Case report

Progression of bisphosphonate-associated impending atypical femoral fracture despite prophylactic cephalomedullary nailing: A case report and review of literature

Aditya V. Maheshwari, Samantha J. Yarmis, Justin Tsai, Julio J. Jauregui*

SUNY Downstate Medical Center, Department of Orthopaedic Surgery and Rehabilitation, Brooklyn, NY, United States

ARTICLE INFO

Article history:

Received 6 April 2016

Received in revised form 1 May 2016

Accepted 8 June 2016

Available online 29 June 2016

Keywords:

Bisphosphonates

Atypical femur fractures

Bisphosphonate associated fractures

Pathologic fractures

Stress fractures

ABSTRACT

While bisphosphonates have been shown to be effective in reducing the incidence of typical osteoporotic fractures, long-term bisphosphonate may be associated with atypical femoral fractures. We report a case of a bisphosphonate-related impending atypical femoral fracture which progressed despite prophylactic cephalomedullary nailing. The fracture healed without further surgical intervention after correcting the patient's bone metabolic profile and stopping the possible offending factors. Although prophylactic fixation of these fractures is recommended, our case and relevant literature review demonstrate that a simple fixation without optimizing other possible predisposing factors may not prevent progression of these fractures.

© 2016

1. Introduction

Bisphosphonate-related atypical fractures of the femur (AFF) have distinct clinical and radiologic presentations, including prodromal pain, cortical hypertrophy, and unicortical "beaking".¹ The recognition of these features provides opportunities for prophylactic fixation, which has been suggested as the treatment of choice for bisphosphonate-related AFF.^{2–4} We present a case of AFF where the fracture progressed despite prophylactic fixation of the femur, and provide a review of literature on similar cases. The patient was informed that data concerning the case would be submitted for publication, and she consented.

2. Case report

A 70-year-old African-American female (BMI 26.5) with a history of hypertension, hyperlipidemia, and multiple myeloma (MM) presented with worsening right hip/thigh pain for 3 months. Her MM was diagnosed one year previously after she had sustained a displaced pathologic fracture of her left femur. This had been

treated by a cephalomedullary nail followed by radiation (3000 cGy in 15 fractions) by a different surgeon (Fig. 1A). She was then placed on lenalidomide (25 mg, 21 days on/7 days off cycle) with dexamethasone 40 mg/week. She had been on alendronate 35 mg/week for 3 years, but was switched to monthly infusions of 4 mg zoledronic acid after the fracture and initiation of the myeloma treatment one year ago. A skeletal survey showed multiple lytic lesions in several long bones. In addition to the typical AFF related lateral cortical beaking in the subtrochanteric region on the right side, some cortical hypertrophy was also seen on the medial cortex (Fig. 1A and B). Although pathologic fractures are excluded from definition of AFF,⁵ this appeared more like an AFF rather than a myeloma-related pathologic fracture because of its typical beaking, absence of a typical myeloma lytic lesion at the beaking site, and use of bisphosphonate. Because of her symptoms, multiple lytic lesions, increased risk for another pathologic fracture, and possible AFF, she was indicated for prophylactic cephalomedullary nailing (Gamma III, 12 mm × 400 mm × 125°, 2 distal locking screws, Stryker, Mahwah, NJ; Fig. 2A). Reamings sampled for MM were negative, but the tumor board recommendation was to radiate her femur/hemipelvis (3000 cGy × 15 fractions). Bisphosphonates were stopped, while her treatment for MM was continued.

Although she was asymptomatic, follow-up radiographs showed slight worsening of the subtrochanteric beaking with a

* Corresponding author at: SUNY Downstate Medical Center, Department of Orthopaedics, 450 Clarkson Avenue, MSC 30, Brooklyn, NY 11203, United States. Tel.: +1 718 221 5270.

E-mail address: juljau@gmail.com (J.J. Jauregui).

