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Methotrexate-induced osteopathy in a male patient with psoriasis: A case report

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Abstract

Methotrexate-induced osteopathy is an uncommon but increasingly recognized complication of long-term methotrexate therapy, characterized by insufficiency fractures that predominantly affect weight-bearing bones. We report the case of a patient treated with low-dose methotrexate for over 15 years who presented with multiple bilateral insufficiency fractures of the knees and calcanei, with imaging findings characteristic of methotrexate-related osteopathy. Despite the presence of underlying osteoporosis, no alternative etiology such as malignancy, Paget's disease, or osteomalacia was identified. Clinical improvement was limited due to non-adherence to instructions for methotrexate discontinuation. This case highlights the importance of early recognition of methotrexate-induced osteopathy, prompt withdrawal of methotrexate, and initiation of appropriate anti-osteoporotic therapy to prevent further fractures and functional decline.

Keywords: Methotrexate-induced osteopathy; Insufficiency fractures; Osteoporosis; Magnetic Resonance Imaging (MRI).

Abbreviations: MRI: Magnetic Resonance Imaging; BMD: Bone Mineral Density; CT: Computed Tomography; TBS: Trabecular Bone Score; VAS: Visual Analogue Scale.

Introduction

Insufficiency fractures occur when normal physiological mechanical stress is applied to bone that has reduced structural integrity. Such fractures are typically associated with conditions that compromise bone strength, including advanced osteoporosis, osteomalacia, Paget's disease, metastatic bone involvement, prior radiotherapy, and medication-induced secondary osteoporosis. Less commonly, multiple insufficiency fractures have been reported as a manifestation of methotrexate-induced osteopathy.

Methotrexate is the cornerstone therapy for autoimmune rheumatic diseases such as rheumatoid arthritis, psoriasis, and psoriatic arthritis. At high doses, it acts as a folate antagonist by inhibiting DNA

synthesis, whereas at low doses it exerts anti-inflammatory and immunomodulatory effects through increased adenosine production and inhibition of cytokines such as TNF, IL-2 and IL-8 [1].

Methotrexate-induced osteopathy was first described by Ragab in 1970, who reported five children with severe osteoporosis and atypical lower-limb fractures after long-term methotrexate treatment, administrated at doses of (5-30 mg/m^2 daily or twice weekly for periods ranging from six months to three years). The characteristic findings included: 1) atypical bone pain, 2) osteoporosis, and 3) atypical insufficiency fractures at sites not typical for osteoporotic fractures. Clinical improvement was observed following discontinuation of methotrexate [2].

We present a rare case of an adult male who developed multiple insufficiency fractures of both knees and calcanei due to methotrexate-induced osteopathy.

Case Presentation

A 60-year-old man with a 40-year history of psoriasis was referred to the Rheumatology Department of KAT General Hospital by an orthopedic surgeon due to multiple insufficiency fractures of both knees and calcanei, in the absence of any preceding traumatic event. He had been receiving methotrexate 15 mg weekly along with folic acid 5 mg weekly for the past 15 years. His medical history was also significant for epilepsy since the age of 16, treated with carbamazepine and phenytoin, medications known to contribute to secondary osteoporosis.

On clinical examination, the patient reported pain during ambulation and weight-bearing of the lower extremities. There were no signs of arthritis or enthesitis. Cutaneous examination revealed limited psoriatic plaques on the fingertips, lumbar region, and groin. The remaining of the clinical examination was unremarkable.

One year prior to our evaluation, the patient developed pain in the right knee and right heel. Magnetic Resonance Imaging (MRI) of the right knee demonstrated insufficiency fractures of the medial femoral condyle and the posterior aspect of the lateral femoral condyle, accompanied by bone marrow edema, a metaphyseal bone infarct of the tibia, a horizontal tear of the medial meniscus, and chondropathy of the femoral and tibial condyles (Figure 1). MRI of the right calcaneus revealed a stress fracture located inferior to the posterior facet (Figure 2). Despite off-loading measures, follow-up imaging performed one year later demonstrated persistent knee findings and a new stress fracture in the body of the calcaneus.

