Very Low Dose Methotrexate-Induced Rheumatoid Nodules Localized in Buttocks and Palmar Aspects of Phalanges: Case Report

Kalça ve Parmakların Palmar Yüzlerinde Lokalize ve Çok Düşük Doz Metotreksat ile Ortaya Çikan Romatoid Nodüler

**ABSTRACT** Rheumatoid nodules are the most common extra-articular lesions. They usually occur in rheumatoid factor positive patients and indicate activity and severity of the disease. These nodules characteristically occur subcutaneously on extensor surfaces over the elbows or other bony prominences. They may be overlooked if they occur in sites other than well-known areas. We present a case with rheumatoid arthritis (RA) who developed multiple subcutaneous, histologically-proven rheumatoid nodules in both buttocks as well as on palmar aspects of phalanges after 3.5 years of very low-dose weekly methotrexate (MTX) treatment. These nodules occurred abruptly while there was not active arthritis in any joint. MTX-induced large nodules may occur even with very low doses of MTX, in atypical localizations such as both buttocks.

**Key Words:** Arthritis, rheumatoid; rheumatic nodule

**ÖZET** Romatoid nodüler en sık ekstra-artiküler lezyonlardır. Genellikle romatoid faktör pozitif hastalarda oluşur ve hastalığın şiddeti ve aktivitesini gösterirler. Bu nodüler karakteristik olarak ekstansör yüzeylerde дирsek veya diğer kemik çıkmınların üzerinde cilt altında ortaya çıkarlar. İly bilinen yerlerde olduğu gibi, bu nodüler gözden kaçabildir. Biz romatoid artrit (RA) tanılı ve 3.5 yıllık çok düşük doz haftalık metotreksat (MTX) tedavisi sonrası her iki kalça yanı sıra parmakların palmar yüzlerinde birden çok sayıda subkutan, histolojik olarak kanıtlananın romatoid nodüler gelişmiş bir hastayı sunmaktadır. MTX ile indüklenen nodüler çok düşük MTX dozlarında da her iki kalça gibi atıpkı lokalizasyonlar ve RA’ın komplet remisyonda olduğu sırada oluşabilir.

**Anahtar Kelimeler:** Artrit, romatoid; romatoid nodüler

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Rheumatoid arthritis (RA) is a chronic systemic disease involving synovial joints and causing symmetric polyarthritis.\(^1\)

Rheumatoid nodules are the most common extra-articular lesions, seen approximately in 20% to 30% of rheumatoid arthritis patients.\(^2\) They usually occur in rheumatoid factor positive patients and indicate activity and severity of the disease. These nodules characteristically occur subcutaneously on extensor surfaces over the elbows or other bony prominences. However, they may occur in any organ or tissue layer. Rheumatoid nodules over the sacrum are seldom looked for. They may lead to pressure ulcers, and act as a source of infection and even cause fatal septicemia in RA pati-
The nodule size may be variable ranging from several millimeters to 4 cm. The differential diagnosis of these nodules includes gouty tophi, xanthomata, and lipomata.

Onset or worsening of rheumatoid nodules due to methotrexate (MTX) treatment is a well known phenomenon, as shown by numerous case reports and short series. However, a recent review concluded that the evidence for causality was still poor. Hereby, we report a patient developing rheumatoid nodules with atypical localizations after very low dose MTX treatment.

**CASE REPORT**

The patient is a 64-year-old man with a 4-year history of non-erosive, seropositive rheumatoid arthritis diagnosed in October 2002 and followed up at the Ege University Hospital, Division of Rheumatology.

This study was performed according to the principles of the Declaration of Helsinki and informed consent was obtained from the patient.

The initial treatment included MTX (10 mg weekly) and low doses of steroids (deflazacort 6 mg/day). The dose of MTX was reduced to 7.5 mg weekly in May 2003, then to 5 mg weekly in June 2004 due to gastrointestinal intolerance. In April 2005, he was admitted to the hospital with palpable, non-painful subcutaneous nodules located on fingers, and painful, tumor-like lesions in buttocks. He had morning stiffness less than one hour, arthralgia of wrists, metacarpophalangeal and proximal interphalangeal joints. At that time, the patient was on treatment of MTX (5 mg/week), folic acid (5 mg/week) and methylprednisolone (4 mg/day).

Physical examination revealed one nodule on the palmar aspect of the left first proximal phalanx and one on the right third proximal phalanx, approximately 1 cm in size. Tumor-like lesions in the buttocks were 4 x 1 cm in the right buttock and 3 x 1 cm in the left buttock. They were characterized by redness, tenderness and local heat. There were no systemic symptoms. The articular signs were very mild.