Fig. 1. (A) AP radiograph of pelvis and proximal femur showed a healed fracture over a cephalomedullary nail on the left side (white arrow). On the right side, multiple permeative lesions are seen in the entire femur and pelvis (yellow arrows). A subtle beaking is also seen on the right side (black arrow). (B) A frog table lateral radiograph showed multiple permeative lesions in the entire femur and pelvis (yellow arrows). An area of sclerosis is also seen in the subtrochanteric region (black arrow).

Fig. 2. (A) AP radiograph of the proximal femur at one month postoperatively clearly showing the beaking and sclerosis on both sides (black arrow). (B) AP radiograph at 4 months postoperatively showing slight worsening of the beaking (black arrow). (C) The frog table lateral view showed a subtle radiolucent line, indicating a fracture line (black arrow).

radiolucent fracture line, more obvious on the oblique views (Fig. 2A–C). Blood work showed a low Vitamin D, 25-OH, total level of 16.4 $\mu\text{g/dl}$ (normal: 30–95). Other results included a normal complete blood count, normal comprehensive metabolic profile, intact parathyroid hormone level (29.8 pg/ml, normal: 15–65), calcium (9.4 mg/dl, normal: 8.2–10), phosphate (3.5 mg/dl, normal: 2.5–4.5), alkaline phosphatase (35 U/L, normal: 34–104), C-reactive protein (<4 mg/L, normal: 0–8), and ESR (20 mm/h, normal: 0–30). A dual-energy X-ray absorptiometry (DEXA) scan of the lumbar spine showed mild osteopenia (T-score 1.2). The patient was then started on cholecalciferol 50,000 U/week for the next 12 weeks along with calcium supplements of 1000 mg/day. Because of history of skeletal malignancy, teriparatide was not

considered. She had no restriction in her activities and weight-bearing status.

Serial radiographs showed progression of her subtrochanteric fracture over a course of one year (Fig. 3A–C). Her vitamin D levels were 24.9 $\mu\text{g/dl}$ after 4 months, and 28.9 $\mu\text{g/dl}$ one year later after another 12 doses of 50,000 U/week. At 12 months postoperatively, her MM treatment was discontinued after a negative laboratory work-up and bone marrow biopsy. She was then maintained on 2000 U/day of cholecalciferol and 1000 mg/day of calcium. At 15 months postoperatively, the fracture began to heal (Fig. 3D), which consolidated at 18 months (Fig. 4A and B). At 55 months follow-up, radiographs showed further consolidation of the fracture and she remains myeloma-free and asymptomatic (Fig. 5A and B).

Fig. 3. (A–C) Serial AP radiographs of the proximal femur showed progressive worsening of the fracture line over a course of one year (black arrows). (D) Some bridging callus is seen in this 15 months postoperative AP view (black arrow). Please note the progressive maturation of the heterotrophic ossification proximal to the greater trochanter.

Fig. 4. (A) AP and (B) frog table lateral radiographs at 18 months showed further consolidation and sclerosis of the fracture site (black arrows).

3. Discussion

Although controversial, prolonged use of bisphosphonates has been linked with increased risk of AFF.⁶ These fractures have distinct clinical and radiological features, including prodromal

pain, cortical hypertrophy and unicortical “beaking”.^{1,7,8} The recognition of these features provides opportunities for prophylactic fixation, which has been associated with a reduced rate of progression to complete fracture and reduced hospital length-of-stay.^{2,3,9} The predominant hypothesis regarding the pathophysiology of atypical

Fig. 5. (A) AP and (B) oblique radiographs at latest follow-up (55 months) demonstrated full consolidation of the fracture site (black arrows).

femur fracture is that bisphosphonate induced suppression of bone turnover leads to the accumulation of bone microdamage, a reduction in matrix heterogeneity, and an increase in advanced glycation end-products, leading to impaired stress fracture healing, and the development of an insufficiency fracture at the point of maximal, weight-bearing stress, namely at the subtrochanteric or diaphyseal femur.^{10,11}

