

## Clinical Quiz

# Atypical fractures of the femur and ulna and complications of fracture healing in a 76-years-old woman with Sjögren's syndrome

K.D. Stathopoulos<sup>1</sup>, C. Kosmidis<sup>2</sup>, G.P. Lyritis<sup>3</sup>

<sup>1</sup>Bone Metabolic Unit, First Orthopaedic Department, University of Athens, "Attikon" University General Hospital, Greece; <sup>2</sup>IKA, Athens, Greece; <sup>3</sup>Post-graduate Course on Metabolic Bone Disease, University of Athens, Greece

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## Case

A 76-years-old Caucasian woman was referred for consultation due to spontaneous fractures of the femur and ulna and complications of fracture healing following surgical treatment of the femur. The patient had a medical history of Sjögren's Syndrome under low doses of methotrexate (7.5-10 mg *per os* weekly) since 1992, and hypertension. She had osteoporosis since 2001, and had been treated with 6 annual doses of iv zoledronic acid 4 mg until 2006, followed by teriparatide 20mg s.c. daily for 24 months (2007 until June 2009), and an additional iv infusion of zoledronic acid 5 mg on June 2009. The patient reported acute onset of spontaneous pain at the lower outer third of the right thigh on May 2006. At that time, plain radiographs of the right femur revealed thickening of the lateral cortex at the supracondylar area with a periosteal stress reaction, while bone-scanning with Tc 99m was suggestive of a supracondylar stress fracture (Figure 1A). Seven months later (December 2006), while walking, the patient sustained an oblique, complete, displaced fracture of the right femur at the same area where the stress fracture had previously occurred. She was then treated surgically with open reduction and internal fixation (90° angulated plate and sliding screw), but 21 months later there was no radiological sign of fracture healing, and pseudarthrosis was diagnosed (September 2008) (Figure 1B). One year later (October 2009), and while the fracture had still not healed, the patient sustained a new fracture at the supracondylar area of the right femur

at the upper limit of the plate fixation and was operated again, this time with intramedullary nailing. Signs of fracture healing appeared 2 months later (December 2009) and the fracture healed on October 2010 (Figure 1C). However, on June 2010, the patient suffered a new spontaneous displaced fracture of the right ulna, that was treated with open reduction and internal fixation and which healed 4 months later (Figure 1D). It is of note that, at that time (June 2010), the patient presented with laboratory tests with evidence of secondary hyperparathyroidism due to deficiency of 25 (OH) vitamin D3. The patient was treated with high doses of vitamin D (cholecalciferol, 2000 IU per day) from June 2010 to October 2010, when fracture healing of both the femur and ulna was confirmed radiologically. Table 1 illustrates times of fractures as well as complications of healing, in association with medication, bone mineral density testing (DXA) and all laboratory tests available.

