J Musculoskelet Neuronal Interact 2013; 13(2):251-254

Case Report Article

Hylonome

Pelvic fractures associated with long-term bisphosphonate therapy – Case report

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Abstract

Long term bisphosphonate use has been associated with "atypical" subtrochanteric and diaphyseal fractures of the femoral shaft. We are reporting a case of pelvic fractures in addition to atypical long bone fractures, in a patient with osteopenia treated with bisphosphonate for 8 years, and teriparatide for 2 years. After 5 years of bisphosphonate therapy the patient suffered an atraumatic fracture of the femoral shaft. With an additional 3 years of bisphosphonate use she fractured both the upper and lower pubic rami on the left side. Bone histomorphometry performed on a biopsy of right iliac crest was negative for malignancy and calcification defects. It showed normal to low/normal bone turnover which correlated well with a low NTX level. Post-surgical X-rays revealed cortical thickening of the femur and beaking at the femoral shaft fracture, the classic findings associated with alendronate-related fractures. The pelvic fractures also reveal beaking at the fracture sites. Spontaneous fracture of the pelvis with unusual characteristics, in a patient with an atypical fracture of the femur suggests that the pelvic fracture may be related to long term bisphosphonate therapy.

Keywords: Pelvic Fractures, Bisphosphonate Use, Cortical Thickening, Beaking and Atypical Fractures

Introduction

Osteoporosis is a well-defined and growing public health problem. Bisphosphonates have been the mainstay of osteoporosis therapy. Their anti-fracture efficacy was demonstrated almost two decades ago[1-3]. We have increasingly clear evidence that bisphosphonates given to post-menopausal women with osteoporosis, patients with existing osteoporotic fractures and men with osteoporosis prevent future vertebral and non-vertebral fractures[4].

The use of bisphosphonates has been growing steadily in the last decade. There was a concern that excessive or prolonged bisphosphonate use might cause over suppression of bone remodeling and micro damage accumulation and thus an increase rather than decrease skeletal fragility[5]. Five cases of subtrochanteric fractures and three cases of pelvic fractures (one with pubic rami fractures and 2 with sacral fractures) were first reported in 2005 on patients with severely suppressed bone turnover while on alendronate therapy[6]. Subsequently there have been numerous case reports of "atypical" fractures in patients taking alendronate[7,8]. The increased risk of atypical femur fractures with alendronate use could be more likely caused by osteoporosis than by alendronate therapy[9]. The rates of these atypical fractures were found to be low and similar between placebo and bisphosphonate-treated women in a reanalysis of three large clinical trials [FIT, FLEX, AND HORIZON][10]. We wish to report a case with unusual presentation of pelvic fractures in addition to long bone fractures after long term bisphosphonate use.

Case summary

A 58 year old female, 12 years post menopause, was started on alendronate for "osteoporosis" in 1998. Five years after starting alendronate; in 2003, she suffered an atraumatic fracture of the right hip, requiring surgical repair. The fracture was triggered by just walking on hard floors at work. Alendronate was discontinued and she was placed on Teriparatide. A year later; in 2004, she experienced diaphyseal fracture of the femur from a trivial trauma

The authors have no conflict of interest.

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Edited by: F. Rauch
Accepted 28 March 2013

	Date	Results	Reference Range
TSH	4/2010	1.050	0.45-4.5 μIU/mL
PTH	4/2010	24	15-65 pg/mL
25(OH) Vitamin D	4/2010	38.6	32-100 ng/mL
Serum Electrophoresis	5/2010	Normal	
Endomysial Antibody	5/2010	Negative	
Osteocalcin	5/2010	2.7	2.7-11.5 ng/mL
Collagen Cross Links	5/2010	12.7	6.2-19.0 nMBCE/L
Phosphorus	5/2010	3.6	2.0-4.0 mg/dL
24 hours urine free cortisol	4/2010	22	0-50 μg/24 hours
24 hours urine calcium	4/2010	320	100-300 mg/24 hours

Table 1. Laboratory work up of the patient.

