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CASE REPORT

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Rheumatoid nodulosis during methotrexate therapy in a patient with rheumatoid arthritis

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Abstract We report a 62-year-old man with rheumatoid arthritis (RA) who developed nodulosis after methotrexate (MTX) treatment. The epithelioid cells of nodules were positive for matrix metalloproteinases (MMP)-2, MMP-3, MMP-9, and Ki67. The synovial tissues obtained from the same patient were negative for MMP-3, MMP-9, and Ki67. This study demonstrated that MTX-induced nodules are different from synovial tissues in terms of MMP expression, suggesting the presence of different pathologic mechanisms and differential MTX susceptibility.

Key words Immunohistochemical staining · Matrix metalloproteinase (MMP) · Methotrexate (MTX) · Rheumatoid arthritis (RA) · Rheumatoid nodulosis

Introduction

Rheumatoid nodules are characteristic extra-articular lesions often associated with severe or progressive rheumatoid arthritis (RA). We recently encountered a RA patient who developed multiple rheumatoid nodules despite improvement of joint symptoms by methotrexate (MTX) therapy. Occurrence of MTX-induced nodulosis has previously been reported,[1–6] but the histopathological analyses of such nodules have been limited. We obtained rheumatoid nodules and joint synovial tissues from a patient with MTX-induced accelerated nodulosis and compared their pathological features.

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Case report

The patient was a 62-year-old man who presented with RA in 1986. Gold salt and D-penicillamine therapies were started in 1988, the former being discontinued because of onset of proteinuria. Since his arthritis was not controlled satisfactorily, MTX (5 mg/week) therapy was started in October 1990. He showed remarkable clinical improvement after one month and received 2.5 mg/week of MTX after May 1993. In 1995, at a total cumulative MTX dose of ~1000 mg, multiple subcutaneous nodular masses became apparent, mainly in his extremities, and increased in size and number thereafter. He was also suffered from severe deformities of right toes and forefoot pain during walking. In March 2002, the patient was admitted to our hospital for resection of the nodules and resection arthroplasty of his right toes.

A total of 22 subcutaneous nodules were located on the bilateral elbows, fingers, buttocks, right knee, bilateral ankles, right heel, and bilateral feet. All of these nodules were firm and indolent. The patient had no vascular lesions or peripheral neuropathy.

Laboratory tests showed an erythrocyte sedimentation rate of 22 mm/h, white blood cell count of 6170/μl, red blood cell count of 454×10^4/μl, platelet count of 17.8×10^4/μl, and C-reactive protein level of 0.8 mg/dl, suggesting that there was little inflammation. The levels of CH50 and MMP-3 were within the normal range, being 35 U/ml and 98.8 ng/ml, respectively. However, the rheumatoid factor level was high (883 IU/ml). Human leukocyte antigen (HLA) typing showed that he was HLA-DRB1 *1502 and *0803 positive.

On X-ray, there were no destructive changes to the shoulder, elbow, hip, knee, or ankle joints, but there was marked erosion and deformity of the fingers and toe joints. Chest X-ray showed no abnormalities.