In spite of history of myeloma, we still believe that our case was an AFF rather than a myeloma-related pathologic or stress fracture as there was a typical AFF like beaking, absence of a typical myeloma lytic lesion at the beaking site, and over 4 years of prior bisphosphonate use. Moreover, the fracture progressed after adequate fixation (the stress fracture should have healed not progressed after nailing). On top, the pathology from reaming did not show any plasma cells as the patient had been on myeloma treatment for over a year. An additional finding in our case was a concomitant medial cortical hypertrophy, which has not been described for AFF (but a medial spike is common with a complete AFF).¹⁰ Although prophylactic nailing seems to be the treatment of choice for these impending AFFs, progression of the fracture after nailing is not expected, as happened in our case. We are aware of only two other reports where bisphosphonate-related AFF progressed even after intramedullary nailing (Table 1). Although the fracture pattern, risk factors and subsequent treatment were different, ours' and these cases bring out an important association with bisphosphonates. In contrast to other cases, we successfully managed our case non-surgically due to timely diagnosis and correction of the risk factors, and we have a much longer follow-up. Fang et al.⁴ recommended against a slotted nail to increase the stiffness of the implant and Schemitsch et al.¹⁰ recommended use of larger diameter nail, more distal placement of nail, use of two distal locking screws and a period of protected weight bearing. Despite following all these recommendations (except that our patient was, in fact, weight bearing as tolerated), our patient still had a progression of the AFF even after fixation. This explains the multifactorial nature of these AFF and need for a custom treatment.

Although the original definition of AFF excludes periprosthetic fractures,⁵ similar bisphosphonate-associated fractures have also

been reported in the setting of orthopedic implants. Lee et al. reported on 11 low-energy peri-implant (mostly plates and one periprosthetic stemmed total knee arthroplasty) fractures in 10 ambulant females (mean age 80 years, on bisphosphonates for mean 5 years, range 1–10), 48 months (range 6–108) after the index surgery.¹² They hypothesized that dynamic strains under tension may be accentuated, contributing to local micro-damage that overwhelms the impaired healing capacity of the anti-resorptive treated bone. There are also several case reports on similar fractures after total hip arthroplasty in patients on bisphosphonates, in spite of the intramedullary stems, analogous to an intramedullary fixation (Table 2). These findings are important as use of bisphosphonates have been paradoxically encouraged to increase the periprosthetic bone mineral density and improve implant survival in patients who have undergone a total joint arthroplasty of the lower limb.¹³ Moreover, this may call for a revision of the definition of AFF or introduction of a newer entity as these bisphosphonates associated peri-prosthetic/peri-implant fractures (BAPF) appear similar to AFF in terms of etiology.

There is also a report on a patient with bilateral AFF, who healed without surgery after stoppage of alendronate (drug holiday).¹⁴ However, she was restarted on ibandronate at 5 years and subsequently developed bilaterally displaced AFF after 7 months. These cases demonstrate that a simple fixation without optimizing other predisposing factors may not prevent progression of these fractures. Associated factors such as concomitant estrogen, glucocorticoid, or proton pump inhibitor therapy, as well as various comorbidities, including inflammatory conditions, diabetes mellitus, metabolic bone disease, and metastatic bone disease may predispose to these atypical fractures, even in the absence of bisphosphonate use.³ In our case, correction of metabolic profile, cure from myeloma, adequate time frame after radiation, and stoppage of bisphosphonate and steroids correlated with ultimate fracture healing. The treatment dose of Vitamin D in adults with deficiency has no universal recommendation and varies geographically.^{15,16} Our patient was treated based on the presumptive common dosage prevalent in the United States. Physicians must use their clinical judgment, based on monitoring of laboratory

Table 1
Atypical femoral fractures that progressed despite prophylactic nailing.

