METHOTREXATE-RELATED OSTEOPATHY AS AN OVERLOOKED COMPLICATION:
A CASE SERIES

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Mesut Ajder* https://orcid.org/0009-0004-2403-4675
Reşit Yıldırım https://orcid.org/0000-0003-4040-0212
Erdal Bodakçi https://orcid.org/0000-0002-0402-1525
Döndü Üsküdar Cansu https://orcid.org/0000-0001-6543-3905
Cengiz Korkmaz https://orcid.org/0000-0003-2679-0699

*Corresponding author:
Döndü Üsküdar Cansu, Department of Rheumatology, Faculty of Medicine, Eskişehir Osmangazi University, 26480, Eskişehir, TURKEY;
Twitter handle: @dnd52298582; E-mail: ducansu@hotmail.com

Abstract
Low dose methotrexate (MTX) still remains as the cornerstone in the treatment of rheumatic diseases such as rheumatoid arthritis (RA) and psoriatic arthritis. Clinicians have been aware of common side effects of MTX for over five decades, whereas there have been rarely seen and relatively easily overlooked complications that had been reported to be associated with MTX in the literature, such as MTX osteopathy. The use of high doses of MTX has been demonstrated to have negative effects on bone formation and bone mineral density as well as long-term low dose, which is relatively less common. Diagnosis of MTX osteopathy might be challenging as there is no specific clinical features. Herein, we present 3 patients with RA diagnosis who developed MTX osteopathy during follow-ups.

Keywords: Methotrexate, Bone formation, Osteopath, Outcome


INTRODUCTION
Methotrexate (MTX), a folate antagonist, is the most preferred anchor drug in inflammatory arthritis patients for over five decades. While influenza-like syndrome, gastrointestinal intolerance and alterations in liver function tests are most common seen adverse reactions in clinical practice, there are also rarely reported serious drug-related adverse events such as myelosuppression, liver fibrosis, pneumonitis, and relatively lesser, osteopathy [1]. MTX-related osteopathy was first described in 1970 in patients receiving high dose MTX for acute lymphoblastic leukemia and solid bone tumors [2]. In contrast, despite rare, this adverse event has also been identified in rheumatoid arthritis (RA) and psoriasis with low dose usage in the following years [3, 4]. Our aim with this
As she was on etanercept and MTX (15 mg/week, subcutaneously). Her examination was noncontributory. Her cumulative steroid dose was 3 grams of prednisolone for the past 2 years. Pelvic radiography showed fracture in both sides of pubis and left ischium (Figure 1B). She reported no recent history of trauma. Bone scan was supporting osteopenia (T score for lumbar and femur neck: -2.1 and -1.5). All laboratory findings were normal. Diagnosis of MTX osteopathy was considered and alendronate sodium was started in line with MTX cessation.

Case 3.
A 60 year-old female was admitted by acute onset pain in the left ankle and foot, and unable to walk for the last two weeks. Her past medical record showed that she was diagnosed with RA at age 40 and given MTX (10 mg/week, subcutaneously) and prednisolone for the initial 8 years and then switched to leflunomide, and infliximab during follow-ups due to active disease. Her cumulative corticosteroid dose was not able to calculate due to missing follow ups for 3 years. Three months earlier, a fracture in left ischium was detected at external hospital which conservative treatment was recommended. Physical examination was remarkable for tenderness in the left ankle. No history of trauma was reported and all laboratory parameters including vitamin D, calcium and phosphorus were normal. Radiologic examination revealed marked destruction in left talus, fracture in distal tibia (Figure 1C). Bone scan showed significant decrease of density in femur neck (T score : -2.5). Based on location of fracture and past medical usage of MTX, despite not taking MTX currently, MTX related osteopathy was considered and ibandronic asit was started.

DISCUSSION
MTX osteopathy consists of bone pain, osteoporosis and fracture, mostly seen in female population [3]. Nearly all cases develop in lower extremities particularly distal and proximal tibia, calcaneus, talus and metatarsal bones [3]. The main mechanism is considered as stres related and many presented by multiple, bilateral and recurrent fractures [3, 4]. Clinical features might be challenging: bone pain in the absence of trauma and swelling in lower extremities mimicking arthritis [4]. In the presence of these symptoms, direct radiography examinations might not be sufficient, therefore MR imaging is strongly advised. A meander-shaped appearance along the growth plate (epimetaphyseal osteolysis) or band-like sclerosis appears to be a characteristic radiologic feature [4].

