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Case Report

Atypical Insufficiency Fractures Associated with Long-Term Bisphosphonate Therapy: 3 Case Reports

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Abstract

Atypical femoral fractures as defined by the American Society for Bone and Mineral Research (ASBMR) are linked with long-term bisphosphonate therapy. We report the cases of 3 patients treated with bisphosphonates, and presenting non femoral atypical fracture. Our first patient presented with a series of fractures after being treated with risedronate: the left tibia, bilateral tibial plateau successively, the left femoral and tibial metaphysis, the right tibia and calcaneus, the left talus, and the left talar dome. The second patient had been taking alendronate and presented with a spontaneous fracture of the spine of the left scapula. The third patient had been treated with alendronate and presented with a fracture of the upper right tibial diaphysis with an unusual oblique orientation. These fractures could be suggestive of bisphosphonate therapy failure or stress fractures. However, the number of fractures in our first case, the fracture site in the second and the fracture line orientation in the third brings to mind the hypothesis of atypical non femoral fractures associated with bisphosphonate therapy. We therefore suggest the possibility of a new type of atypical fracture in patients treated with bisphosphonates, and whose causal relationship with bisphosphonates is even more difficult to demonstrate.

Keywords: Bisphosphonates; Atypical fractures; Non femoral; Stress fractures; Insufficiency fracture

Introduction

Atypical femoral fractures (AFF) in patients receiving bisphosphonate therapy were first described in 2005 by Odvina [1]. According to the American Society for Bone and Mineral Research (ASBMR), AFF can be located anywhere along the femur from just distal to the lesser

trochanter to just proximal to the supracondylar flare and present at least 4 of 5 major criteria to be confirmed. Minor criteria are given for information but are not required for the diagnosis [2]. Although it is now clear that they occur in patients receiving bisphosphonate (BP) therapy, the causal relationship remains difficult to prove.

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We report the cases of three patients who presented with unexplained spontaneous fractures during oral BP therapy.

Case Reports

Our first patient was a 58 year-old post-menopausal woman with a history of rheumatoid arthritis. X-rays taken in January 2007 to investigate mechanical left medial sub-malleolus pain were normal. The MRI evidenced a distal metaphyseal-epiphyseal fracture of the left tibia. The only abnormal result in the laboratory test workup was vitamin D deficiency (14.2 µg/L), with secondary hyperparathyroidism (PTH at 83 ng/l). Her corrected calcium level was 9.84 mg/dL. Her condition improved after non-weight bearing. At the time, her treatment consisted of methotrexate, prednisone 7.5 mg, hydroxychloroquine and risedronate. Risedronate had been initiated 5 years before because of a T-score of -2.4 SD (standard deviation) at the lumbar spine and -1.9 SD at the femoral neck on corticosteroid treatment. A new bone density scan (BDS) showed inchange BMD values. In June 2010, she reported right knee pain after jumping. The laboratory test workup was normal with the exception of vitamin D deficiency (18.7 µg/l) and the synovial fluid was non-inflammatory. Corrected calcium level was still normal at 9.88 mg/dL. The bone scintigraphy was suggestive of a subchondral fracture of the right medial tibial plateau, confirmed by MRI.

Risedronate was discontinued. In January 2011, she started with strontium ranelate treatment, which was discontinued in August 2011 at her request.

This patient went on to present with more fractures diagnosed from her standard x-rays, bone scans or MRI scans, including a subchondral fracture of the left medial tibial plateau in February 2011, left distal metaphyseal femoral and proximal metaphyseal tibial fractures in November 2011 (Figure 1) and fractures of the calcaneus and right lower extremity of the tibia, and of the left talus in April 2012. BMD increased by 0.4 SD at the spine and non-significantly decreased by 0.2 SD at total hip compared to the results obtained in 2007.

She was then prescribed teriparatide. Her vitamin D deficiency (17.6 µg/L) was supplemented. After 17 months of treatment with teriparatide, she reported progressive onset of mechanical pain in the left ankle generated by a subchondral fracture of the left talar dome, diagnosed from the MRI images (Figure 2).

