AACE Clinical Case Rep. 10 (2024) 170–173

Clinical Case Reports™
www.aaceclinicalcasereports.com

Case Report

Treatment of Bisphosphonate-Associated Atypical Femur Fracture With a Combination of Teriparatide and a Novel Surgical Technique

Aditi H. Chincholi, MD [1,*], Anna R. Cooper, MD, MPH, FAAOS [2], Jamie A. Mullally, MD [1]

[1] *Department of Endocrinology and Metabolism, Westchester Medical Center, Valhalla, New York*
[2] *Department of Orthopedic Surgery, Westchester Medical Center, Valhalla, New York*

ARTICLE INFO

Article history:
Received 15 February 2024
Received in revised form
30 April 2024
Accepted 6 May 2024
Available online 8 May 2024

Key words:
atypical femur fracture
bisphosphonates
teriparatide
novel surgical technique

ABSTRACT

Background/Objective: Atypical femur fractures (AFFs) caused by long-term bisphosphonate use are associated with high rates of delayed healing and nonunion.
Case Report: A 64-year-old woman with osteopenia on alendronate for 15 years sustained a displaced left AFF following a fall from standing height. Imaging showed an acute displaced transverse diaphyseal left femur fracture with lateral cortical thickening and beaking. She underwent an open reduction and internal fixation with insertion of a cephalomedullary nail placed in compression mode, utilizing a novel technique involving intraoperative removal of the endosteal hypertrophied cortical bone at the fracture site. Alendronate was stopped and teriparatide was initiated postoperatively. Radiographs at 3.5 months postsurgery showed evidence of normal fracture union with mature callus formation.
Discussion: AFFs caused by prolonged bisphosphonate use have a high rate of delayed healing and nonunion due to abnormal bone remodeling. Use of teriparatide postoperatively has been shown to reduce healing time in small observational studies in surgically treated patients. Our case demonstrates an expedited healing time of 3.5 months using teriparatide combined with a novel surgical technique involving removal of a portion of the abnormally remodeled bone and placement of an intramedullary nail in compression mode.
Conclusion: Our case demonstrates an expedited healing time of 3.5 months compared to the average reported healing time for AFF of 10.7 months, supporting the use of the combination of teriparatide and a novel surgical technique.

Introduction

Bisphosphonates, denosumab, and romosuzumab are effective in reducing the risk of fragility fracture but are rarely associated with atypical femur fracture (AFF).[1] The risk of AFF increases with the duration of use and declines after discontinuation.[2] AFFs often exhibit delayed healing with time to union averaging 9 to 12 months after surgical treatment and frequently require revision surgery. We report a case of a patient on long-term bisphosphonate therapy who sustained an AFF and was treated with a novel surgical technique involving removal of part of the bone at the fracture site followed by treatment with teriparatide, a parathyroid hormone (PTH)-analog agent, postoperatively. This novel treatment strategy resulted in an expedited time to union of 3.5 months.

Case Report

A 64-year-old Hispanic female with a history of osteopenia presented to the emergency room with severe left thigh pain after a fall from standing height. She had been treated with alendronate 70 mg weekly for 15 consecutive years for osteopenia. She reported antecedent left thigh pain for 7 months prior to presentation and had sought medical attention, but no imaging was done, nor diagnosis made.

On physical examination, she had a shortened and externally rotated left lower extremity with ecchymosis in the anteromedial region of the mid-thigh and pain with any movement of that extremity. Radiographs of the left femur showed an acutely displaced

Abbreviation: AFF, atypical femur fracture.

* Address correspondence to Dr Aditi H. Chincholi, Department of Endocrinology and Metabolism, Westchester Medical Center, 100 Woods Road, Valhalla, NY 10595.
E-mail address: chincholiaditi@gmail.com (A.H. Chincholi).

https://doi.org/10.1016/j.aace.2024.05.001

fracture in the subtrochanteric region (Fig. 1). The fracture line was transverse and became oblique medially with the presence of "beaking" at the fracture site on the lateral cortex and thickened cortices. Given these characteristic radiologic features and the supporting history of minimal trauma and long-term bisphosphonate use, the diagnosis of an AFF was made. A contralateral femur radiograph showed increased cortical thickening of the right femoral diaphysis, suggestive of impending AFF.

