“Atypical” atypical femur fractures and use of bisphosphonates

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Summary

Background. Atypical femur fractures (AFFs) present a rare but serious condition associated with use of bisphosphonates. Underlying mechanisms and clinical risk factors remain unclear. According to the diagnostic criteria formulated by the ASBMR, a lateral localization of an AFF is required. Case history. We present a patient who developed bilateral leg pain while using an oral bisphosphonate and aromatase inhibitor in the course of adjuvant treatment for breast cancer. Initially she was diagnosed with bone metastases and received radiotherapy on the right femur. However, the bilateral periosteal reactions of the subtrochanteric femur are highly suggestive of AFFs. Our case meets all criteria for AFF except that she presented with lesions at the medial side of the femur. Therefore they could be best described as “atypical” atypical femur fractures. Discussion. Since the pathogenesis of AFFs is not fully understood, we cannot rule out that AFFs also occur in the medial femur or in other weight-bearing bones. Hence we propose that medial stress reactions belong to a spectrum of atypical fractures associated with use of antiresorptive drugs. The localization may depend on yet unknown biomechanical factors.

Conclusion. We propose that these periosteal reactions of the subtrochanteric femur are in fact AFFs with uncommon medial localization and could hence be considered “atypical” AFFs. We recommend being alert of AFFs in patients with bone pain and medial subtrochanteric lesions. More epidemiological studies are needed to investigate the occurrence of both medial and lateral AFFs and to gain more insight into its frequency and pathogenesis.

KEY WORDS: atypical femur fracture; osteoporosis; bisphosphonates; bone scintigraphy; bone radiographs.

Background

Bisphosphonates are highly effective for prevention of osteoporotic fractures and are therefore used by millions of patients worldwide for treatment of osteoporosis. A recent concern is that especially long-term use of bisphosphonates is associated with the occurrence of atypical femur fractures (AFFs) (1-4). This rare but severe condition involves a low-energetic subtrochanteric fracture, which often affects both legs and shows delayed healing (5, 6). Although AFFs occur more often in patients using bisphosphonates, no causal relationship has yet been demonstrated. Occasionally AFF have been observed in bisphosphonate-naïve individuals (4, 7). At present underlying mechanisms and specific clinical risk factors remain unclear. It has been suggested that AFFs are stress or insufficiency fractures (5, 6). Unlike classical stress fractures that are seen in athletes, it is thought that AFFs originate from the lateral cortex of the femur (8). A lateral localization of AFFs is even required to fulfill the diagnostic criteria as formulated by the American Society for Bone and Mineral Research (ASBMR) (5, 6). We report a case of what could be best described as an “atypical” AFF, since it meets the ASBMR criteria except for medial instead of lateral localization.

Case history

A 50-year-old woman of Iraqi descent was treated elsewhere for stage III ductal mamma carcinoma. She underwent mastectomy with axillary lymph node dissection in January 2008. In July 2008 she completed six regimens of adjuvant TAC-chemotherapy (docetaxel, adriamycin, cyclophosphamide). She was subsequently treated with local radiation therapy of the breast and tamoxifen. After three months she switched to anastrozol because of side effects. Given the use of this aromatase-inhibitor a DXA-scan was performed in June 2009, which showed osteoporosis (T-score lumbar spine -2.5 SD, T-score left femur neck -1.3 SD). She was prescribed calcium and vitamin D at first, followed by alendronate 70 mg weekly in April 2010. She had several clinical risk factors for osteoporosis, including inadequate calcium intake, positive family history for osteoporosis and low BMI (<17 kg/m2) during adolescence. Evaluation of her bone status is shown in Table 1.

In October 2010 she presented with pain in her left hip without any prior trauma. A previous bone scan taken in 2008 during staging of breast cancer was normal (Figure 1A). Now, a radiograph of...
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Table 1 - General characteristics and laboratory measurements.

<table>
<thead>
<tr>
<th>Clinical and laboratory findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Asian</td>
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<tr>
<td>Weight (kg)</td>
<td>61</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>151</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>26.8</td>
</tr>
<tr>
<td>25-OH-vitamin D (nmol/l)</td>
<td>49</td>
</tr>
<tr>
<td>P1NP (µg/l)</td>
<td>10</td>
</tr>
<tr>
<td>Total alkaline phosphatase (U/l)</td>
<td>44</td>
</tr>
<tr>
<td>Bone-specific alkaline phosphatase (µg/l)</td>
<td>8</td>
</tr>
<tr>
<td>Serum C-terminal telopeptide (µg/l)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

All bone markers were measured one year after the patient had received radiation therapy and eight zoledronic acid infusions.

ii Whilst on vitamin D supplementation.