Six months later, the patient developed pain in the left knee and left heel. MRI of the left knee revealed a fracture of the medial femoral condyle, a tibial bone infarct, chondropathy of the femoral condyles, and horizontal tears of both the medial and lateral menisci (Figure 3). MRI of the left calcaneus demonstrated a fracture involving the posterior body of the calcaneus (Figure 4). Bone scintigraphy showed increased radiotracer uptake at all fracture sites (Figure 5).

Bone Mineral Density (BMD) assessment demonstrated osteoporosis at both the lumbar spine (BMD L1–L4: 0.892 g/cm^2, T-score: –2.7) and the femoral neck (BMD: 0.709 g/cm^2, T-score: –2.9) (Figure 6). The

Trabecular Bone Score (TBS) was markedly reduced (TBS: 0.990), indicating impaired lumbar trabecular microarchitecture. Laboratory evaluation, including bone turnover markers, revealed no abnormalities (Table 1).

Given the patient's osteoporosis and long-term use of antiepileptic drugs, osteoporotic fractures were initially considered. However, the fracture distribution was atypical for primary or secondary osteoporosis, which most commonly affects the spine, hip, or distal radius. Osteomalacia was also considered unlikely, as the patient lacked diffuse bone pain, biochemical abnormalities, or radiographic evidence of Looser's zones. In addition, there was no history of malignancy, radiotherapy, or Paget's disease. Therefore, methotrexate-induced osteopathy was considered the most plausible diagnosis, consistent with the characteristic pattern of lower-limb insufficiency fractures.

Methotrexate was discontinued, and the patient was started on calcium and vitamin D supplementation, along with anti-osteoporotic therapy using intravenous zoledronic acid. Apremilast was initiated for psoriasis management. At the two-month follow-up, the patient reported self-initiated re-introduction of methotrexate due to worsening psoriasis and persistent lower-limb pain. Methotrexate was discontinued again, and treatment with secukinumab was initiated. Follow up imaging is ongoing.

Table 1: Laboratory evaluation.

WBC	6600/µL	4600-10200
PLT	327.000/µL	130.000-400.000
ESR	20 mm	0-20
CRP	0.35 mg/dl	<0.31
Creatinine	0.88 mg/dl	0.7-1.3
Calcium	9.6 mg/dl	8.4-10.2
Phosphorus	3.7 mg/dl	2.5-4.7
Albumin	4.5 gr/dl	3.5-5.5
SGOT	15 IU/L	5-34
SGPT	13 IU/L	<55
ALP	136 IU/L	40-150

TSH	2.34 µU/ml	0.35-4.94
24-hour Urinary Calcium	282 mg/24h	100-300
25OHD	39.8 ng/ml	20-50

Albumin	53.5%	52-68
α1	3.1%	1.5-4.5
α2	14.9%	6.5-13.5
β	13.3%	8-15.9
γ	15.2%	10.5-20.5

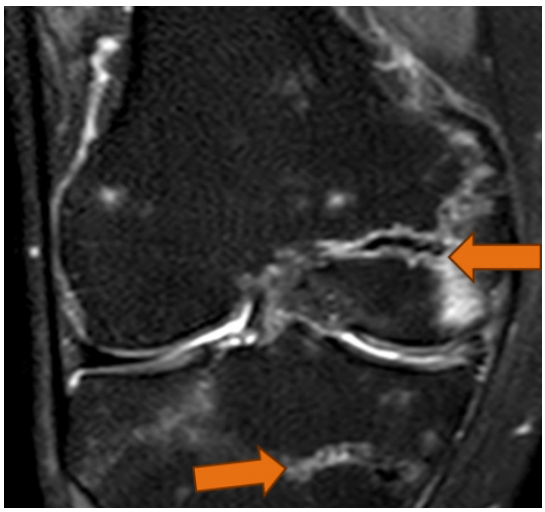

Figure 1: MRI of the right knee, STIR sequence. A fracture of the medial femoral condyle with associated bone marrow edema, and a bone infarction located in the tibial metaphysis.

