Stress fracture in long term methotrexate treatment for psoriatic arthritis

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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 (99mTc) 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...
the mid-point of the radius was found. In patients with RA low dose MTX treatment did not seem to affect the BMD. 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. 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. 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 

\[ ^{99m} \text{Tc} \] 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.

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