The hematological examination revealed a white blood cell count of 10,800/mm³, hemoglobin level of 10.5 g/dl, C-reactive protein 0.74 mg/dl (a slight increase over normal). Rheumatoid factor was 90 IU/ml (normal < 40 IU/ml) and anti-CCP was 100 RU/ml (normal < 5RU/ml). Antinuclear antibodies, anti-Ro, anti-La, antineutrophil cytoplasmic antibodies and double-stranded DNA antibodies were negative.

The plain radiograph of the hands demonstrated non-erosive rheumatoid arthritis. The pelvis and chest X-rays were normal.

In June 2005, nodules on the phalanges were seen as hypoechoic masses with regular margins, ranging from 9 to 12 mm on ultrasonographic examination. On the other hand, the tumors in the right and left gluteal regions were 5 x 1.5 cm and 4 x 2 cm in size, respectively.

The patient refused any further investigation including biopsy. Therefore we discontinued MTX in June 2005 and called him back in September 2005. Because of the persisting nodules located on the fingers and the masses in the buttocks, we planned pelvis magnetic resonance imaging (MRI) first.

In October 2005, pelvis MRI was performed because of the masses in both buttocks. T1-weighted images showed low signal intensity masses in subcutaneous fat tissue of intergluteal region (Figure 1). T2-weighted images (with fat saturation) showed hyperintense masses in same region (Figure 2). These MRI findings were non-specific for soft tissue masses and a biopsy was required for diagnosis.

**FIGURE 1:** MRI of the case. T1-weighted axial image shows masses in subcutaneous fat tissue of intergluteal region symmetrically and bilaterally. The signal intensity is low compared to subcutaneous fat tissue.
In November 2005, biopsy of tumor in the right buttock disclosed histopathological findings of a rheumatoid nodule. Histological examination showed fibrinoid material surrounded by palisaded histiocytes (Figure 3). After excisional biopsy, the nodule did not recur at the same site.

With the discontinuation of MTX in June 2005, the nodules on the phalanges and in the left buttoc showed regression within a period of nine months. The patient was treated with methyl prednisolone 4 mg/day and the clinical course was satisfactory. Follow-up period was 4 years when this article was written and the nodule in the right buttock did not recur again.

**DISCUSSION**

Although MTX-induced nodulosis is a well known phenomenon, our case may deserve attention because of the very low dose of MTX received, atypical localizations of the large nodules and complete disappearance after discontinuation of MTX. The patient had been receiving only 5 mg MTX weekly for the last one year, when he developed nodules. Thirty-two months had already passed from the initiation of MTX treatment. The initial weekly dose of 10 mg had been gradually reduced to 5 mg weekly dose, after the first seven months, due to gastrointestinal intolerance. The cumulative dose of MTX was approximately 900 mg at the time of the occurrence of nodules. In literature, the time between MTX prescription and nodule formation has been reported to range from months to years.6-8

MTX-induced nodules may be seen on different parts of the body, mostly including the fingers (overlying the extensor surfaces of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints) and the feet (especially over or under the metatarsophalangeal joints). These nodules may also have rare and atypical localizations such as both buttocks,9 as in our case. Besides, visceral organ localizations such as heart, lungs or brain have also been reported. However, we could not detect visceral organ involvements in our case.

MTX induces adenosine release at sites of inflammation; and the pathogenesis of MTX-induced nodulosis seems to be related with the interaction of increased adenosine with adenosine A1 receptors. In in vitro models, adenosine A1 receptor agonists have been shown to promote cellular migration, aggregation and fusion into multinucleated giant cells.7 However, despite the classical view, a recent review suggested that, the evidence for causality in MTX-induced nodules was still poor.5

Distinguishing rheumatoid nodules secondary to RA from MTX-induced nodules is difficult because of the similar histology. However, MTX-induced nodules tend to occur away from the joints that are normally affected by RA. Besides, MTX-induced nodules are generally smaller in diameter (less than 5 mm);3 however in our patient, the nodules in the buttocks were 5 x 1.5 cm and 4 x 2 cm respectively. On the other hand, MTX-induced nodules generally regress with discontinuation of
MTX as in our case, while rheumatoid nodules may regress with MTX treatment. In our patient, the MTX-induced nodules showed regression in months after cessation of MTX. Sometimes, different drugs including colchicine, D-penicillamine, hydroxychloroquine, sulfasalazine and azathioprine may be used for treatment of MTX-induced nodules in addition to discontinuation of MTX.\(^5,9-14\)

Although leflunomide which is a disease modifying anti-rheumatic drug with a similar efficacy to MTX may also be considered, there are case reports about rheumatoid nodules occurring during leflunomide treatment.\(^15,16\)

In conclusion, MTX-induced large nodules may occur even with very low doses of MTX, in atypical localizations such as buttocks.

### REFERENCES