Laboratory tests showed serum calcium of 8.8 mg/dL (8.6-10.2 mg/dL), serum 25-hydroxy vitamin D level of 20.2 ng/mL (30-80 ng/mL), and an elevated serum intact-PTH of 124.8 pg/mL (8.7-77.1 pg/mL), thought to be secondary to vitamin D deficiency. A dual energy X-ray absorptiometry scan from an outside facility 4 days prior to her presentation showed a T-score of −2.1 at the left femoral neck, −1.4 at the left hip, and −1.4 at the lumbar spine.

She underwent open reduction and internal fixation with insertion of a cephalomedullary nail placed in compression mode. A novel technique of intraoperative removal of the endosteal hypertrophied cortical bone at the fracture site with a Midas rex cutting burr was utilized and there was excellent cortical contact after reduction. She had immediate relief of her pain and was permitted to fully bear weight postoperatively.

Alendronate was stopped immediately. Teriparatide was initiated at a dose of 20 μg daily 7 weeks after surgery, and continued for 8 months. At follow-up 3.5 months postsurgery, she was pain--free and fully weight-bearing, and her radiographs showed normal fracture union with mature callus formation (Fig. 2).

Prophylactic surgery of the contralateral side with intramedullary nailing was recommended due to high risk for impending AFF, but the patient opted to defer surgery.

Discussion

AFFs are rare but feared adverse events associated with the use of antiresorptive therapies. A large population study found the incidence of AFF to be 1.74 per 10 000 patient years, increasing to 13.1 with >8 years of cumulative bisphosphonate use, and rapidly declining to 0.5, 15 months after discontinuation.[3] While no data directly comparing incidence of AFF with oral and intravenous bisphosphonate use is available, a secondary analysis of 3

Highlights

- Surgically treated atypical femur fractures (AFF) have high complication rates.
- Teriparatide is an anabolic agent that stimulates bone formation by osteoblasts.
- There are limited data supporting the use of teriparatide for treatment of AFF.
- We report expedited AFF healing with teriparatide and a novel surgical technique.

Clinical Relevance

Bisphosphonate-associated atypical femur fractures are challenging to treat, with high rates of delayed union and nonunion. We report use of a novel surgical technique with removal of abnormal bone at the fracture site with intramedullary nailing followed by treatment with teriparatide, resulting in an expedited healing time of 3.5 months.

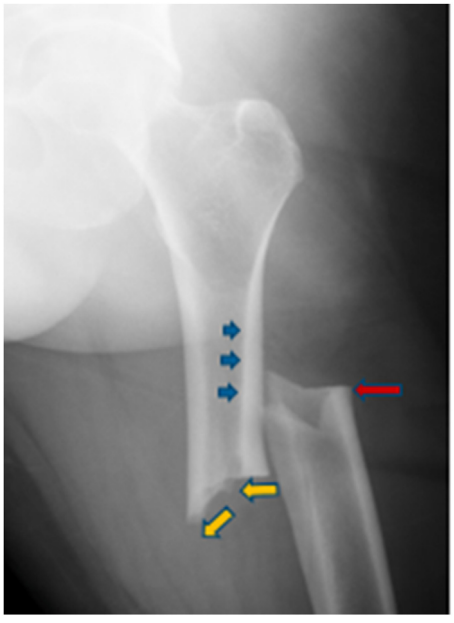

Fig. 1. Preoperative radiograph. Atypical femur fracture showing transverse fracture line with medial obliquity (yellow arrows), flaring at the lateral cortex at the fracture site (pink arrow), thickening of the diaphysis of the lateral cortex (blue arrows).

Fig. 2. Postoperative radiograph. At 3.5 months depicting mature callus formation at fracture site.

randomized controlled trials estimated the relative hazard of AFF among patients on zolendronic acid compared to placebo to be 1.50 after a mean of 3 years of use, and on alendronate to be 1.03 after 4.2 years, and 1.33 after 10 years of use.[4] Population studies suggest a higher risk in Asian and Hispanic individuals and in patients with a history of prolonged glucocorticoid use.[1] Rheumatoid arthritis and 25 hydroxy vitamin D levels <16 ng/mL were also identified as risk factors for AFF in a small case series but not corroborated by other studies.[5]

AFFs are distinguished from other fractures by specific clinical and radiographic criteria (Table).[6] To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare and must have at least 4 out of 5 major features. None of the minor features are required but are often characteristic of these fractures. In our case, all major and 2 minor criteria were present.