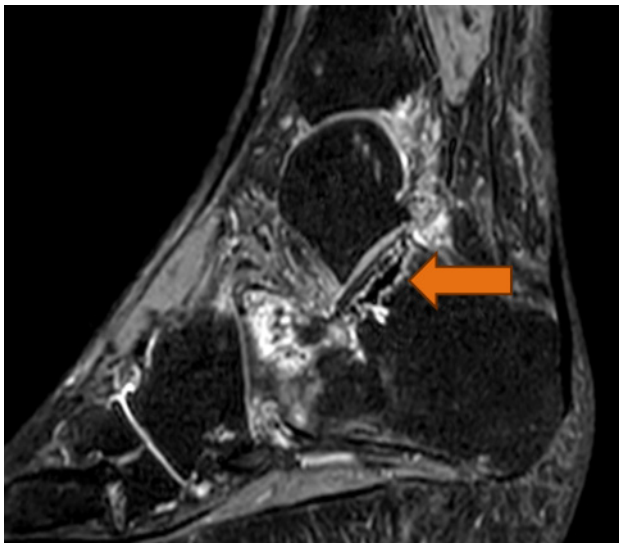

Figure 2: MRI of the right ankle, STIR sequence. Linear fracture of the calcaneus beneath the posterior facet.

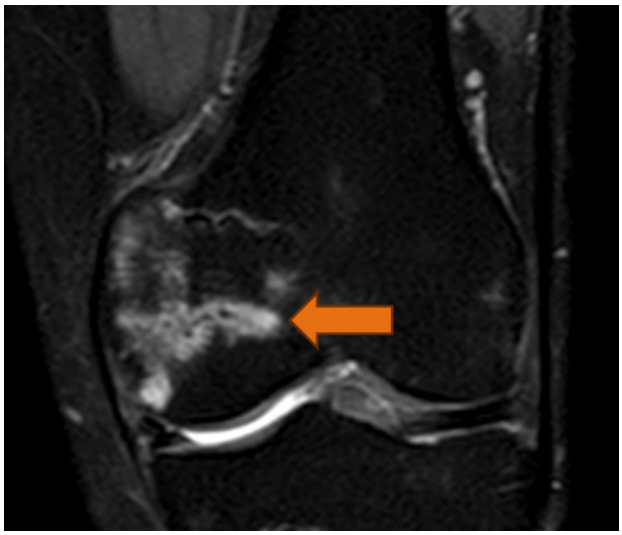

Figure 3: MRI of the left knee, STIR sequence. Fracture of the medial femoral condyle.

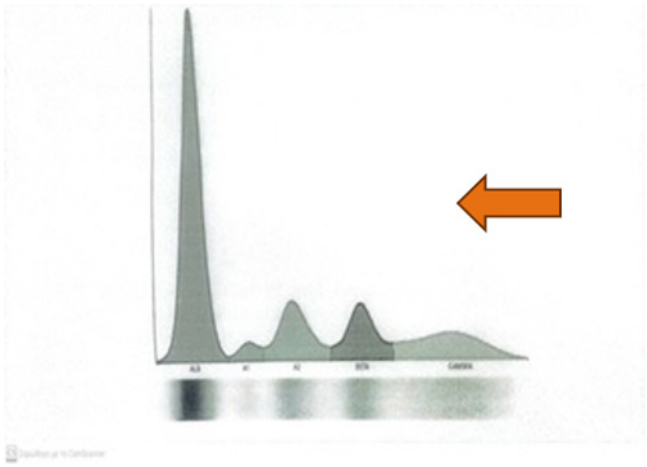

Figure 4: MRI of the left ankle, STIR sequence. Fracture of the posterior body of the calcaneus.

