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 ago1-3. 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 fractures4.

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 fragility5. 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 therapy6. Subsequently there have been numerous case reports of “atypical” fractures in patients taking alendronate7,8. The increased risk of atypical femur fractures with alendronate use could be more likely caused by osteoporosis than by alendronate therapy9.

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 therapy.

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...
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/cm² at the spine and a T-score of -0.7 with a density of 0.913 g/cm² at the hip. In 2010 the bone density at the spine was 0.948 g/cm² with a T-score of -2.0 and at the hip she had a density of 0867 g/cm² 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

<table>
<thead>
<tr>
<th>Date</th>
<th>Result</th>
<th>Female normal mean value</th>
<th>Z-Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>4/2010</td>
<td>1.050</td>
<td>0.45-4.5 μIU/mL</td>
</tr>
<tr>
<td>PTH</td>
<td>4/2010</td>
<td>24</td>
<td>15-65 pg/mL</td>
</tr>
<tr>
<td>25(OH) Vitamin D</td>
<td>4/2010</td>
<td>38.6</td>
<td>32-100 ng/mL</td>
</tr>
<tr>
<td>Serum Electrophoresis</td>
<td>5/2010</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Endomysial Antibody</td>
<td>5/2010</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>5/2010</td>
<td>2.7</td>
<td>2.7-11.5 ng/mL</td>
</tr>
<tr>
<td>Collagen Cross Links</td>
<td>5/2010</td>
<td>12.7</td>
<td>6.2-19.0 nMBCE/L</td>
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<tr>
<td>Phosphorus</td>
<td>5/2010</td>
<td>3.6</td>
<td>2.0-4.0 mg/dL</td>
</tr>
<tr>
<td>24 hours urine cortisol</td>
<td>4/2010</td>
<td>22</td>
<td>0-50 μg/24 hours</td>
</tr>
<tr>
<td>24 hours urine calcium</td>
<td>4/2010</td>
<td>320</td>
<td>100-300 mg/24 hours</td>
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Table 1. Laboratory work up of the patient.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Female normal mean value</th>
<th>Z-Scores</th>
</tr>
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<tbody>
<tr>
<td>Cancellous Bone Volume %</td>
<td>10.4</td>
<td>21.8</td>
<td>-1.751</td>
</tr>
<tr>
<td>Osteoid Volume%</td>
<td>1.478</td>
<td>1.235</td>
<td>0.352</td>
</tr>
<tr>
<td>Osteoid Width micrometers</td>
<td>11.1</td>
<td>12.3</td>
<td>-0.393</td>
</tr>
<tr>
<td>Osteoid Surface %</td>
<td>7.30</td>
<td>8.44</td>
<td>-0.092</td>
</tr>
<tr>
<td>Osteoblast-Osteoid Interface %</td>
<td>3.87</td>
<td>22.10</td>
<td>-1.544</td>
</tr>
<tr>
<td>Osteoclast Per Length mm</td>
<td>4.7</td>
<td>3.0/100</td>
<td>0.459</td>
</tr>
<tr>
<td>Eroded Surfaces %</td>
<td>0.44</td>
<td>2.29</td>
<td>-2.303</td>
</tr>
<tr>
<td>Volume Based Bone Formation Rate mm/³(mm²/year)</td>
<td>0.155</td>
<td>0.250</td>
<td>-0.582</td>
</tr>
<tr>
<td>Surface Based Bone Formation Rate mm³(mm²/year)</td>
<td>0.008</td>
<td>0.019</td>
<td>-1.049</td>
</tr>
</tbody>
</table>

Table 2. Histomorphometry of bone during bisphosphonate therapy
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. 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. 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, 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. 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. Plain X-rays reveal an ellipsoid thickening in lateral cortex where fracture appears to occur 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. Atypical subtrochanteric fractures have been reported in patients with mutations of the Cathepsin K gene as seen in pycnodysostosis. 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. Although there is a high prevalence of current bisphosphonate use among patients with atypical fractures, the magnitude of the absolute risk is small. With correct indication, the benefits of fracture prevention with bisphosphonate use greatly outweigh the risk of atypical femoral fracture. 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. So we agree that the use of bisphosphonates is beneficial in patients at risk of os-
teporotic fracture and the use of bisphosphonates in this popu-
lation is highly recommended. The ability of Teriparatide to
stimulate bone formation makes it an attractive option for atyp-
cal fractures related to bisphosphonate therapy given the sup-
pression of bone turnover noted on bone biopsy. 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 be-
Yond 2 years of Teriparatide treatment are available so far. Two
pelvic insufficiency fractures associated with severe suppres-
sion of bone turnover (SSBT) have been reported.

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
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 but more recent data using registry classification,
suggested that this was not the case. Developing an interna-
tional registry for cases of bisphosphonates-related fractures
may help clarify the magnitude of the problem, and aid in iden-
tifying factors that may be associated with atypical fractures.
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 associated with long term bisphosphonate therapy.

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