The pelvis showed no abnormalities (Figure 1B), nor did CT and MRI of the pelvic area. In contrast, a new bone scintigraphy demonstrated increased uptake at the medial side of the proximal left femur (Figure 2A). Also, a focus of increased uptake in the ribs was noted. A repeated radiograph of the left femur in April 2011 was initially interpreted as normal. However, in retrospect, it showed localized cortical thickening at the site of the hotspot (Figure 2B). In February 2011 she developed pain in her right groin and upper leg as well. At this time a bone scan also displayed a hotspot at the medial side of the right proximal femur (Figure 3A). MRI revealed a signal abnormality in the right femur corresponding with the location of increased uptake. A diagnosis was made of metastatic bone disease from primary breast cancer. There were no signs of metastases to other organs on abdominal and chest CT. She received radiation therapy once on the right upper leg in May 2011 and she was further treated with i.v. zoledronic acid 4 mg monthly. A radiograph taken of the right femur in September 2011 appeared normal at first, but in hindsight it also showed discrete localized cortical thickening at the medial aspect of the femur (Figure 3B).

In January 2012 the aching in both upper legs had considerably worsened. Another bone scan was performed on which the hotspot on the right side had increased with a linear uptake (Figure 4A). On MRI the radiologist reported bilateral periosteal reactions at the same level as the hotspots on bone scintigraphy. The diagnosis of bone metastases was then called into question. First of all, it was remarkable that conventional radiographs consistently did not show any lesions that one would expect in metastatic bone disease. Furthermore, the abnormalities on bone scintigraphy, MRI and radiographs had an uncharacteristic localization for disseminated breast cancer. Moreover, tumor marker CA15-3 that was elevated pre-operatively was within normal ranges during follow-up. Hence it was proposed that the patient might have insufficiency fractures. Zoledronic acid was discontinued after eight infusions in total.

In February 2012 an incomplete oblique fracture line was observed on radiographs of the right femur without signs of consolidation (Figure 4B). After she was referred to the Bone Center of our Erasmus MC, we made the presumptive diagnosis of bilateral ‘atypical’ atypical femur fractures associated with the use of bisphosphonates. She was prescribed strontium ranelate, whereupon the pain in both legs diminished and the fracture line healed slowly over the course of 6-8 months.

Discussion

We present a patient who developed sequential bilateral leg pain while using an oral bisphosphonate and an aromatase inhibitor in the course of adjuvant treatment for breast cancer. Based on increased uptake in both femora at the medial side on a bone scan and a localized abnormality on MRI of the right femur, she was
Figure 2 A, B: A: Bone scintigraphy with a hotspot at the medial side of the left femur in November 2010. B: Radiograph of the left femur, in retrospect showing localized cortical thickening at the medial aspect of the femur (arrow) in April 2011.

Figure 3 A, B: A: Bone scintigraphy showing a new hotspot at the medial side of the right femur in March 2011. B: Radiograph of the right femur, in retrospect showing localized cortical thickening at the medial side (arrow) in September 2011.
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diagnosed with bone metastases. Subsequently she was treated with zoledronic acid and local radiation therapy on her right leg. Only several months after the hotspots were noted on the bone scans, a localized periosteal reaction became visible on plain radiographs and MRI of the femora. Apart from the medial localization, this case fulfills all of the major ASBMR criteria for an AFF: a subtrochanteric, non-comminuted, incomplete fracture, non-traumatic and with localized periosteal reaction at the fracture site (5, 6). Moreover, our patient displayed all four minor criteria: she experienced prodromal pain in the groin and thigh, radiographs showed increased generalized thickness of her femoral cortices, she had bilateral symptoms and delayed healing of the fracture. The fracture line that became visible after radiation on the right leg had a predominantly oblique orientation instead of the more classical transverse orientation. This may be explained by the effects of the previous radiotherapy. The ASBMR criteria specifically exclude pathological fractures related to primary or metastatic bone tumors. Although the existence of bone metastases was not definitively excluded by a bone biopsy, the disease course makes the existence of bone metastases highly unlikely. The small focus in the ribs remained stable on bone scans during follow-up and was therefore interpreted as degenerative disease.