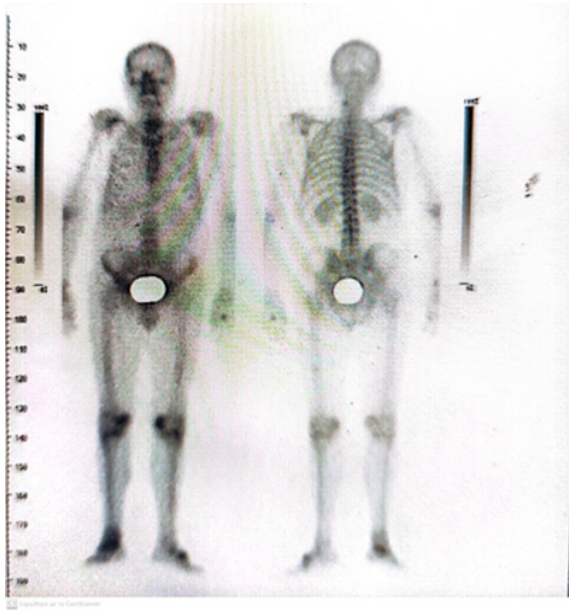

Figure 5: Bone scintigraphy of the patient.

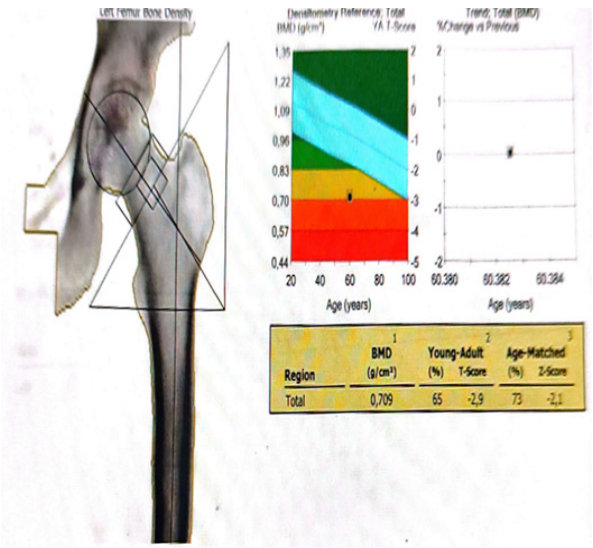

Figure 6: Bone mineral density measurement.

Discussion/Conclusion

Methotrexate-induced osteopathy is a rare but well-recognized complication, initially described in children receiving high-dose methotrexate for the treatment of malignancies, most commonly acute lymphoblastic leukemia. In these children, delayed bone growth was observed as a result of inhibited osteoblastic activity, disruption of endochondral ossification particularly involving the calcification zone of the epiphysis, and abnormal formation of primary spongiosa in the metaphysis. Impaired fracture healing due to abnormal bone remodeling was also reported [3,4].

Clinically affected children presented with significant lower-limb pain, while radiographic findings included severe osteopenia, insufficiency fractures of the lower limbs, and characteristic abnormalities such as multiple growth-arrest lines and scurvy-like changes [4].

The pathogenic mechanism of methotrexate-induced osteopathy is not yet fully understood. Experimental data in rodent models have shown that methotrexate affects multiple bone cell populations. At high doses, it suppresses chondrocyte proliferation, reduces growth plate thickness, and limits primary spongiosa formation. Even at low doses, chronic administration increases osteoclastic activity and reduces osteoblast density, while folic acid appears to exert a protective effect [5]. These findings support a dose-dependent bone toxicity of methotrexate.

Moreover, low-dose methotrexate has been shown to suppress bone alkaline phosphatase in precursor osteoblastic cells [6]. Recent in vitro studies further demonstrated that methotrexate impairs mechanotransduction in osteocytes by disrupting their response to physiological mechanical loading via integrin pathways and IL-1β–dependent auto-/paracrine signaling. This impaired mechanical responsiveness leads to inadequate bone adaptation to mechanical loads, reduced osteoblastic activity, and increased susceptibility to insufficiency fractures [7]. Through these mechanisms, methotrexate increases bone fragility and creates a microenvironment favoring insufficiency fractures.

