LESSON OF THE MONTH

Stress fracture in long term methotrexate treatment for psoriatic arthritis

M Wijnands, A Burgers

Case history

A 42 year old woman presented at the outpatient rheumatology department with severe, incapacitating pain of her left leg. There was no previous trauma. The patient did not recall fever or malaise.

Psoriasis had been diagnosed at age 17 years. Initially, topical drugs were prescribed. Periodically etretinate, a synthetic analogue of retinoid acid, and photochemotherapy were prescribed as additional treatment. The patient did not receive cyclosporin. Oligoarthritis of her knees and ankles first appeared at an age of 25 years. Management with non-steroidal anti-inflammatory drugs and sporadically an intra-articular injection of corticosteroids was adequate to control the symptoms. At age 37 a severe polyarthritis of elbows, wrists, finger joints, ankles, and metatarsophalangeal joints developed. Treatment with methotrexate (MTX) was started at an initial dose of 7.5 mg weekly, resulting in a good clinical response. Two years later the dosage was gradually increased to 20 mg weekly because of a flare.

On examination there was little pretibial oedema with tenderness of the distal tibia, especially at the lateral margin. There was an active arthritis of the left knee, wrists, metacarpophalangeal and proximal interphalangeal joints. A cardiorespiratory examination was

unremarkable and the patient was afebrile. Laboratory investigations showed a slight increase in erythrocyte sedimentation rate of 20 mm/1st h. Full blood count, renal and hepatic function, creatine kinase, calcium, serum protein electrophoresis, thyroid stimulating hormone, parathyroid hormone, and vitamin D were all normal. Urine analysis was negative.

Standard anteroposterior and lateral x ray pictures showed no abnormalities on either tibia or fibula. Technetium-99m (^{99m}Tc) scintigraphy disclosed a longitudinal hot spot in the middle third of the tibia on the left (fig 1). Computed tomography showed a clear longitudinal fissure with minimal displacement and starting callus formation (fig 2). Bone mineral density (BMD) measured by dual x ray absorptiometry of the lumbar spine and femoral neck showed no manifest osteoporosis.

Treatment was started with a Sarmiento brace. As an MTX related stress fracture was considered, the MTX dosage was tapered to 7.5 mg weekly and within weeks the symptoms of the left tibia evanesced. Unfortunately, the arthritis symptoms flared and an intramuscular injection of a depot corticosteroid was given. A few months later pain on weight bearing emerged in the right foot. Repeated bone scintigraphy showed a normal left tibia, but new lesions in the right midfoot and the fifth rib at the right. An x ray examination showed a fracture of the 2nd and 3rd metatarsal bone and of

Department of
Rheumatology,
TweeSteden
ziekenhuis, Tilburg,
The Netherlands
M Wijnands

Department of
Orthopaedic Surgery,
TweeSteden ziekenhuis
A Burgers

Correspondence to:
Dr M Wijnands, Department
of Rheumatology,
TweeSteden ziekenhuis, PO
Box 90107, 5000 LA
Tilburg, The Netherlands
mwijnands@tsz.nl

Accepted 27 February 2001

Figure 1 Technetium-99m scintigram (anterior view, delayed image) of the legs. Longitudinal hot spot in the middle third of the tibia.

Figure 2 Computed tomography of the left tibia. Fissure with minimal displacement and starting callus formation.

the rib mentioned. MTX was stopped. Thereafter the pain of the right foot diminished very slowly. Again an increase of the arthritis was noticed, and azathioprine was prescribed. This drug had to be discontinued after a few days owing to severe gastrointestinal complaints. Subsequently, hydroxychloroquine was prescribed, which was stopped because of an itchy dermatitis. Then, a rechallenge with a low dose MTX (7.5 mg weekly) was performed. After a follow up period of four months, no recurrence of a stress fracture has been noticed. The arthritis activity is regarded as modest, but acceptable for the patient.

Discussion

Stress fractures are a well recognised complication in arthritic patients.¹⁻⁶ Osteopenia (juxta-articular or generalised, or both) caused by extensive rheumatoid involvement, corticosteroid treatment, or relative immobility is a predisposing factor. Furthermore, deformations, flexion contractures (especially valgus deformities of knees and subtalar joints) and increased mobility after arthroplasties leading to increased stress on juxta-articular bone also contribute to this condition. Stress fractures in rheumatoid arthritis (RA) preferentially affect the long bones of the legs, the neck of the femur, and the pelvis.