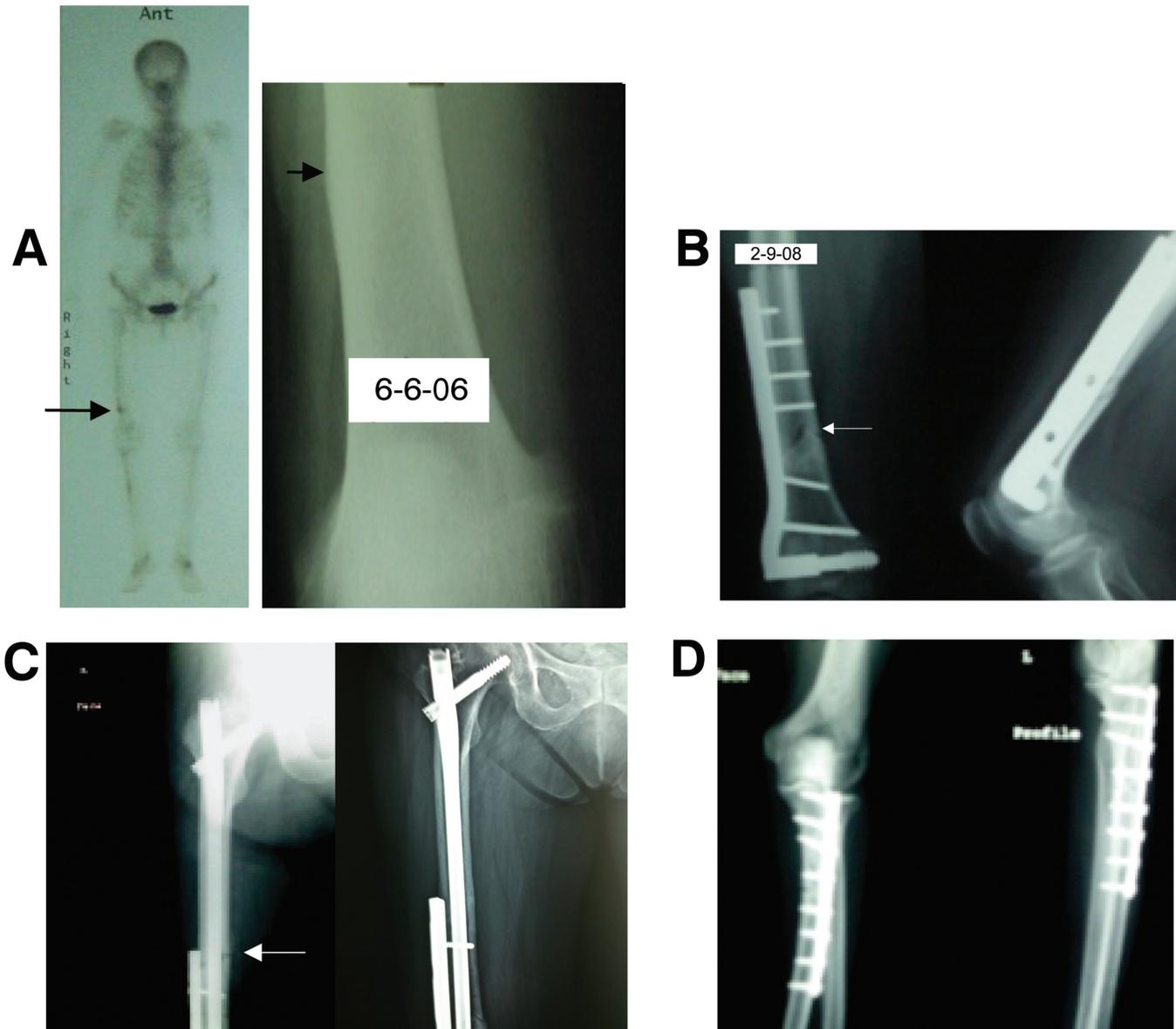
## Commentary

Long-term treatment with bisphosphonates has been recently associated with "atypical" subtrochanteric and diaphyseal femoral fractures. According to the ASBMR Task Force Report on atypical femoral fractures<sup>1</sup>, these fractures may occur anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal femoral metaphysis. The fracture usually occurs as a result of no or minimal trauma, may be complete (transverse or short oblique) or incomplete, and is usually associated with thickening of the lateral cortex at the fracture site or even generalized thickening of both cortices bilaterally. Atypical fractures may be bilateral; there are often prodromal symptoms such as pain in the groin or thigh, and healing of the fractures may be delayed<sup>1</sup>. Atypical fractures may be associated with a variety of comorbid conditions such as rheumatoid arthritis and diabetes mellitus and the use of pharmaceutical agents (glucocorticoids, proton pump inhibitors). The diagnosis of atypical fractures

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Corresponding author: Konstantinos D. Stathopoulos, MD, Xylouri 28-30, Athens 14123, Greece  
E-mail: kossta51@hotmail.com

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**Figure 1. A:** Stress fracture of the right femur as shown with bone-scanning (left picture) and plain radiograph (right picture). **B:** Pseudarthrosis of the complete fracture of the right femur 21 months after surgical treatment. **C:** New Fracture of the right femur on the upper limit of the fixation plate, treated with intramedullary nailing, and pseudarthrosis 12 months later. **D:** Ulna Fracture treated with open reduction and internal fixation.

specifically excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with local primary or metastatic bone tumors, and periprosthetic fractures. Interestingly, atypical fractures of the femur in patients with Sjögren's syndrome receiving treatment with bisphosphonates (alendronate) have been described before only in one occasion<sup>2</sup>. Moreover, from a total of 310 cases reviewed in the Task Force Report, 160 fractures occurred after alendronate monotherapy, 4 with a combination of intravenous pamidronate followed by intravenous zoledronic acid (myeloma) and only 2 following intravenous zoledronic acid (renal cell carcinoma and osteoporosis). Re-

cently, Black et al<sup>3</sup> reported a secondary analysis of three large randomized clinical trials of bisphosphonates, two of oral alendronate (FIT and FLEX) and one of zoledronic acid (HORIZON PIVOTAL FRACTURE TRIAL). In the HORIZON trial twelve subtrochanteric/diaphyseal fractures were found in 10 subjects, 3 of whom had not received bisphosphonates (relative hazard ratio of zoledronic acid versus placebo 1.5)<sup>3</sup>. Possible pathogenetic mechanisms associated with atypical femoral fractures include alterations to the normal pattern of collagen cross-linking, microdamage accumulation, increased mineralization, reduced heterogeneity of mineralization, variations in rates of bone turnover, and reduced vascularity and antiangiogenic-