The second patient was a 79 year-old post-menopausal woman with unclassified inflammatory rheumatism since the age of 58. She was admitted



Figure 1: Coronal STIR on the left and T1-weighted MR images on the right show fracture lines of the distal metaphysis of the femur (arrow) and proximal metaphysis of the tibia (arrow) associated with marrow edema.

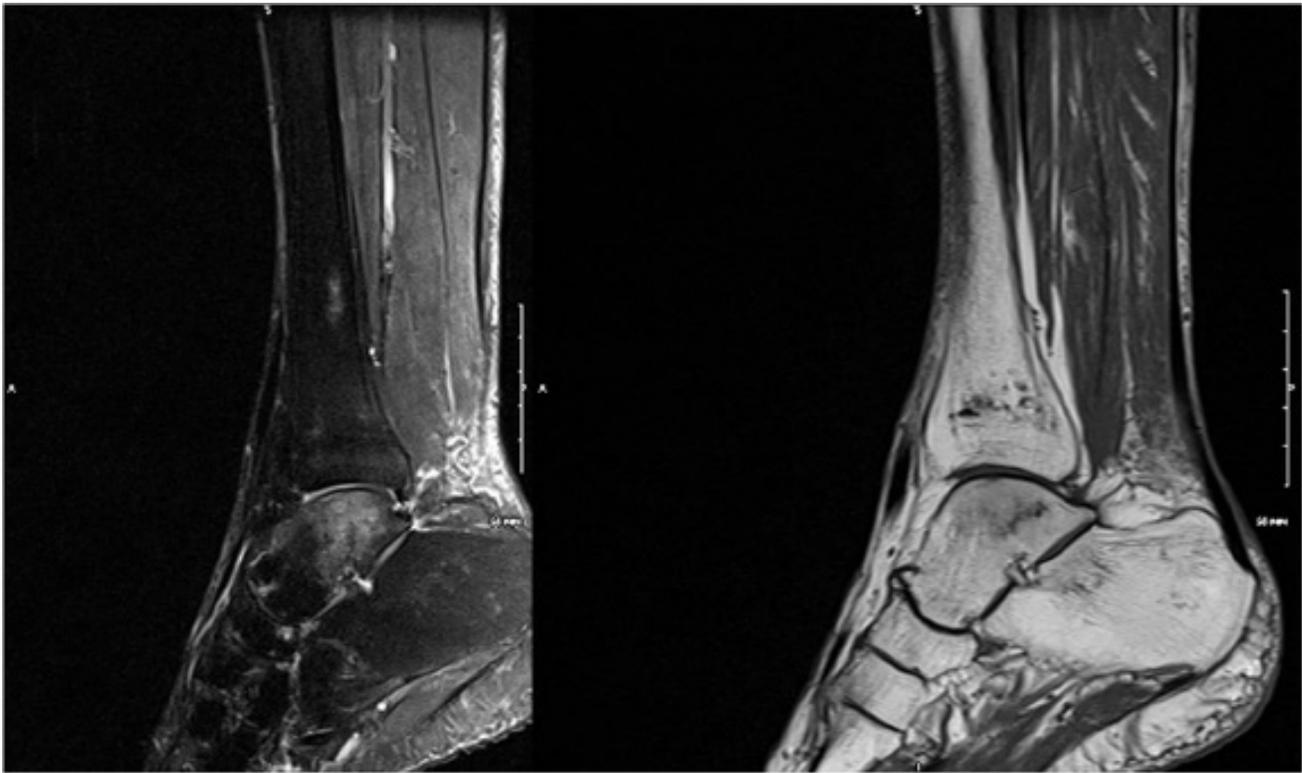


Figure 2: Sagittal T2 Fat Sat (on the left) and T1-weighted MR images of the left ankle show fracture line (arrows) of the talus