Author, year	Age, gender	Symptoms	Risk factors	Mode of trauma	Fracture and location	Progression	Workup	Treatment	Outcome and FU	Author recommendations
Fang 2014, case 1 ⁴	71F	Thigh pain	Alendronate × 5 years but stopped 14 months prior to fracture Surgical menopause	Fall on level ground	Atypical mid femur shaft fracture	Displaced comminuted fracture of femur at original site of stress fracture	Radiographs No metabolic/endocrine work up	The original 10 mm slotted stainless steel nail was exchanged to non slotted cannulated Titanium cephalomedullary nail; calcium carbonate, multivitamin supplements, strontium ranelate	Fracture union at 4 months postop	Select a more rigid implant that can bear stress throughout extended period of time for biologically compromised femur to heal
Fang 2014, case 2 ⁴	78F	Hip pain	Alendronate × 2.5 years	Low energy fall	Oblique fracture of distal femur shaft	Displaced subtrochanteric stress fracture at the proximal locking site with bending of IM nail	Radiographs No metabolic/endocrine work up	The original 11 mm slotted stainless steel nail was exchanged to non slotted cannulated Titanium cephalomedullary nail. Alendronate was stopped	Fracture union at 4 months postop	
Schemitsch 2015 ¹⁷	43F	Thigh pain	Bisphosphonate 1 year, premature idiopathic menopause at 35 years, HRT	Fall from standing height	Impending femoral stress fracture	Spontaneous complete fracture of prophylactically nailed femur at site of lateral cortical stress lesion	Radiographs Dexa scan showed osteoporosis Normal Vitamin D and PTH levels	She was originally treated by a 9 mm size cephalomedullary nail with 1 distal locking screw. After the fracture this was supplemented by a 4.5 mm broad compression plate with autologous bone graft and later addition of Teriparatide	Solid osseous union of femoral fracture at 2 years postop	Use larger nail, insert it more distally, and/or use 2 locking screws rather than 1, and period of limited weight-bearing

Table 2

Bisphosphonate-associated periprosthetic femur fractures after total hip replacement.