A recent systematic review of 32 studies including 80 patients with rheumatic diseases reported that 95% developed insufficiency fractures of the lower limbs and 5% developed medial tibial stress syndrome. The majority of patients were treated with low to moderate doses of methotrexate, with a mean cumulative dose of 2.6 g and an average treatment duration of six years. Fractures were frequently multiple, bilateral, recurrent, predominantly located in the metaphysis or diaphysis of the tibia and in the calcaneus, and often displayed a characteristic band-like or meandering morphology. A large proportion of these patients were not receiving glucocorticosteroids, while most had osteoporosis or osteopenia (58.1% and 36.7%, respectively) [8]. Another retrospective study of 34 patients with rheumatic diseases revealed similar findings. Cone-beam CT (Computed Tomography) assessment demonstrated four stages of damage: epimetaphyseal osteolysis, coalescent microcallus, a sclerotic band, and ultimately fracture. Bone biopsy in a patient with methotrexate osteopathy showed an increased number of osteoclasts and reduced osteoblast density per bone surface, confirming the imbalance in bone metabolism [9].

Discontinuation of methotrexate was associated in most cases with clinical and imaging improvement, as well as increases in bone mineral density. Furthermore, anti-osteoporotic therapy, particularly the combination of teriparatide and denosumab, appeared to offer significant benefits in improving BMD in these patients [8,9]. The importance of early recognition of methotrexate-related insufficiency fractures and prompt discontinuation of the drug to prevent further bone damage is underscored by a recent retrospective study. In a cohort of 33 patients with methotrexate-induced osteopathy, continuation of methotrexate following the initial fracture was associated with a markedly increased risk of subsequent fractures. In contrast, discontinuation of methotrexate significantly reduced the risk of future fractures and was associated with improved clinical outcomes, including pain reduction and weight-bearing capacity during fracture healing [10].

However, studies targeting the effects of methotrexate on bone mass in patients with rheumatic diseases did not demonstrate that long-term low-dose methotrexate accelerated generalized bone loss

[11,12]. Therefore, it is likely that methotrexate predominantly induces regional osteoporosis in weight-bearing bones.

The distinction between methotrexate-induced osteopathy and osteoporotic fractures is further clarified in a recent study of 173 patients (83 with methotrexate-related insufficiency fractures and 89 with osteoporotic fractures). One of the key differences was fracture location: methotrexate osteopathy predominantly affected the lower limbs and high–load-bearing regions, whereas osteoporotic fractures occurred mainly in the spine and peripheral sites such as the distal radius. Moreover, patients with methotrexate osteopathy reported higher pain scores (Visual Analogue Scale - VAS) and had higher T-scores on BMD measurements. Importantly, methotrexate discontinuation was essential for pain reduction, mobility restoration, and fracture healing in methotrexate osteopathy, and anabolic therapy was associated with superior outcomes in mobility for these patients. These differences likely reflect the distinct underlying pathophysiological mechanisms: methotrexate osteopathy involves low bone turnover due to osteoblastic inhibition and predominantly affects trabecular bone, whereas osteoporosis is characterized by high bone turnover due to increased osteoclastic activity [13].

Numerous case series and case reports have described similar cases of insufficiency fractures attributable to methotrexate-induced osteopathy [14-21].

In our patient, long-term exposure to methotrexate for more than 15 years resulted in multiple insufficiency fractures with locations and morphology typical for methotrexate-induced osteopathy. The coexistence of osteoporosis and the absence of alternative etiologies (malignancy, Paget's disease, osteomalacia) strongly support methotrexate as the primary pathogenic factor. Unfortunately, non-adherence to medical instructions regarding methotrexate discontinuation, resulted in inadequate clinical response. This case underscores the importance of early recognition of methotrexate-induced osteopathy, prompt discontinuation of methotrexate, and initiation of appropriate anti-osteoporotic therapy to prevent further fractures and functional decline.

It is important to remain aware of methotrexate-induced osteopathy, even though it is a rare condition, in order to differentiate it from arthritis or arthralgia in patients with rheumatic diseases who have been receiving long-term methotrexate therapy. When clinical suspicion is high, MRI should be performed.

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