Subcutaneous Nodules in Rheumatoid Arthritis

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A 29 year old male with rheumatoid arthritis (RA) of 10 years duration presented with multiple subcutaneous nodules of one month duration while on methotrexate (7.5 mg once a week), salazopyrine (1000 mg/day) and methyl prednisolone (4 mg/day). The nodules involved tendons of metacarpophalangeal joints (Figure 1) and base of left great toe (Figure 2), were painless and did not interfere with his daily activities. There was mild synovitis of left ankle. No other extra-articular manifestations were present. ESR was 17mm at 1hr. Methotrexate induced accelerated nodulosis (MIAN) was diagnosed. Methotrexate (MTX) was continued at the same dose. There was no change in number and size of nodules at three months follow-up.

MIAN is a rare, but unique side effect of methotrexate therapy seen most commonly in RA patients and rarely in patients with psoriatic arthritis, juvenile rheumatoid arthritis, dermatomyositis and systemic lupus erythematosus.¹⁻³ MIANs can develop in the absence of rheumatoid nodules, bear no association with rheumatoid factor,¹ duration of MTX therapy (12 to 60 months) and cumulative MTX dose (60 to 2400 mg).¹ MIANs may be difficult to differentiate clinically from rheumatoid nodules. Rapid development of multiple nodules, atypical sites especially finger tendons, quiescent arthritis and absence of extra-articular features favour MIAN. Other affected sites are elbows, knees and occasionally feet. MIANs can involve vital areas such as the larynx, lungs, and heart without any external nodules.¹ MIANs can be solitary or multiple, firm and painless, typically subcutaneous and often adherent to underlying peristeum, tendons or bursae.² Histologically MIANs are identical to rheumatoid nodules.¹⁻²

Being associated with minimal or no discomfort and morbidity in majority of patients, MTX can be continued. The nodules often regress with discontinuation or on reduction of MTX dose, but may reappear when MTX is reintroduced. Hydroxychloroquine, D-penicillamine, colchicine and sulfasalazine have been reported to reduce frequency of MIAN.²

The exact mechanism of MIAN is not known. MTX exerts its anti-inflammatory actions through a number of cellular mechanisms. Other than the antifolate activity, MTX exerts its anti-inflammatory action by inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, an enzyme involved in purine synthesis, resulting in enhanced release of adenosine. Adenosine is a potent endogenous anti-inflammatory mediator that activates specific receptors on different cells. This mechanism is likely to play a role in MTX toxicities, including MIAN. Adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes is a suggested mechanism for MIAN.⁵ Also, it has been shown that 2756 GG Genotype of Methionine Synthase Reductase Gene is associated with MIAN.⁶

References