Author, year	Age, gender	Symptoms	Bisphosphonate	Radiology, DEXA	Metabolic profile	Risk factors	Treatment	Outcome
Bhattacharyya 2014 ¹⁸	72F	Thigh pain	Alendronate 10 y	XR, Unremarkable, CT oblique vertical split, BS, Abnormal appearance of the right femoral shaft	Unremarkable	Rheumatoid arthritis, osteoporosis, prednisolone	D/C alendronate, protected weight bearing	Fracture healing at 3 m
Cross 2012 ¹⁹	81F	Thigh pain	Alendronate 12 y, D/C 8 m prior	XR, Transverse, subtrochanteric femur fracture; BS Increased uptake in lateral cortex of the subtrochanteric region	NA	Post-menopausal osteoporosis	D/C alendronate, teriparatide for 6 months	Fracture consolidation and symptom resolution at 4.5 m
Curtin 2011 ²⁰	52F, 72F, 85F	1. Upper thigh pain 2. Hip pain; 3. Hip pain	1. Alendronate 5 y; 2. Risedronate unspecified; 3. Alendronate 9 y	1. XR, Anterolateral stress fracture below the prosthesis, BS positive for femoral loosening; 2. XR, negative, BS, positive for diaphyseal stress; 3. XR, lateral cortex fracture	NA	Post-menopausal osteoporosis, rheumatoid arthritis, prednisolone, rheumatoid arthritis	D/C bisphosphonate, begin Ca + VitD or teriparatide	Radiograph evidence of healed fracture
Niikura 2015 ²¹	69F	NA	Alendronate 7 y, D/C 7 m prior	Complete non-comminuted transverse fracture at tip of stem; DEXA, Bone mineral density 0.644 g/cm ² (82% of young adult mean)	NA	Prednisolone to treat dermatomyositis and interstitial pneumonia	ORIF locking compression plate	Fracture healing
Reb 2013 ²²	74F	Groin and thigh pain	Unspecified bisphosphonate for 10 y, d/c 3 m prior	Anterolateral subtrochanteric femoral cortical thickening without transverse lucency	NA	Osteoarthritis, osteoporosis	Femoral revision with tapered modular stem, Ca + VitD	Fracture healing and pain resolution
Sayed-Noor 2009 [23]	55F, 78F	Pain, swelling, leg shortened and externally rotated	1. Alendronate for 10 y, d/c 8 m prior; 2. Alendronate for 9 y	1. XR, Thickening of shaft cortex with fracture line below the tip of the femoral stem; 2. XR, transverse subtrochanteric fracture with cortical hypertrophy and medial spiking	1. Normal CBC, CRP, serum calcium, phosphate, and vitamin D, 2. Supplement vitamin D.	1. Post-menopausal osteoporosis; 2. Chronic alcohol liver disease and post-menopausal osteoporosis	1. D/C alendronate, ORIF angle-stable plating system with cable grip; 2. Gamma nail	Fracture healing and pain resolution
Schaeffer 2012 ²⁴	79F	Thigh pain	Alendronate for 8 y, then ibandronate for 2 y	XR, periprosthetic stress fracture with cortical thickening of lateral femoral cortex at level of distal femoral stem, medial extension and widening of fracture	Negative for infection	Osteoporosis	Femoral revision, D/C bisphosphonate	Fracture healing
Chen 2015 ²⁵	69F	Thigh and knee pain	Ibandronate for 4 y d/c ibandronate 9 m	XR, incomplete Vancouver type-C transverse fracture with medial oblique propagation	NA	Osteoporosis; rheumatoid arthritis	Femoral condylar locking plate, D/C Ibandronate	Fracture healing
Chen 2012 ²⁶	81F	Thigh and knee pain	Alendronate for 4 y and ibandronate 4 m	XR, cortical thickening, beaking, and a horizontal fracture line near the tip of the left femoral prosthesis	NA	Osteoporosis	4.5-mm locking plate D/C bisphosphonate	Fracture healing and pain resolution

M, male; F, female; y, years; m, months; XR, X-ray; CT, computerized tomography; BS, bone scan.

markers of bone health in order to determine proper supplementation of these medications.

Because of ever-increasing use of bisphosphonates for osteoporosis and bone metastases, AFF/BAPF should be considered in patients who complain of thigh/hip pain even with intramedullary fixation or prostheses. It is also important to note these patients may or may not be symptomatic until complete fracture occurs. Therefore, regular clinical and radiological follow-up is encouraged and should be part of the discussion with the patient prior to surgical intervention. Moreover, stoppage of bisphosphonates, correction or modification of other risk factors, and implant selection are all important considerations.

Conflicts of interest

The authors have none to declare.

