Accelerated nodulosis immediately after initiating weekly low dose methotrexate for rheumatoid arthritis

Sir,

There have been many reports of the occurrence of subcutaneous nodules in rheumatoid arthritis (RA) patients after methotrexate (MTX) treatment (1-6). This phenomenon has been named accelerated nodulosis (AN). AN has also been observed in psoriasis (7), during azathioprine therapy (8), with vasculitis (1), and in RA with the development of pleural effusion and pericardial tamponade (5, 6). A review of the English literature shows that AN usually develops during long-term MTX therapy (2 months to 5 years) with a cumulative dose of at least 60 mg (2). We describe a patient with RA who developed AN immediately after the initiation of weekly low dose MTX therapy.

A 41-year-old man presented to our hospital in November 1996 with polyarthritis of 5 years duration. The patient showed arthritis of the wrists and the small joints of the hands, elbows, knees, and ankles. No subcutaneous nodules were detected and he had no other extraarticular manifestations. His Ritchie index was 5 and his functional class was II. Blood tests showed the following: ESR (Wintrobe method) 20 mm/hr, CRP 0.36 mg/L (normal < 0.8), RF 105 IU/ml, and the absence of antinuclear antibodies. Joint radiographs showed erosive changes on the metatarsophalangeal joints of the feet and the mandibular condyle.

RA was diagnosed and sulfasalazine 1.5 g/day, prednisolone 2.5 mg/day, and piroxicam 20 mg/day were instituted. The arthritis was markedly reduced until December 1997, when the disease flared with severe polyarthritis. Laboratory findings were: CRP 3.64 mg/L, RF 217 IU/ml, and ESR 50 mm/hr. Weekly low dose MTX (7.5 mg/week) was added. After 2 weeks, however, the patient developed slightly tender and firm nodules (1 x 1 cm) on the extensor surfaces of both elbows (Fig. 1). On his own initiative the patient discontinued oral MTX. There was a gradual decrease in the size of the nodules, and 2 weeks later they had completely disappeared. We attempted a re-challenge, administering MTX 10 mg/week, plus hydroxychloroquine 400 mg/d and sulfasalazine 1.0 g/d due to a flare of arthritis. Although the MTX dosage was higher, the patient did not develop nodules until 8 weeks later.

Accelerated nodules differ from spontaneously occurring subcutaneous nodules in many ways (7). First, they develop and grow rapidly. Secondly, they occur preferentially in the fingers whereas subcutaneous nodules are generally located either on the Achilles tendon or on the extensor surface of the forearm distal to the olecranon. Finally, they are generally smaller in size (< 0.5 cm in diameter).

AN usually disappear within several weeks or months after MTX is stopped, but their development is not necessarily a contraindication for the continuation of MTX therapy, since they may regress even with MTX (7, 9, 10) or by adding hydroxychloroquine (4). In our patient the nodules occurred immediately after the initiation of weekly low-dose MTX therapy (cumulative dose 15 mg). To our knowledge there are no reports in the literature of AN developing after such a small dose, and in such an unusual location. Furthermore, the nodules were relatively large (≈ 1 cm in size). The patient denied any previous eruption of subcutaneous nodules.

We conclude that AN may occur in RA despite a very small cumulative dose of MTX. However, we do not know whether the successful re-challenge was serendipedous or due to the addition of hydroxychloroquine.

J.-B. JUN, *MD, PhD, Assistant Professor*
H.K. KOH, *MD, Fellow in Rheumatology*
S.-C. BAE, *MD, PhD, MPH, Asst. Professor*
D.-H. YOO, *MD, PhD, Associate Professor*
S.Y. KIM, *MD, PhD, Professor, Director*

The Hospital for Rheumatic Diseases,
Department of Internal Medicine
Hanyang University College of Medicine,
Seoul, Korea.
Address for correspondence and reprint requests: Dr. Jae-Bum Jun, Haengdang-dong 17, Sungdong-gu, Seoul 133-792, Korea.

Fig. 1. Accelerated nodulosis (white arrow) over the extensor surface of the forearm distal to the olecranon.

References

1. SEGAL R, CASPI D, TISHLER M, FISHEL B, YARON M: Accelerated nodulosis and vasculitis during methotrexate therapy for rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 1182-5.
2. KERSTENS PJ, BOERBOOMS AM, JEURISSEN ME, FAST JH, ASSMANN KJ, VAN DE PUTTE LB: Accelerated nodulosis during low dose methotrexate therapy for rheumatoid arthritis. An analysis of ten cases. *J Rheumatol* 1992; 19: 867-71.
3. ALARCON GS, KOOPMAN WJ, McCARTY MJ: Nonperipheral accelerated nodulosis in a methotrexate-treated rheumatoid arthritis patient. *Arthritis Rheum* 1993; 36: 132-3.
4. COMBE B, GUTTIERREZ M, ANAYA JM, SANY J: Possible efficacy of hydroxychloroquine on accelerated nodulosis during methotrexate therapy for rheumatoid arthritis. *J Rheumatol* 1993; 20: 755.
5. ABU-SHAKRA M, NICOL P, UROWITZ MB: Accelerated nodulosis, pleural effusion, and pericardial tamponade during methotrexate therapy. *J Rheumatol* 1994; 21: 934-7.
6. SMITH MD: Accelerated nodulosis, pleural effusion, and pericardial tamponade during methotrexate therapy. *J Rheumatol* 1995; 22: 1439.
7. BERRIS B, HOUPT JB, TENENBAUM J: Accelerated nodulosis in a patient with psoriasis and arthritis during treatment with methotrexate. *J Rheumatol* 1995; 22: 2359-60.
8. LANGEVITZ P, MAGUIRE L, UROWITZ M: Accelerated nodulosis during azathioprine therapy. *Arthritis Rheum* 1991; 34: 123-4.
9. THOMPSON RN: Is the appearance of rheumatoid nodules in a rheumatoid patient well controlled on methotrexate an indicator to stop the drug? *Br J Rheumatol* 1992; 31: 86.
10. KERSTENS PJ, BOERBOOMS AM, VAN DE PUTTE LB: Possible efficacy of hydroxychloroquine on accelerated nodulosis during methotrexate therapy for rheumatoid arthritis (letter). *J Rheumatol* 1993; 20: 756.