Osteoporotic fractures associated with MTX treatment were reported for the first time in 1970 in children treated for acute leukaemia with a high dosage.⁷ This "methotrexate osteopathy" was characterised by osteoporosis, bone pain, and compression fractures, mostly occurring in the distal tibiae. When the drug was stopped the pain regressed and the fracture healed. To our knowledge Ansell *et al* for the first time drew attention to the occurrence of stress fractures as a possible complication of MTX treatment for non-neoplastic diseases.⁸ Since then several case reports including patients treated for psoriasis and rheumatic diseases have been published.⁹⁻¹⁵

During MTX treatment high concentrations of the drug have been found in the synovial membrane and in cortical and trabecular bone.¹⁶ In children treated with MTX increased urinary and faecal excretion of calcium have been reported, suggesting an increase in bone resorption.¹⁷ In vitro studies showed a strongly inhibitory effect of MTX on human osteoblast proliferation but not differentiation.¹⁸

Animal studies showed a significant reduction in bone formation caused by MTX.^{19,20} However, in rats with adjuvant induced arthritis a three week low dose methotrexate treatment resulted in a significant increase of periarticular BMD in the femur. In control rats BMD was unchanged by this short term, low dose MTX treatment.²¹ An animal study using bone cement containing MTX reported no significant differences of the microradiographic bone structure.²² In humans treated for osteosarcoma a dose dependent effect of MTX on BMD of the trabecular distal point of the radius has been reported and has been attributed to the inhibition of osteogenesis.²³ In this study no significant reduction of BMD at

the mid-point of the radius was found. In patients with RA low dose MTX treatment did not seem to affect the BMD.²⁴⁻²⁶ However, patients treated additionally with prednisone showed a greater loss of BMD in the lumbar spine than patients treated with a similar dose of corticosteroids without MTX.²⁷ Dequeker *et al* reported a retrospective study in which a cumulative, dose dependent, cortical bone loss at the radius in patients with RA treated with low dose methotrexate was found.²⁸ These conflicting reported data about the effects of MTX on bone may be explained by differences in dosage, duration of treatment and/or follow up, co-medication (corticosteroids), underlying disease, and site of assessing BMD. Furthermore, a deteriorating effect of MTX on bone architecture may not be represented by a decrease in BMD.

The publications reviewed suggest, but not beyond doubt, that methotrexate may enhance osteoporosis. Especially in patients with inflammatory rheumatic diseases, already prone to osteoporosis, MTX might induce stress fractures. The clinical picture of pain, aggravated by weight, in the leg should lead to a consideration of stress fractures. If plain radiology does not provide a diagnosis an adequate diagnostic procedure should be performed. Although ^{99m}Tc bone scintigraphy is sensitive for bone disorders which correlate with increased osteoblast activity, the procedure is not specific. Both magnetic resonance imaging and computed tomography (in later stages of the disease) can provide a definite diagnosis.

Lessons

- In arthritic patients stress fractures must be considered when there is pain in the foot, aggravated by weight.
- In arthritic patients symptoms caused by stress fractures, especially of the distal tibia, should be discriminated from active synovitis.
- In case of a stress fracture a conventional x ray examination may be normal.
- If stress fracture of a long bone is suspected but not shown by plain radiology, either magnetic resonance imaging or bone scintigraphy is recommended, depending on the medical community.
- MTX may be an additive risk factor for stress fractures in arthritic patients, who are already "at risk" for (local or generalised) osteoporosis.

- 1 Baer GJ. Fractures in chronic arthritis. *Ann Rheum Dis* 1940;2:269-73.
- 2 Schneider R, Kaye JJ. Insufficiency and stress fractures of the long bones occurring in patients with rheumatoid arthritis. *Radiology* 1975;116:595-9.
- 3 Young A, Kinsella P, Boland P. Stress fractures of the lower limb in patients with rheumatoid arthritis. *J Bone Joint Surg Br* 1981;63:239-43.
- 4 Fam AG, Shuckett R, McGillivray DC, Little AH. Stress fractures in rheumatoid arthritis. *J Rheumatol* 1983;10:722-6.
- 5 Hooyman JR, Melton LJ III, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. *Arthritis Rheum* 1991;34:912-15.
- 6 Alonso-Bartolomé P, Martínez-Taboada VM, Blanco R, Rodríguez-Valverde V. Insufficiency fractures of the tibia and fibula. *Semin Arthritis Rheum* 1999;28:413-20.
- 7 Ragab AH, Frech RS, Vietti TJ. Osteoporotic fractures secondary to methotrexate therapy of acute leukemia in remission. *Cancer* 1970;25:580-5.