Parameter	Result	Female normal mean value	Z-Scores
Cancellous Bone Volume %	10.4	21.8	-1.751
Osteoid Volume%	1.478	1.235	0.352
Osteoid Width micrometers	11.1	12.3	-0.393
Osteoid Surface %	7.30	8.44	-0.092
Osteoblast-Osteoid Interface %	3.87	22.10	-1.544
Osteoclast Per Length mm	4.7	3.0/100	0.459
Eroded Surfaces %	0.44	2.29	-2.303
Volume Based Bone Formation Rate mm^9/mm^3/year	0.155	0.250	-0.582
Surface Based Bone Formation Rate mm^9/mm^2/year	0.008	0.019	-1.049

Table 2. Histomorphometry of bone during bisphosphonate therapy

(sheer force of a wave on a lake hitting a boat in which she was seated). She was treated with Teriparatide for 2 years (2003-2005). Six months after cessation of therapy with Teriparatide, the patient was given Ibandronate for two years (2006-2008). In May 2009, she received an intravenous infusion of Zoledronic acid 5 mg. In all she has received 8 years of bisphosphonate therapy. She presented to our Osteoporosis clinic in June 2010 with pelvic pain since March 2010. Pain had started while she was vacuuming. Subsequently X-ray of the pelvis showed fractures of both the upper and lower pubic rami on the left side.

She has a past medical history of hypertension, treated with trandolapril.

Her risk factors were reviewed. She has been quite inactive related to the fractures. She experienced menopause at 46 years, but took hormone replacement therapy between the years 2000 and 2007. Her mother (who apparently had kyphosis but no fractures) and a maternal aunt had osteoporosis. She drinks a glass of wine daily and has a 5 pack year history of smoking, but she stopped in 1987. She took steroids for a very brief period (less than 3 months) about 8 months prior to the pelvic fracture. She takes narcotic analgesics and non steroidal anti-inflammatory drugs to manage pain. There has been no significant weight change or diarrhea.

Physical Examination was significant for slight Cushinoid appearance. Thyroid was not enlarged, and no kyphosis was noted. She had very limited ability to rise and walk because of her multiple fractures.

Laboratory work up revealed normal TSH, PTH, Vitamin D levels, serum electrophoresis and 24 hour urine cortisol. Endomysial antibodies were negative. Serum Osteocalcin was suppressed. 24 hours urine calcium was normal suggesting adequate calcium intake and absorption (see Table 1).

Her bone density did not decrease significantly (<4%) between 2005 and 2010. In October 2005 BMD measured by DXA scan revealed a T-score of -1.9 with a density of 0.995 g/cm^2 at the spine and a T-score of -0.7 with a density of 0.913 g/cm^2 at the hip. In 2010 the bone density at the spine was 0.948 g/cm^2 with a T-score of -2.0 and at the hip she had a density of 0867 g/cm^2 with a T-score of -1.1.

Tetracycline labeled bone biopsy of right iliac crest was performed. Histomorphometry while on bisphosphonate therapy was negative for malignancy, mast cells and calcification defects. It was suggestive of normal/low-normal bone turnover which correlates well with low osteocalcin and low-normal

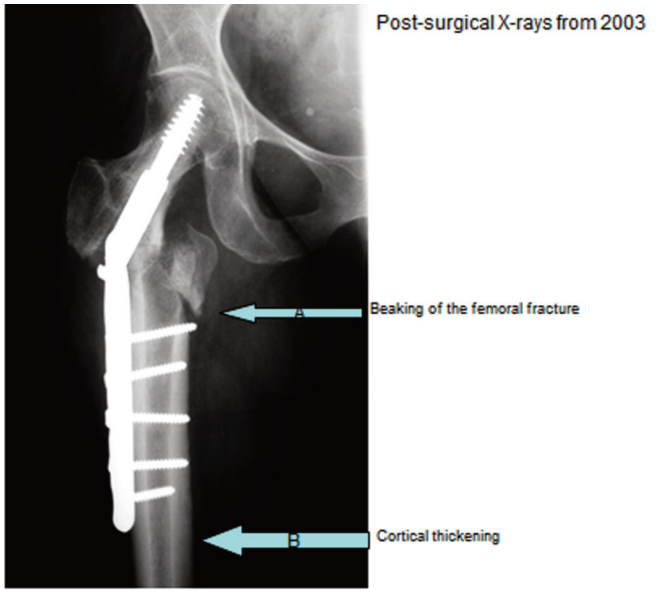

Figure 1. Post-surgical X-rays of the femoral fracture from 2003 revealing the cortical thickening and beaking of the fracture site.