DATE	EVENT	PROCEDURE	MEDICATION	DXA L1-L4 (Hologic)	LABO
2001-5/2006	-	-	-MTX 7.5-10 mg -ZOL 4 mg iv Annually -Ca 500 mg	2001: 0.637 (-3.72)	-
5/2006	Stress fx Femur (R)	- Bed rest (4 w) - Partial weight bearing (4w)	-MTX 7.5-10 mg -Ca 500 mg	0.694 - (-3.21)	
12/2006	Displaced fx Femur (R)	- Open reduction & internal fixation (90° angulated plate and sliding screw)	- MTX 7.5-10 mg -Ca 500 mg	-	-
6/2007	Delayed union Femur (R)	- Partial weight bearing	- MTX 7.5-10 mg - Teriparatide 20 mg sc daily - Ca 500 mg	-	-
9/2008	Non-union Femur (R)	- Partial weight bearing	- MTX 7.5-10 mg -Teriparatide 20 mg sc daily until 6/2009	0.798 (-2.26)	-
10/2009	New fx Femur (R)	- Intramedullary nailing (g-nail)	- MTX 7.5-10 mg - ZOL 5 mg (6/2009) - Ca 500 mg	0.820 (-2.06)	Ca = 9.9 P = 3.3 PTH = 44
6/2010	Ulna fx	- Open reduction & internal fixation	- MTX 7.5-10 mg - Ca + vit D (500 mg+400IU)	-2.0 (Lunar)	Ca = 10.2 P= 3.3 PTH= 80↑ 25(OH) vit D3= 4.0↓↓
10/2010	Porosis Femur (R)	- Full weight bearing	MTX 7.5-10 mg -vit D 2000 IU per day + Ca	-	PTH= 44.2 25 (OH) vit D= 14.7

**Table 1.** Chronological order of events, procedures, medication and available tests.

genic effects<sup>1</sup>. According to the ASBMR Task Force, in cases of atypical femoral fractures, teriparatide should be considered in patients who suffer such fractures, particularly if there is little evidence of healing by 4 to 6 weeks after surgical intervention<sup>1</sup>.

The concomitant use of methotrexate could also be of importance in the case of our patient. Methotrexate (MTX), an antimetabolite, is a folic acid antagonist which competitively inhibits the reduction of tetrahydrofolate by dihydrofolate reductase, thus inhibiting the synthesis of DNA and RNA. MTX is commonly used at high doses (100-1000 mg/m<sup>2</sup>) in the treatment of lymphoma, lymphoblastic leukemia, and osteosarcoma. In autoimmune diseases, MTX is used at low doses (up to 30 mg once weekly) given orally or by intramuscular or subcutaneous injections. The use of high-dose MTX has been associated with osteopathy, characterized by severe bone pain, localized osteoporosis, and spontaneous insufficiency fractures of the lower extremities (mainly distal tibia). MTX osteopathy was first described in children with leukemia who were treated with high doses of MTX<sup>4</sup>. However, reported cases of low dose MTX osteopathy are exceed-

ingly rare compared with the number of patients treated with MTX (no more than ten reported cases in adults)<sup>4</sup>.

Although data for the *in vitro* effect of MTX on osteoblasts are conflicting, there is growing evidence to refute the fact that MTX has clinically significant effects on bone mineral density (BMD) or bone turnover<sup>4</sup>. Nevertheless, in a recently published systematic review of case/case series studies of atypical femoral fractures associated with bisphosphonate therapy, 3.2% of patients with concomitant use of methotrexate were reported to suffer such fractures<sup>5</sup>.

Finally, delayed union or pseudarthrosis of surgically treated fractures of either typical or atypical nature is believed to be multifactorial. Well known factors influencing fracture healing include among others age, type of fracture, osteoporosis, method of treatment including fracture reduction, adequate immobilisation and/or surgical technique, nutrition, comorbidities such as systematic or autoimmune diseases and infection.

In conclusion, spontaneous atypical fractures of the femur and ulna in this patient, as well as complications of fracture

healing, could be attributed to long-term concomitant treatment with bisphosphonates (zoledronic acid) and methotrexate. It is probable that other factors, including old age, osteoporosis, autoimmune disease as well as secondary hyperparathyroidism due to vitamin D deficiency, also contributed to the clinical presentation of delayed healing and pseudoarthrosis.

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## Questions

### 1. Atypical femoral fractures:

- A. Occur above the lesser trochanter
- B. May be complete or incomplete, often have prodromal symptoms and are associated with local or bilateral thickening of the cortex
- C. Occur in most osteoporotic patients receiving bisphosphonate therapy

#### *Critique*

Atypical femoral fractures occur anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal femoral metaphysis. Atypical subtrochanteric/femoral fracture in bisphosphonate users is an extremely rare event compared to the number of patients receiving bisphosphonate therapy for osteoporosis, and such fractures have also been described in non-bisphosphonate users. The possible etiopathogenesis has not yet been established.

The correct answer is B.

### 2. Methotrexate:

- A. Inhibits osteoclastogenesis
- B. Has been associated with spontaneous insufficiency fractures of the lower extremities in very few patients.
- C. Has deleterious effects on bone remodeling and bone mineral density.

#### *Critique*

Methotrexate *in vitro* has been shown by some authors to affect osteoblasts, although the proliferation and further maturation of cells of the osteoblastic lineage is shown by other authors not to be affected. There is growing evidence that MTX has clinically no significant effects on bone mineral density (BMD) or bone turnover.

The correct answer is B.