AFFs are thought to result from changes in the mechanical properties of the bone caused by suppressed bone turnover, evidenced by significantly lower levels of bone turnover markers (procollagen type 1 N-terminal propeptide, tartrate resistant acid phosphatase 5b, and undercarboxylated osteocalcin) within the first 24 hours compared to typical femoral fractures,[7] and the formation of microcracks with impaired healing.[1] These fractures typically undergo poor healing, with 1 study demonstrating an average time to union of 10.7 months after surgery.[8] Moreover, there are frequent complications including nonunion, malunion, deformity, continued pain, and need for surgical revision.[9]

In patients treated with bisphosphonates, the risk of AFF can be reduced with the use of a "drug holiday." This is the practice of temporarily discontinuing a drug to avoid long-term cumulative adverse effects with chronic use. The timing and use of drug holidays must be individualized, taking into account the risk of osteoporotic fragility fractures off therapy.[3] For bisphosphonates, a drug holiday should be considered after 3 to 5 years of treatment for individuals with low to moderate risk of fracture for a period of 1 to 2 years to decrease the risk of AFF.[10] Unfortunately, our patient was treated for 15 consecutive years with a bisphosphonate without a drug holiday even though she was at low risk of a fragility fracture. In contrast, a drug holiday is not recommended for denosumab due to a rapid decline in bone mineral density and an increased risk of vertebral fractures upon discontinuation.[11]

Moreover, it is important to recognize clinical signs and symptoms which could indicate impending AFF in a patient on bisphosphonate therapy. Our patient reported anterior thigh pain, characteristic of impending AFF,[12] in the months leading up to her presentation but unfortunately an impending AFF was not recognized. The International Society of Clinical Densitometry recommends bilateral full-length femur images to screen for localized cortical abnormalities in patients with a cumulative bisphosphonate exposure of ≥3 years.[13] If features of AFF are found, antiresorptive therapy should be discontinued, with use of alternative pharmacologic therapy in those with continued high fracture risk. In symptomatic patients who meet criteria for incomplete AFF, prophylactic intramedullary nail fixation is recommended.[8]

Our patient's AFF was surgically treated with a novel technique of open reduction and internal fixation with insertion of a cephalomedullary nail placed in compression mode, which involves maximizing cortical opposition, minimizing cortical gapping at the fracture site, and placing force through the cortices intraoperatively.[14] This was achieved by placing the distal interlocking screws first and then forcing the fracture to compress through the nail in a retrograde fashion. Additionally, as the hypertrophied bone in AFF has abnormal remodeling characteristics, it was removed from the fracture site with a Midas rex cutting burr. The burr was placed intramedullarly and used to contour the cortices for excellent direct cortical opposition. These technical modifications are not routinely performed for intramedullary nail fixation of femur fractures.

Teriparatide and abaloparatide are PTH and parathyroid hormone related protein analogs respectively which stimulate bone formation. The use of teriparatide in AFFs after surgical treatment has been associated with improved healing times in small studies. Pooled data from observational studies showed that radiologic healing was achieved in 6 months in 76% of surgically treated patients with complete AFFs on teriparatide vs 51% in the non-teriparatide group.[15] However, these studies were heterogenous and insufficiently powered to demonstrate a clear benefit with teriparatide. A recent meta-analysis of 7 cohort studies demonstrated lower rates of delayed union, nonunion, and shorter healing times (mean difference 1.69 months) in patients with AFF who received teriparatide compared to those who did not.[16] While this data supports teriparatide use, larger studies with randomized controlled trials are needed to determine its efficacy for AFF. The duration of teriparatide use in AFF is not well defined, with experts recommending a 3 to 6 month course to enhance fracture healing. Furthermore, it is important to recognize the challenges with obtaining anabolic therapies for off-label use due to high cost and possible lack of insurance coverage. To our knowledge, no studies on the use of abaloparatide in patients with AFF have been published, although mouse models have shown a similar effect of abaloparatide as teriparatide on fracture healing.[17]

In our patient, teriparatide use was combined with a novel surgical technique involving removal of abnormally remodeled bone at the fracture site followed by intramedullary nail fixation in compression mode. This approach led to excellent clinical and radiologic results and an expedited healing time of 3.5 months. Furthermore, our patient had radiologic features of an impending AFF on the contralateral side. Prophylactic surgery was recommended but she has opted to be managed conservatively. She

Table
ASBMR Task Force 2013 Revised Case Definition of AFFs[6]

Major features	Minor features
Associated with minimal or no trauma	**Generalized increase in cortical thickness of the femoral diaphyses**
Fracture line originates at the lateral cortex, is substantially transverse in its orientation—may become oblique as it progresses medially	**Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh**
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex	Bilateral incomplete or complete femoral diaphysis fractures
Noncomminuted or minimally comminuted	Delayed fracture healing
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")	

Abbreviations: AFF = atypical femur fracture; ASBMR = American Society of Bone and Mineral Research.
Bolded criteria were observed in our patient.

continues to remain fracture and pain-free on the contralateral side after treatment with teriparatide for 8 months. This suggests a possible role of teriparatide in preventing impending AFF, although further study is needed to explore this observation.

