineffective trochanteric bursa injection. Physical therapy was not helpful. The pain worsened. She started using a cane, then a walker for support. On the day of the event, she was walking, pivoted on her left leg, and felt her hip give way. She experienced excruciating pain and lowered herself to a seat without falling. She had an obvious deformity. She was emergently transported and admitted. Comorbidities include severe depression with decades of frequent electroconvulsive therapy, stage 1A infiltrating ductal carcinoma of the breast treated with lumpectomy and radiation, but no hormonal treatment, gastroesophageal reflux, and pulmonary embolism.

### **Diagnosis:**

X-ray showed a transverse fracture just below the hardware from her hip replacement (fig 2). No component loosening was seen on CT. She had an open reduction internal fixation of the left femur and was discharged to rehab. Her diagnosis was a peri-prosthetic atypical femur fracture, in the setting of long-term anti-resorptive medication use. She had been treated for her osteoporosis for at least 13 years with bisphosphonates, including alendronate, ibandronate, and risedronate. The exact dates of each drug are unclear, but she was on bisphosphonates from 2005 until late 2018. She then had a brief drug holiday until her first dose of denosumab 5/19. Her spinal T-score had improved from -3.9 to -2.9 from 1/2005- 12/2017 while on these medications. (Fig 3) Seven months prior

to this fracture she started on denosumab every 6 months and had received 2 injections (5/2019, 11/2019).

#### Discussion:

Periprosthetic femoral fractures are fractures that occur in the presence of an orthopedic implant. These occur both intra-operatively and post-operatively, usually in the context of a low energy fall. They are often associated with implant loosening (1). Atypical femur fractures are rare side effects associated with long term anti-resorptive medication use, and usually occur without trauma. Frequently there is a prodrome of pain before the spontaneous break (2). This case has more features of an atypical fracture. There are numerous cases published in which the periprosthetic femur fractures resemble an atypical femur fracture, all associated with bisphosphonate use (3). Periprosthetic atypical femur fractures are likely caused by a combination of stress forces at the implant site and suppression of bone turnover due to the anti-remodeling medication. In this context the stress induced micro-fractures cannot heal, leading to a complete break. Periprosthetic atypical femur fractures usually occur spontaneously or result from a low trauma, defined as a fall from a standing height or less. They can be anticipated by prodromal symptoms such as mild thigh or groin pain, discomfort on weight bearing, pain with daily activities, and relief with rest. (4)

It is important to treat osteoporosis to prevent hip fractures and peri-prosthetic fractures. Bisphosphonates are recommended as a first line treatment as they are efficacious, well established, and safe. Unfortunately, increasing reports of atypical femur fractures have required rethinking long-term bisphosphonate use. The risk of atypical femur fractures is shown to increase significantly after 5-7 years of bisphosphonate use, and it falls dramatically (>70%) in the first year after discontinuation. This data provides an argument for a drug holiday. Drug holidays in osteoporosis treatment can be defined as the temporary, or permanent, discontinuation of a bisphosphonate after continuous use (5). This works because bisphosphonates accumulate and reside in bone for years and have therapeutic effects after stopping (6). While there is no consensus on when or how long to discontinue bisphosphonate use, there seems to be a clinically important benefit of a drug holiday regarding atypical femur fracture risk (5). For patients at extremely high fracture risk, a non-bisphosphonate treatment may be considered during the holiday from the bisphosphonate. This patient had stopped her bisphosphonate and received two injections of denosumab, another anti-resorptive medication. Most patients diagnosed with atypical femur fracture while receiving denosumab also have a history of extensive bisphosphonate exposure (8).

If a similar patient presents with aching pain in the thigh or groin, obtain an x-ray to look for cortical thickening in a transverse orientation of the upper femur, and if no stress fracture is seen, CT or MRI is recommended. Anti-resorptive medications should be stopped during this workup (9). If diagnosed prior to a major break, an atypical femur fracture can be treated by stopping the potentially offending medication, limiting weight bearing, and at times surgical intervention. In patients at substantial risk for subsequent fragility fractures, an anabolic agent should be considered (7).