No link between MTX use and osteoporosis has been demonstrated in bone mineral density-based studies thus far [5]. However, in vitro and in vivo models have shown that either osteoblastic and osteoclastic activities mainly in metaphyseal region are affected by MTX use [6, 7]. Even if the mechanisms remain unclear, all these cellular changes are consistent with local bone loss, especially at the trabecular level. Furthermore, in vivo and vitro rat studies have revealed that daily injection of MTX 0.75 mg/kg for 5 days might increase osteocyte apoptosis, particularly in primary spongiosa, which is reversible following folinic acid replacement [8]. Of note, in a systematic review by Ruffer at al, it appears that MTX osteopathy might occur even in low dose, and long-term usage is not mandatory for altering bone formation. In this review, it was observed that MTX related osteopathy can develop at various doses (5 to 25 mg per week), with nearly half of them (45%) being low to moderate doses of weekly MTX. Median cumulative dose of MTX was calculated to be 2.6 g at the time of fracture occurrence and median duration was found to be 6.0 years. Moreover, nearly one third of the patients did not receive any steroids at least 3 years before fracture development [4]. Although, as seen in the literature, MTX osteopathy is generally expected to occur over long term MTX usage, however...
in our case series, it can happen as early as two years of medication usage. On the other hand, some comorbidities particularly having altered bone formation either during off before MTX usage appear to increase the risk of osteopathy development.

MTX osteopathy may progress without treatment, leading to persistent bilateral fractures, resulting with longstanding immobility. MTX discontinuation is the cornerstone of management along with anti-resorptive medications in the presence of osteoporosis confirmed by BMD [4]. In our index case (Case 1), as we were not aware of this rare side effect, MTX was continued for two years until definitive diagnosis. However, there is no consensus among experts whether which bone specific agent should be preferred for better outcome.

In conclusion, clinicians should be cognizant of MTX osteopathy among differential diagnoses especially when a patient on long-term MTX presents with atypical bone findings. In the presence of such a scenario, radiologic examination should be performed and assessed attentively. Further studies are needed to enlighten the accurate prevalence and nature of this rare adverse event.

References


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CONFLICTS OF INTERESTS
Both authors have completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/; available on request from the corresponding author). Both authors declare that there are no potential conflicts of interest.

INFORMED CONSENT
Written informed consent was obtained from the patients for publication of this case report.

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Figure 1. Radiographic images of patients who developed methotrexate osteopathy
МЕТОТРЕКСАТТЫҢ ҚОЛДАНАУМЕН БАЙЛАНЫСТЫ ОСТЕОПАТИЯ ҰМЫТЫЛҒАН АСҚЫНУН РЕТИНДЕ: БІРҚАТАР ЖАҒДАЙЛАР

Түйіндеме
Метотрексаттың (МТХ) темен мәлшерлери ревматоидтық артрит (РА) және псориаздық артрит сияқты ревматикалық ауруларды емдеуде әлі де негіз болып қалада. Клиниктер метотрексаттың жалпы жанама асерлері тұралы бес оңжылдықтан астан үақыт бойы білді, ал адебиеттерде, айдыңғы адеиеттерде хабарларларын өңдеуді, метотрексатпен остеопатия сияқты метотрексатпен байланысты аскынұлар сирек байқалды және салыстырмала түрде өңдайды ескерілмейді.

Метотрексаттың қоғамдай мәлшерлерін қолдану сүйкеті түзілуіне және сүйкетінің минералды тығыздығына тәріз асер ететіндігі көрсестіліп, үксақ асерлер темен мәлшерлерді үзәк үақыт қолдануға мүмкіндік береді, бұл салыстырмала түрде сирек кездеседі. МТХ остеопатиясының диагностикалық қын болыс мүмкін, біткені нәкті клиникалық өзгееліктері қоң. Бұл мақалада біз бақылау кезінде МТХ остеопатиясының жаңа малга РА диагностикасы бар үшін пациенттің жағдайларының ұсынысы.

Түйінді сөз: метотрексат, сүйкетінің тұлауы, остеопатия, нағыз.

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ОСТЕОПАТИЯ, СВЯЗАННАЯ С ПРИМЕНЕНИЕМ МЕТОТРЕКСАТА, КАК ЗАБЫТОЕ ОСЛОЖНЕНИЕ: СЕРИЯ СЛУЧАЕВ

Резюме
Низкие дозы метотрексата (MTX) по-прежнему остаются краеугольным камнем в лечении ревматических заболеваний, таких как ревматоидный артрит (RA) и псориатический артрит. Клиницисты знали о распространенных побочных эффектах метотрексата на протяжении более пяти десятилетий, тогда как в литературе редко наблюдались и относительно легко упускались из виду осложнения, которые, как сообщалось в литературе, были связаны с метотрексатом, такие как остеопатия метотрексатом. Было продемонстрировано, что использование высоких доз метотрексата оказывает негативное влияние на костеобразование и минеральную плотность костей, подобные эффекты дают длительное применение низких доз, что встречается относительно реже. Диагностика остеопатии MTX может быть сложной, поскольку специфических клинических особенностей нет. В данной статье мы представляем случаи трез пациентов с диагнозом RA, у которых во время наблюдения развилась остеопатия MTX.

Ключевые слова: метотрексат, костеобразование, остеопатия, результат.

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