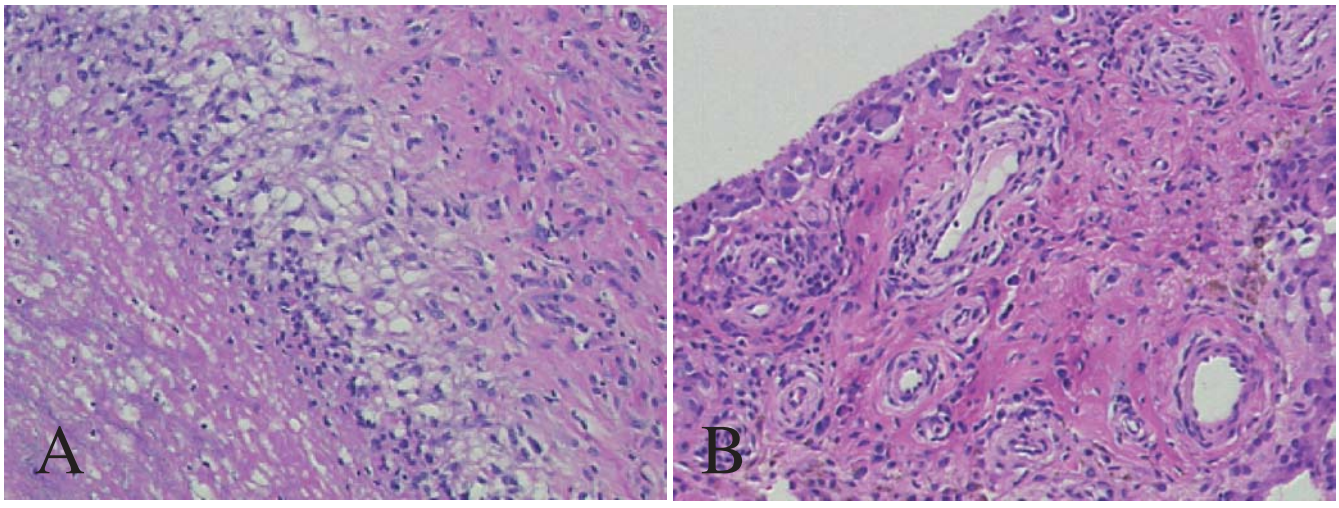

Fig. 1. A Photomicrograph of the resected subcutaneous nodules showed an amorphous necrotic substance containing neutrophils at the center of nodule, surrounded by epithelioid cells in a palisading pattern and lymphocytes. **B** Synovial tissue from the same patient showed multilayered synovial cells without pronounced villous proliferation. (**A,B** H&E stain, ×50)

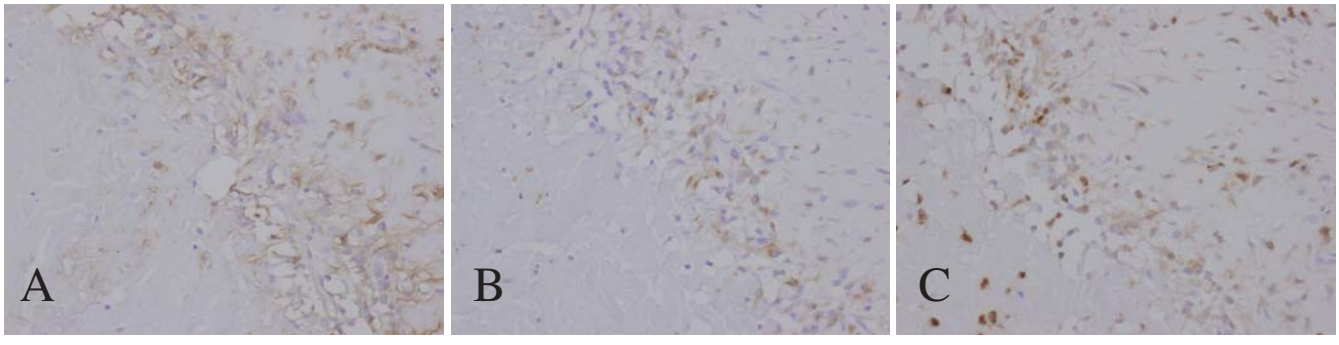

Fig. 2. A Immunohistochemical staining of the nodules showed that the epithelioid cells were positive for human leukocyte antigen-DR. Epithelioid cells in nodule were CD68-positive (**B**) and lysozyme-positive (**C**). (**A–C** ×50)

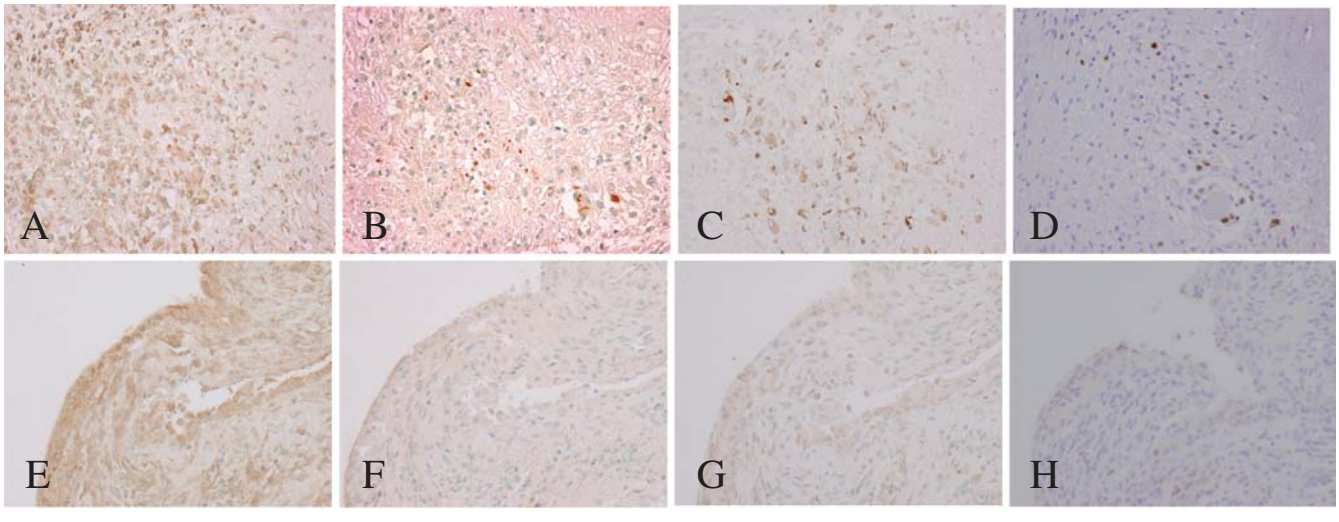

Fig. 3. A Epithelioid cells surrounding the necrotic center of the nodules expressed matrix metalloproteinase (MMP)-2 strongly. Some of the epithelioid cells were positive for MMP-3 (**B**), MMP-9 (**C**), and Ki67 (**D**). Immunohistochemical staining of synovial tissues showed MMP-2 expression (**E**), but MMP-3 (**F**), MMP-9 (**G**), and Ki67 (**H**) were not expressed. (**A–H** ×100)