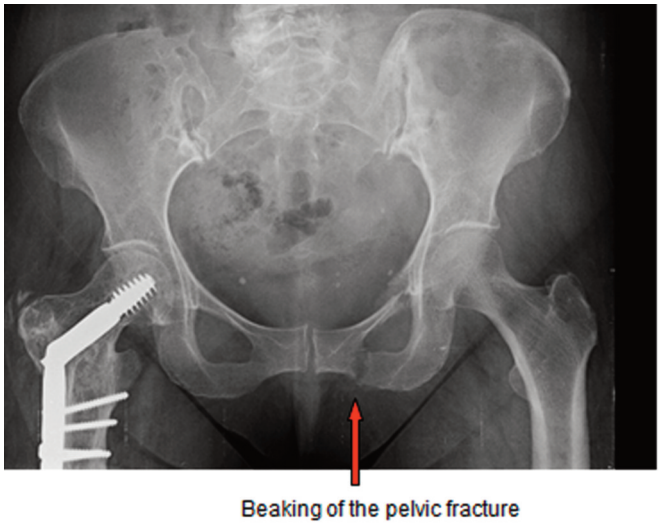

Figure 2. Pelvic X-rays from 2010 revealing the beaking of the fracture site and persistent cortical thickening of both the femurs.

NTX. (See Table 2: Histomorphometry of bone during bisphosphonate therapy).

Post-surgical X-Rays of the hip from 2003 revealed cortical thickening of the femur along with beaking of the fracture (see Figure 1). Pelvic X-ray from 2010 also reveals the bilateral femoral cortical thickening along with beaking of the pelvic fracture (see Figure 2).

Discussion

A 58 year old woman with an 8 year history of bisphosphonate use, presented with a history of spontaneous fracture of the femur and subsequently of the left superior and inferior pubic rami. The patient has low/normal markers of bone turn over, correlating with low bone formation rate seen on bone histomorphometry, which is typically seen with fractures associated with bisphosphonate therapy[6]. A search for other causes of pathological fracture was negative. The cortices of the femur were unusually thick and there was cortical beaking at both the femoral and pelvic fracture sites.

Vitamin D deficiency and secondary hyperparathyroidism are commonly associated with osteoporotic pelvic fractures and these patients, unlike the patient presented here, typically have high markers of bone turnover[11]. Spontaneous fracture of the pelvis with unusual characteristics, an atypical fracture of the femur and suppressed markers of bone turnover in a young vitamin D sufficient patient with osteopenia (as opposed to osteoporosis) suggests that the pelvic fracture may not be related to osteoporosis, but to long term bisphosphonate therapy.

Atypical fractures associated with bisphosphonate therapy generally occur after long term use of bisphosphonates, usually more than 3 years, median 7 years[12], but they also occur in patients not taking a bisphosphonate. The diaphyseal fractures of the femoral shaft can be bilateral. Patients report presence of prodromal thigh and/or groin pain[12]. These atypical subtrochanteric fractures are generally either transverse or slightly oblique as opposed to typical femur fractures which are located at the femoral neck or inter-trochanteric region and are generally oblique[12]. Plain X-rays reveal an ellipsoid thickening in lateral cortex where fracture appears to occur[12] and also some cortical beaking as seen in our case.

Health care professionals need to routinely ask patients taking bisphosphonates about warning symptoms; i.e. thigh or groin pain, and if present, investigate further by looking for the radiologic changes described above[12]. Atypical subtrochanteric fractures have been reported in patients with mutations of the Cathepsin K gene as seen in pycnodysostosis[13]. Patients with atypical diaphyseal fractures could be polymorphic for factors inhibiting osteoclastic activity and long term bisphosphonate therapy may simply unmask this potential. This is speculation and needs future investigation. Further research is needed to examine candidate gene mutations for polymorphism in patients with atypical fractures.