Conclusion

A combination of a novel surgical technique and postoperative teriparatide was associated with an excellent clinical and radiologic outcome in our patient with a bisphosphonate-associated AFF. Further studies are needed to explore the effectiveness of this novel surgical approach as well as the use of teriparatide in the treatment of AFF.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

This case report was published as an abstract only at the AACE Annual Meeting 2023 (Abstract #1408105).

References

1. Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical femur fractures: review of epidemiology, relationship to bisphosphonates, prevention, and clinical management. *Endocr Rev*. 2019;40(2):333–368. https://doi.org/10.1210/er.2018-00001
2. Lo JC, Grimsrud CD, Ott SM, Chandra M, Hui RL, Ettinger B. Atypical femur fracture incidence in women increases with duration of bisphosphonate exposure. *Osteoporos Int*. 2019;30(12):2515–2520. https://doi.org/10.1007/s00198-019-05112-5
3. Black DM, Geiger EJ, Eastell R, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med*. 2020;383(8):743–753. https://doi.org/10.1056/NEJMoa1916525
4. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med*. 2010;362(19):1761–1771. https://doi.org/10.1056/NEJMoa1001086
5. Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. *N Engl J Med*. 2010;362(19):1848–1849. https://doi.org/10.1056/NEJMc0910389
6. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2014;29(1):1–23. https://doi.org/10.1002/jbmr.1998
7. Iizuka Y, Iizuka H, Kaneko T, et al. Bone turnover markers and the factors associated with atypical femur fractures among Japanese patients. *Injury*. 2016;47(11):2484–2489. https://doi.org/10.1016/j.injury.2016.09.031
8. Cho JW, Oh CW, Leung F, et al. Healing of atypical subtrochanteric femur fractures after cephalomedullary nailing: which factors predict union? *J Orthop Trauma*. 2017;31(3):138–145. https://doi.org/10.1097/BOT.0000000000000743
9. Schultz DS, Gass 4th HM, Barfield WR, Demos HA, Hartsock LA. Surgical complications associated with atypical femur fractures attributed to bisphosphonate use. *J Surg Orthop Adv*. 2018;27(1):14–20.
10. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105(3):dgaa048. https://doi.org/10.1210/clinem/dgaa048
11. McClung MR. Cancel the denosumab holiday. *Osteoporos Int*. 2016;27(5):1677–1682. https://doi.org/10.1007/s00198-016-3553-3
12. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract*. 2020;26(5):564–570. https://doi.org/10.4158/GL-2020-0524
13. Shuhart CR, Yeap SS, Anderson PA, et al. Executive summary of the 2019 ISCD position development conference on monitoring treatment, DXA cross-calibration and least significant change, spinal cord injury, peri-prosthetic and orthopedic bone health, transgender medicine, and pediatrics. *J Clin Densitom*. 2019;22(4):453–471. https://doi.org/10.1016/j.jocd.2019.07.001
14. Berkes MB, Shaw JC, Warner SJ, Achor TS. Medialized trochanteric starting point and focused lateral endosteal beak reaming to optimize success of intramedullary nailing in atypical femur fractures: a technical trick and case series. *J Orthop Trauma*. 2019;33(8):e313–e317. https://doi.org/10.1097/BOT.0000000000001511
15. van de Laarschot DM, McKenna MJ, Abrahamsen B, et al. Medical management of patients after atypical femur fractures: a systematic review and recommendations from the European Calcified Tissue Society. *J Clin Endocrinol Metab*. 2020;105(5):1682–1699. https://doi.org/10.1210/clinem/dgz295
16. Byun SE, Lee KJ, Shin WC, Moon NH, Kim CH. The effect of teriparatide on fracture healing after atypical femoral fracture: a systematic review and meta-analysis. *Osteoporos Int*. 2023;34(8):1323–1334. https://doi.org/10.1007/s00198-023-06768-w
17. Bernhardsson M, Aspenberg P. Abaloparatide versus teriparatide: a head to head comparison of effects on fracture healing in mouse models. *Acta Orthop*. 2018;89(6):674–677. https://doi.org/10.1080/17453674.2018.1523771