#### The Takeaway:

Primary care physicians need to know that atypical femur fractures exist, what the prodrome looks like, and that long term use of anti-resorptive medications for osteoporosis can contribute to the cause of these fractures. However, the number of fractures that are prevented with bisphosphonate treatment far outweighs the risk of this rare side effect. It is estimated that treatment of 1,000 women with osteoporosis for up to 3 years would be associated with less than 1 atypical femur fracture per 100 osteoporotic fractures prevented (7).

Patients should be warned to report symptoms that may indicate atypical femur fractures. When this happens start with x-ray but advance to CT or MRI if no cause is found.

Consider the holiday from bisphosphonates around 3-5 years of treatment for patients not in a high fracture risk category. Start and stop/reassess dates on the problem list, as well as a careful review of risk and options for further treatment could help decrease morbidity and mortality from this disease. For complex patients, a referral to an osteoporosis clinic is warranted.

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Fig 1

Xray obtained several weeks prior to fracture to evaluate hip pain. Read as negative for fracture or hardware loosening.

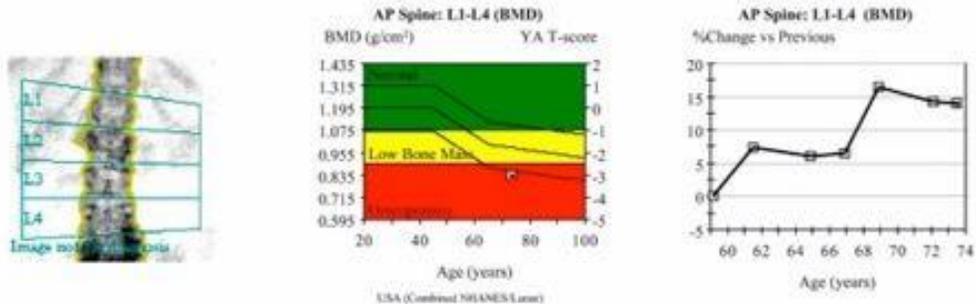


Fig 2  
Images of the atraumatic fracture

The Osteoporosis Center

Bone Densitometry Report: Images and Comparison to Previous if Identified

MONITORING - AP SPINE RESULTS:



Region	Measured Date	Measured Age	WHO Classification	Young Adult T-score	BMD g/cm <sup>2</sup>	Change Previous vs gm/cm <sup>2</sup>	Change Previous vs %	Significant Change
L1-L4	5/3/2019	73.5	Osteoporosis	-3.0	0.829 g/cm <sup>2</sup>	-0.002 g/cm <sup>2</sup>	-0.2%	
L1-L4	12/8/2017	72.1	Osteoporosis	-2.9	0.831 g/cm <sup>2</sup>	-0.019 g/cm <sup>2</sup>	-2.2%	
L1-L4	10/22/2014	68.9	Osteoporosis	-2.8	0.850 g/cm <sup>2</sup>	0.077 g/cm <sup>2</sup>	10.0%	*
L1-L4	10/17/2012	66.9	Osteoporosis	-3.4	0.773 g/cm <sup>2</sup>	0.003 g/cm <sup>2</sup>	0.4%	
L1-L4	10/14/2010	64.9	Osteoporosis	-3.4	0.770 g/cm <sup>2</sup>	-0.010 g/cm <sup>2</sup>	-1.3%	
L1-L4	5/3/2007	61.5	Osteoporosis	-3.3	0.780 g/cm <sup>2</sup>	0.054 g/cm <sup>2</sup>	7.4%	*
L1-L4	1/17/2005	59.2	Osteoporosis	-3.8	0.726 g/cm <sup>2</sup>	-	-	

Fig 3

DEXA over the years- pre-fracture

Date of fracture- 12/14/2019

Medication dates:

-Risedronate was used prior to ibandronate- timing unclear as before electronic record, and paper chart is not available- likely was started 1/2005 after first DEXA.

-Ibandronate was being used at least from 10/24/10-3/28/11.

-Alendronate started 4/8/11 and was stopped sometime between 8/29/18 and 12/14/18.

She started denosumab 5/19

There is documentation for continuous use of BPs for at least 8 years, and it is likely she was being continuously treated with a BP from 1/2005-12/2018: 14- years of use.