Atypical fractures can be caused by osteoporosis itself rather than bisphosphonate therapy[9]. Although there is a high prevalence of current bisphosphonate use among patients with atypical fractures, the magnitude of the absolute risk is small[14]. With correct indication, the benefits of fracture prevention with bisphosphonate use greatly outweigh the risk of atypical femoral fracture[15]. Using age-adjusted rates, it was recently estimated that for every 100 or so reduction in typical femoral neck or intertrochanteric fractures, there was an increase of one subtrochanteric fragility fracture[15]. So we agree that the use of bisphosphonates is beneficial in patients at risk of os-

teoporotic fracture and the use of bisphosphonates in this population is highly recommended. The ability of Teriparatide to stimulate bone formation makes it an attractive option for atypical fractures related to bisphosphonate therapy given the suppression of bone turn over noted on bone biopsy[16]. Teriparatide is not indicated for more than 2 years in view of possible risk of osteosarcoma. No clear guidelines on managing patients with atypical fractures related to bisphosphonate therapy beyond 2 years of Teriparatide treatment are available so far. Two pelvic insufficiency fractures associated with severe suppression of bone turnover (SSBT) have been reported[16,17].

Our patient has taken estrogen for 7 years. Estrogen therapy may have further suppressed bone remodeling in our patient It is still questionable if such suppressed bone formation and bone resorption markers as seen in our case and others[17] indicate the expected therapeutic effect of bisphosphonates or indicate impending stress fracture from SSBT. Whether this can be prevented by intermittent use or drug holiday is not known. There are no clear guidelines for drug holiday.

In the past it was proposed that glucocorticoids and proton-pump inhibitors are likely to contribute to the risk of atypical fractures[18,19] but more recent data using registry classification, suggested that this was not the case[14]. Developing an international registry for cases of bisphosphonates-related fractures may help clarify the magnitude of the problem, and aid in identifying factors that may be associated with atypical fractures[12]. Pelvic fractures with atypical features related to bisphosphonate therapy have been reported infrequently. We add this case to the five other case reports of pelvic fractures that we are aware of[6,16-17] associated with long term bisphosphonate therapy.

References

1. Watts NB, Harris ST, Genant HK et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990;323:73-9.
2. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333:1437-43.
3. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.
4. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006;296:2927-38.
5. Burr DB. Targeted and non targeted remodeling. Bone 2002;30:2-4.
6. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005;90:1294-301.
7. Goh SK, Yang YK, Koh JS, Wong KM Chua YS, Chua TC, Howe TS. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br 2007;89:349-53.
8. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury 2008;39:224-31.
9. Bo Abrahamsen, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res 2009;24:1095-102.
10. Black DM, Kelly MP, Genant HK. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med 2010;362:1761-71.
11. Breuil V, Roux CH, Testa J, Albert C, Chassang M, Brocq O, Euller-Ziegler L. Outcome of osteoporotic pelvic fractures: An underestimated severity. Survey of 60 cases. Joint Bone Spine 2008;75:585-8.
12. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster D, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Koval K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Sen HT, van der Meulen MC, Weinstein RS, Whyte M; American Society for Bone and Mineral Research. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010;25:2267-94.
13. Yates CJ, Bartlett MJ, Ebeling PR. An atypical subtrochanteric femoral fracture from pycnodysostosis: A lesson from nature. J Bone Miner Res 2011;26:1377-9.
14. Scorhilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and Atypical fractures of the femoral shaft. N Engl J Med 2011;364:1728-37.
15. Wang Z, Bhattacharyya T. Trends in Incidence of Subtrochanteric Fractures and Bisphosphonate Use among the US Elderly, 1996-2007. J Bone Miner Res 2011;26:553-60.
16. Reina AV, Nicola N, Kathryn D et al. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tissue Int 2009;85:37-44.
17. Imai K, Yamamoto S, Anamizu Y, Horiuchi T. Pelvic insufficiency fractures associated with severe suppression of bone turnover by alendronate therapy. J Bone Miner Metab 2007;25:333-6.
18. Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. N Engl J Med 2010;362:1848-9.
19. Odvina CV, Levy S, Rao S, Zerwekh JE, Sudhaker Rao D. Unusual mid-shaft fractures during long term bisphosphonate therapy. Clin Endocrinol (Oxf) 2010;72:161-8.