All subcutaneous nodules were surgically excised. On gross examination at surgery, the nodules were grayish-white, firm, and adherent to the subcutaneous tissue.

Histopathologic study of the resected nodules showed amorphous necrotic substance surrounded by epithelioid cells in a palisading pattern, which is a typical picture of rheumatoid nodules. Lymphocytic infiltration was noted in the surrounding tissues (Fig. 1A). Synovial specimen harvested from the metatarsophalangeal (MTP) joint of the right great toe showed multilayered synovial cells. However, villous proliferation and cell infiltration were unremarkable (Fig. 1B).

Immunohistochemical staining of the rheumatoid nodules showed that the epithelioid cells surrounding the necrotic center of each nodule were positive for HLA-DR (Fig. 2A). These cells consisted of numerous CD68-positive and lysozyme-positive macrophages (Fig. 2B,C). Analysis of matrix metalloproteinase (MMP) expression indicated that MMP-2 was strongly expressed by the epithelioid cells. MMP-3, MMP-9, and the cell-cycle related gene Ki67 were also detected in some of the epithelioid cells surrounding the necrotic center of the nodules (Fig. 3A–D), suggesting the presence of active inflammatory granulomatous process. Synovial tissues also showed MMP-2 expression; however, MMP-3, MMP-9, and Ki67 were not expressed by the synovial lining cells or interstitial cells (Fig. 3E–H).

Discussion

In 1986, Kremer and Lee[1] reported the occurrence of multiple subcutaneous nodules in 3 out of 29 patients on MTX therapy. Subsequently, MTX-induced multiple subcutaneous nodules were reported by various authors,[2–5] including cases accompanied by other extra-articular lesions such as vasculitis and skin ulcers, and bronchiolitis obliterans with organizing pneumonia (BOOP). Interestingly, multiple rheumatoid nodules developed following improvement of arthritis by MTX therapy in all reported cases, including the present patient.

Spontaneous rheumatoid nodule is a typical manifestation of aggressive RA and is considered to be a consequence, at least in part, of common pathologic mechanisms of the disease. Analysis of cytokine profiles[6] in such spontaneous rheumatoid nodule suggests that the nodule is a Th1 granuloma and that the damage to synovial joint tissues and subcutaneous tissue is caused by the same inflammatory mechanism. However, the MTX-induced rheumatoid nodules, as observed in the present patient, show marked contrast to spontaneous rheumatoid nodule, in that the MTX-induced nodules develop after effective suppression of synovial lesions.

In the present study, the MTX-induced nodules showed numerous activated epithelioid cells and expression of MMP-3 and MMP-9, suggesting the active nature of the granuloma in spite of regressed synovial lesion. The pathomechanism of such differential effects of MTX on the synovium and rheumatoid nodule in certain susceptible individuals still remains to be clarified. As suggested by Merrill et al.,[7] MTX increases adenosine concentration and shows adenosine A2 receptor-mediated anti-inflammatory effect within joint, whereas in extra-articular tissue, adenosine at relatively lower concentration may enhance nodule formation via ligation of A1 receptor on macrophages. It is thought that the inflammatory process mediated by adenosine A1 receptor induces inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β, and subsequently these cytokines enhance the expression of MMP-3 and MMP-9 in the epithelioid cells of nodules.

Segal et al.[3] reported that all of their patients who developed multiple rheumatoid nodules during MTX therapy were positive for HLA-DR4, and this finding was supported by Jeurissen et al.[4] Ahmed et al.[8] reported that HLA-DRB1*0401 was detected in patients who developed MTX-induced nodulosis (at a frequency of 71.4%). However, HLA-DRB1*0401 was not found in the present patient. Since most of the reports of MTX-induced accelerated nodulosis have been in Caucasians, the immunogenetic background association in non-Caucasians remains to be determined.

In this study, the MTX-induced nodules were different from the synovial tissues in terms of MMP and Ki67 expression, which strongly suggests the presence of different pathologic mechanisms. Possible immunogenetic factors associated with the susceptibility to MTX are thought to be important for mechanisms of accelerated nodulosis, and should be clarified.

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