The pathophysiology of AFFs is not fully understood. Because of the periosteal reaction and transverse orientation, AFFs are considered stress or insufficiency fractures. Strictly, these are two different fracture types (5, 9). Stress or "fatigue" fractures result from abnormal loading in an individual with normal bone quality. In contrast, insufficiency fractures involve poor bone quality and normal loading.

Exercise-induced stress fractures are preferentially located along the medial femur, as a result of excessive medial compression force during weight bearing (8). It is hypothesized that AFFs are the result of failure in bone with abnormal microarchitecture due to increased tensile forces on the lateral femoral side. A link between AFFs and biomechanical factors is apparent considering the often bilateral occurrence with a parallel fracture location in the contralateral femur. It has been suggested that a greater curvature of the femora or malalignment of the mechanical axes predispose patients to an AFF at the lateral side (10).

Bone quality is most likely compromised in patients with AFF, since these patients are usually prescribed bisphosphonates or denosumab. These antiresorptive drugs are indicated when bone strength is reduced. However, the use of these antiresorptives might eventually have a negative impact on bone quality by inhibiting repair mechanisms within the bone. It is known that bisphosphonates change the bone matrix composition, leading to highly mineralized collagen. This may result in a generalized suppression of bone turnover (11-14). Additionally, bisphosphonates accumulate at sites of high bone remodeling including sites of stress fractures. This could affect the intracortical repair of a developing stress fracture and ultimately lead to a complete fracture (5, 6, 11, 15).

We present a patient with unusual spontaneous periosteal reactions of both medial femora. Only recently a case was reported very similar to our patient. It illustrated a medial defect of the subtrochanteric femur without prior trauma in an 81-year-old woman with groin and thigh pain (16). This patient had used the bone resorption inhibitor denosumab. Comparably, the lesion was initially not observed on femoral radiographs. These cases raise the question whether it is correct that the definition of AFF includes only fractures originating from the lateral sides of the femoral cortex. It is conceivable that the localization where these fractures develop is dependent on femur shape or other factors related to bone geometry. Based on the current diagnostic criteria, all medially located fractures are a priori not labeled as AFFs. This approach may overlook fractures with atypical features and a medial localization. Insufficiency fractures related to bisphosphonate-induced suppression of bone turnover have also been reported at sites other

![Figure 4 A, B. A: Bone scintigraphy showing increased linear uptake in the right femur in January 2012. B: Radiograph of the right femur showing an incomplete fracture line originating from localized cortical thickening at the medial side (arrows) in February 2012.](image)
than the femoral diaphysis, including the pelvis, ankle, metatarsals and long bones such as the humerus, fibula and tibia (17, 18). Recently, was described a case of a patient on long-term bisphosphonate therapy who presented with a diaphyseal tibial insufficiency fracture. Again, this case fulfills all the major criteria except for the location. The Authors discussed the need for greater awareness of the possibility of atypical fractures at other sites than the femur, especially in weight-bearing bones (18). Likewise we suggest that one should be aware that also fractures on the medial side of the femur may be considered atypical fractures associated with bisphosphonate use. If not recognized as such, a misdiagnosis like catastrophic bone disease in our patient can be a problematic result. Based on our case and the case on a medial fracture after denosumab use, we suggest that more attention should be given to the potential presence of AFFs arising from the medial cortex as well as from the lateral cortex, both in clinical practice and in research. If more of such cases are identified, this may lead in the future to a modification of criteria for AFF as developed by the ASBMR task force. We propose that both medial and lateral fractures may result from suppression of bone turnover in patients with already compromised bone strength with the exact fracture localization depending on local biomechanical or other, yet unidentified, factors.

Conclusion

We report a bilateral periosteal reaction of the subtrochanteric femur in our patient treated with bisphosphonates and an aromatase inhibitor suggestive of AFFs, though not meeting the current diagnostic criteria because of its medial localization. We propose that these fractures are in fact AFFs with an uncommon medial localization and could hence be considered “atypical” AFFs. Although a causal association has not been demonstrated in our patient nor of AFF in general, we cannot rule out that medial stress reactions belong to a spectrum of atypical fractures that are associated with treatment with antiresorptive drugs. The localization may depend on yet unknown biomechanical factors. We recommend being alert of AFFs in patients with bone pain and medial subtrochanteric lesions. More epidemiological studies are needed to investigate the occurrence of both medial and lateral AFFs and to gain more insight into its frequency and pathogenesis.

Declaration of interest

There is no potential conflict of interest.

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References