to hospital in December 2012 after experiencing unexplained left shoulder pain for the previous 10 days. Her treatment consisted of prednisone 6.5 mg, colchicine, vitamin D and alendronate. Palpation of the spine of the left scapula elicited pain. Standard x-rays showed a fracture of the spine of the left scapula (Figure 3). On the bone scintigraphy, high levels of the tracer were observed in the left scapula and the joints with synovitis. A CT scan confirmed the fracture of the spine of the left scapula without signs of malignancy (Figure 4). The BMD values obtained 7 months previously were impossible to interpret for the spine, and showed T-scores of -2.5 SD at the femoral neck and -1.8 SD at the total hip. The workup (complete blood count, vitamin D, alkaline phosphatases and serum protein electrophoresis) was normal. Corrected calcium level was 9.52 mg/dL. CRP was 38.3 mg/L. The patient had been taking alendronate for more than 6 years that was discontinued after the fracture occurs.

The third patient was a 78 year-old post-menopausal woman with a history of hypertension and chronic obstructive bronchopulmonary disease, left tibial

osteotomy and osteoporosis treated with alendronate for the past 5 years, with a T7 vertebral fracture occurring 2 years after its initiation. She reported sudden onset pain arising in the medial side of the right knee after getting off a bus. The clinical examination found bilateral genu valgum and pain on palpation of the right medial tibial plateau. The standard x-rays revealed a non-displaced, 45° oblique fracture of the upper third of the right tibial diaphysis (Figure 5), confirmed by a bone scintigraphy and an MRI (Figure 6). The workup was normal with the exception of a CRP at 15.9 mg/L, albuminuria at 0.19 g/24 hrs and hypogammaglobulinemia of 5.4 g/L. The serum immunofixation test showed non-significant levels of monoclonal IgG lambda and urine immunofixation evidenced a lambda light chain anomaly without criteria of myeloma. Vitamin D levels and corrected calcium level (9.28 mg/L) were normal. Standard x-rays of the spine did not show any new fracture. The spine BDS was impossible to interpret because of osteoarthritis but the T-scores were -1.6 SD at the femoral neck and $+0.4$ SD for the total hip. Alendronate was discontinued and the control x-ray two months later evidenced signs of fracture consolidation



Figure 3: Standard x-rays of the left shoulder show a fracture (arrow) of the spine of the left scapula.

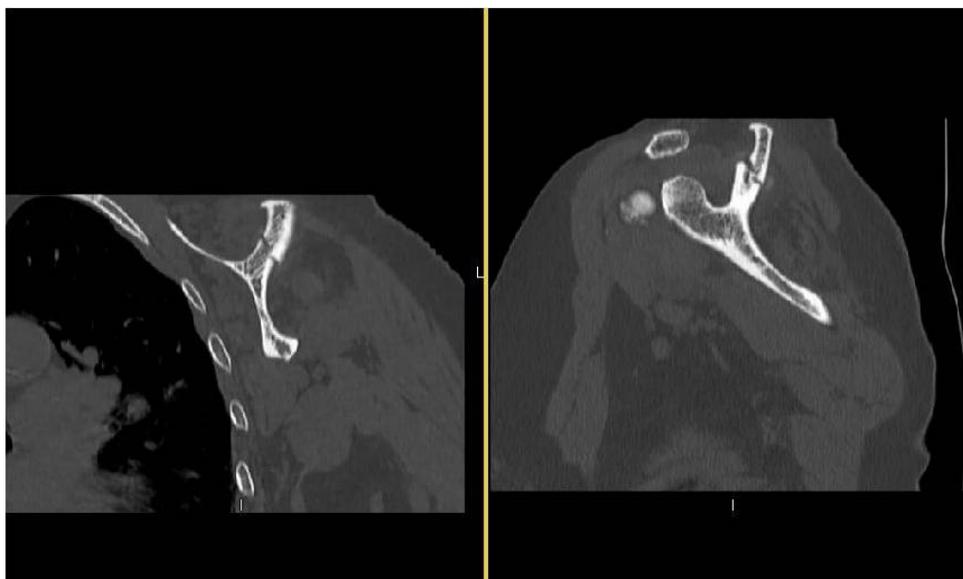


Figure 4: CT scan shows a fracture (arrow) of the spine of the left scapula.

after simple offloading.