- 8 Ansell G, Evans S, Jackson CT, Lewis-Jones S. Cytotoxic drugs for non-neoplastic disease. *BMJ* 1983;287:762.
- 9 Semba CP, Mitchell MJ, Sartoris DJ, Resnick D. Multiple stress fractures in the hindfoot in rheumatoid arthritis. *J Rheumatol* 1989;16:671-6.
- 10 Preston SJ, Diamond T, Scott A, Laurent MR. Methotrexate osteopathy in rheumatic disease. *Ann Rheum Dis* 1993;52:582-5.
- 11 Schapira D, Scharf Y. Insufficiency fracture of the distal tibia mimicking arthritis in a rheumatoid arthritis patient. The possible role of methotrexate treatment. *Clin Exp Rheumatol* 1995;13:130-1.
- 12 Bologna C, Sany J, Jorgensen C. Possible role of methotrexate in the distal tibia fractures in a patient with rheumatoid arthritis. *Clin Exp Rheumatol* 1996;14:343-4.
- 13 Zonneveld IM, Bakker WK, Dijkstra PF, Bos JD, Soesbergen RM van, Dinant HJ. Methotrexate osteopathy in long-term low-dose methotrexate treatment for psoriasis and rheumatoid arthritis. *Arch Dermatol* 1996;132:184-7.
- 14 Maenaut K, Westhovens R, Dequeker J. Methotrexate osteopathy, does it exist? *J Rheumatol* 1996;23:2156-9.
- 15 Singwe M, Le Gars L, Karneff A, Prier A, Kaplan G. Multiple stress fractures in a scleroderma patient on methotrexate therapy. *Rev Rhum Engl Ed* 1998;65:508-10.
- 16 Bologna C, Edno L, Anaya JM, Canovas F, Berghe M van den, Jorgensen C, *et al.* Methotrexate concentration in synovial membrane and trabecular and cortical bone in rheumatoid arthritis patients. *Arthritis Rheum* 1994;37:1770-3.
- 17 Nevinny HS, Krant MJ, Moore EW. Metabolic studies of the effect of methotrexate. *Metabolism* 1965;14:135-40.
- 18 van der Veen MJ, Scheven BAA, van Roy JLAM, Damen CA, Lafeber FPJG, Bijlsma JWJ. In vitro effects of methotrexate on human articular cartilage and bone-derived osteoblasts. *Br J Rheumatol* 1996;35:342-9.
- 19 May KP, West SG, McDermott MT, Huffer WE. The effect of low-dose methotrexate on bone metabolism and histomorphometry in rats. *Arthritis Rheum* 1994;37:201-6.
- 20 Friedlaender GE, Tross RB, Doganis AC, Kirkwood JM, Baron R. Effects of chemotherapeutic agents on bone. I. Short-term methotrexate and doxorubicin (adriamycin) treatment in a rat model. *J Bone Joint Surg Am* 1984;66:602-7.
- 21 Suzuki Y, Nakagawa M, Masuda C, Ide M, Uehara R, Ichikawa Y, *et al.* Short term low dose methotrexate ameliorates abnormal bone metabolism and bone loss in adjuvant induced arthritis. *J Rheumatol* 1997;24:1890-5.
- 22 Degreif J, Rudigier J, Rudig L, Wahlig H, Dingeldein E. Reaction of the bone structure to methotrexate-palacos flow y. *Arch Orthop Trauma Surg* 1989;108:363-7.
- 23 Gnudi S, Butturini L, Ripamonti C, Avella M, Bacci G. The effects of methotrexate on bone. A densitometric study conducted on 59 patients with methotrexate administered at different doses. *Ital J Orthop Traumatol* 1988;14:227-31.
- 24 Katz JN, Leboff MS, Wade JP, Brown EM, Liang MH. Effect of methotrexate on bone density and calcium homeostasis in rheumatoid arthritis [abstract]. *Clin Res* 1989;37:509A.
- 25 Carbone LD, Kaeley G, McKown KM, Cremer M, Palmieri G, Kaplan S. Effects of long-term administration of methotrexate on bone mineral density in rheumatoid arthritis. *Calcif Tissue Int* 1999;64:100-1.
- 26 Bianchi ML, Cimaz R, Galbati E, Corona F, Cherubini R, Bardare M. Bone mass change during methotrexate treatment in patients with juvenile rheumatoid arthritis. *Osteoporos Int* 1999;10:20-5.
- 27 Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose methotrexate on the bone mineral density of patients with reumatoid arthritis. *J Rheumatol* 1997;24:1489-94.
- 28 Dequeker J, Maenaut K, Verwilghen J, Westhovens R. Osteoporosis in rheumatoid arthritis. *Clin Exp Rheumatol* 1995;13(suppl 12):S21-6.