References

1. Ward Sr WG, Carter CJ, Wilson SC, Emory CL. Femoral stress fractures associated with long-term bisphosphonate treatment. *Clin Orthop Relat Res.* 2012;470(3):759–765.
2. Banffy MB, Vrahas MS, Ready JE, Abraham JA. Nonoperative versus prophylactic treatment of bisphosphonate-associated femoral stress fractures. *Clin Orthop Relat Res.* 2011;469(7):2028–2034.
3. Giusti A, Hamdy NA, Papapoulos SE. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. *Bone.* 2010;47(2):169–180.
4. Fang C, Chau JY, Woo SB, Lau TW, Kwan K, Leung F. Propagation of bisphosphonate-related femoral stress fractures despite femoral nailing: a cautionary tale from 2 cases. *Geriatr Orthop Surg Rehabil.* 2014;5(1):14–17.
5. 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.
6. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med.* 2011;364(18):1728–1737.
7. Isaacs JD, Shidiak L, Harris IA, Szomor ZL. Femoral insufficiency fractures associated with prolonged bisphosphonate therapy. *Clin Orthop Relat Res.* 2010;468(12):3384–3392.
8. Rosenberg ZS, La Rocca Vieira R, Chan SS, et al. Bisphosphonate-related complete atypical subtrochanteric femoral fractures: diagnostic utility of radiography. *AJR Am J Roentgenol.* 2011;197(4):954–960.
9. Oh CW, Oh JK, Park KC, Kim JW, Yoon YC. Prophylactic nailing of incomplete atypical femoral fractures. *Sci World J.* 2013;2013:450148.
10. Unnanuntana A, Saleh A, Mensah KA, Kleimeyer JP, Lane JM. Atypical femoral fractures: what do we know about them? AAOS exhibit selection. *J Bone Joint Surg Am.* 2013;95(2). e8 1–13.
11. Girgis CM, Seibel MJ. Atypical femur fractures: a review of the evidence and its implication to clinical practice. *Ther Adv Musculoskelet Dis.* 2011;3(6):301–314.
12. Lee JY, Soh T, Howe TS, Koh JS, Kwek EB, Chua DT. Bisphosphonate-associated peri-implant fractures: a new clinical entity? A series of 10 patients with 11 fractures. *Acta Orthop.* 2015;86(5):622–626.
13. Bhandari M, Bajammal S, Guyatt GH, et al. Effect of bisphosphonates on periprosthetic bone mineral density after total joint arthroplasty. A meta-analysis. *J Bone Joint Surg Am.* 2005;87(2):293–301.
14. Puah KL, Tan MH. Bisphosphonate-associated atypical fracture of the femur: spontaneous healing with drug holiday and re-appearance after resumed drug therapy with bilateral simultaneous displaced fractures – a case report. *Acta Orthop.* 2011;82(3):380–382.
15. Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. *South Med J.* 2005;98(10):1024–1027.
16. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc.* 2010;85(8):752–757. [quiz 757–8].
17. Schemitsch CE, Kuzyk P, McKee MD. Atypical femoral fracture despite prophylactic intramedullary nailing. *J Bone Joint Surg Case Connect.* 2015;5(e57).
18. Bhattacharyya R, Spence S, O'Neill G, Periasamy K. Bisphosphonate-induced periprosthetic fracture: a cause of painful total hip arthroplasty. *Case Rep Surg.* 2014;2014:631709.
19. Cross MB, Nam D, van der Meulen MC, Bostrom MP. A rare case of a bisphosphonate-induced peri-prosthetic femoral fracture. *J Bone Joint Surg Br.* 2012;94(7):994–997.
20. Curtin BM, Fehring TK. Bisphosphonate fractures as a cause of painful total hip arthroplasty. *Orthopedics.* 2011;34(12):e939–e944.
21. Niikura T, Lee SY, Sakai Y, Kuroda R, Kurosaka M. Rare non-traumatic periprosthetic femoral fracture with features of an atypical femoral fracture: a case report. *J Med Case Rep.* 2015;9:103.
22. Reb CCJA, Deirmengian CA, Deirmengian GK. Acute postoperative bisphosphonate-associated atypical periprosthetic femoral fracture a case report. *JBJS Case Connect.* 2013;3(3).
23. Sayed-Noor AS, Sjoden GO. Case reports: two femoral insufficiency fractures after long-term alendronate therapy. *Clin Orthop Relat Res.* 2009;467(7):1921–1926.
24. Schaeffer JADE, Wellman SS. Periprosthetic femoral insufficiency fracture in a patient on long-term bisphosphonate. *Duke Orthop J.* 2012;2(1):66–69.
25. Chen F, Li R, Lall A, Jin Kim S, Hirsh DM, Schwechter EM. Atypical Vancouver type-C periprosthetic fracture complicated by nonunion. *JBJS Case Connect.* 2015;5(2):e44.
26. Chen F, Bhattacharyya T. Periprosthetic fracture of the femur after long-term bisphosphonate use. *JBJS Case Connect.* 2012;2(2):e21.