Discussion

Each of these three cases has atypical features: the number of fractures in the first, the site of the fracture without any traumatic factor in the second, and the orientation of the fracture line in the third.

In addition to the “classic” atypical fractures as defined in the ASBMR criteria, “even more atypical” atypical

fractures have recently been described in the literature. It is generally the location of these fractures that is their most unusual characteristic and we will thus refer to them as “atypical non-femoral fractures” (ANFF). ANFF include fractures of the ulna [3], tibia [4], vertebral pedicles [5] and pelvis [6], but also osteolytic lesions resulting in failure of endosseous dental implants [7]. No specific cause is found for these fractures which, when located in the leg as was the case for our third patient, resemble certain stress fractures caused by static disorders [8]. These stress fractures are



Figure 5: Standard x Rays of the right knee and tibia: oblique fracture (arrow) of the upper third of the diaphysis of the right tibia.

somewhat more difficult to explain when they occur in non-weight bearing zones such as the arms. Non-traumatic fractures of the scapula are indeed a rare entity; most of the cases reported concern patients taking long-term corticosteroid therapy, as was the case here, and who are also osteoporotic and on BP therapy; in these cases, the fracture is combined with rotator cuff tendinopathy [9]. Another case concerned an osteopenic patient with Cushing's disease who presented with multiple fractures [10]; and finally, two cases concerned scapula fatigue fractures [11,12].

The causal link between these ANFF and BP therapy is even more difficult to establish than for AFF. Concomitant treatments such as corticosteroids and comorbidities, for instance inflammatory rheumatism, may play a role, since rheumatoid arthritis is a known risk factor for stress fractures [13]. It may also be the combination of all three parameters that is responsible [9]. A diagnosis of simple stress fractures is also possible, particularly in the case of our first and third patient. Thus, could the fractures we observed in our first and third patients actually be simple fatigue fractures, related to possible undocumented static disorders

of the legs in the former or genu valgum in the latter [14]. The fracture line was nonetheless highly unusual in our third case, since most tibial stress fractures run in a transverse direction and longitudinal lines are rarer. This is what led us to suspect the role of BP. In the case of our first patient whose vitamin D deficiency had been poorly corrected, these fractures could also be the result of treatment failure. Vitamin D deficiency is considered to be a cause of BP therapy failure [15]. However, the recurrent nature of the fractures in this patient is unsettling, hence the suggestion of the role of bisphosphonates. As the fractures recurred numerous years after BP therapy had been withdrawn and in spite of treatment with teriparatide, this hypothesis appears much less plausible. It has been suggested that one such cause in this patient could be methotrexate which is known to cause osteopathy at high doses [16]. Nonetheless, stress fractures, particularly of the tibial plateau [17] but also of the femur and ulna [18], have recently been described in patients treated for inflammatory rheumatism. However, the deleterious impact of methotrexate on bone density and metabolism is controversial [19]. Methotrexate is believed to have a dose-dependent impact on bone mineral density that is



Figure 6: Sagittal T1-weighted MR images showing fracture line associated with edema of the upper third of the diaphysis of the right tibia.

reversible after treatment is discontinued [20].

Finally, our first patient presented with metaphyseal or epiphyseal fractures, i.e. mainly in cancellous bone, which is also the case for the scapula, whereas AFF occur in cortical bone [2].

Key Messages

It is possible that we are describing a new entity, ANFF associated with bisphosphonate therapy. However, this suggestion is based purely on isolated clinical cases which could also be interpreted as stress fractures. These fractures form a heterogeneous group and the role played by bisphosphonates appears even more difficult to demonstrate. A first and crucial step might be to attempt to collect these suspect cases as exhaustively as possible.

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