Mod Rheumatol (2004) 14:414–418
DOI 10.1007/s10165-004-0337-y

CASE REPORT

Takashi Kato · Yoshifumi Ubara · Naoki Sawa
Tetsuo Tagami · Hideyuki Katori · Fumi Takemoto
Akihide Tanimoto · Kenmei Takaichi

A case of rheumatoid arthritis exhibiting accelerating rheumatoid pleurisy during low-dose weekly methotrexate therapy

Received: February 2, 2004 / Accepted: July 2, 2004

Abstract A 75-year-old Japanese man suffering from rheumatoid arthritis (RA) had received methotrexate (MTX) treatment for 9 years and developed bilateral pleural thickening with exudative pleural effusions despite remission of the polyarthritis. A diagnosis of rheumatoid pleurisy, made by exclusion, was supported by the elevated rheumatoid factor level of the pleural fluid. The pleurisy developed concomitantly with MTX-induced leukocytopenia, and discontinuation of the MTX treatment partially improved the CRP level. These findings indicate a causal relation between the rheumatoid pleurisy and MTX and suggest that MTX therapy may be ineffective in the treatment of rheumatoid pleurisy. Treatment with 10 mg of prednisolone and 100 mg of cyclosporine A daily resulted in rapid resolution of the pleurisy. Although MTX-induced rheumatoid pleurisy is a rare condition, MTX therapy should be considered carefully in RA patients with concomitant rheumatoid pleurisy.

Key words Histology · Methotrexate (MTX) · Rheumatoid arthritis (RA) · Rheumatoid pericarditis · Rheumatoid pleurisy

Introduction

Pleurisy associated with rheumatoid arthritis (RA) is a relatively rare extraarticular manifestation of the disease and is detected in only about 5% of RA patients.[1] The pleurisy usually develops with the onset of the articular manifestations of RA.[2] Drug-induced pleurisy may rarely occur in RA patients receiving disease-modifying antirheumatic drugs (DMARDs) such as D-penicillamine as a manifestation of the triad of the yellow nail syndrome.[3] In this report, we describe a case of rheumatoid pleurisy developing during low-dose weekly methotrexate (MTX) therapy despite remission of the polyarthritis. MTX is an analogue of folic acid and a DMARD that has long-term efficacy for the articular synovitis of RA.[4–6] Although various adverse events of MTX such as interstitial pneumonitis, hematological toxicity, liver fibrosis, opportunistic infection, and nodulosis are well described,[4,5] the development of pleurisy in RA patients receiving MTX therapy is a rare occurrence, with only one previously reported case.[7] In addition, we discuss the relation between the development of rheumatoid pleurisy and MTX therapy.

Case report

A 75-year-old Japanese man was admitted to our hospital in June 2003 with a 1-week history of exertional dyspnea and right-sided chest pain. He developed RA in 1974. Despite the administration of several DMARDs, such as gold, D-penicillamine, and bucillamine, the polyarthritis remained persistently active. He developed progressive joint destruction necessitating left hip and right knee joint replacement in 1985 and a left knee joint replacement in 1990. He developed bilateral rheumatoid pleurisy in 1994. The pleurisy and the polyarthritis resolved immediately following treatment with 30 mg of prednisolone (PSL) daily and 7.5 mg of MTX weekly. However, the pleural thickening of the right lower lung field remained evident on the chest radiograph. Although MTX therapy was continued, the dosage of PSL was gradually tapered and eventually discontinued in 1996. Following a moderate flare of the polyarthritis, the dosage of MTX was increased to 8 mg per week, and 1 g of salazosulfapyridine (SASP) daily was added in 1999.

T. Kato[1] (✉) · Y. Ubara · N. Sawa · T. Tagami · H. Katori · F. Takemoto · K. Takaichi
Kidney Center, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan

A. Tanimoto
Division of Pathology, Toranomon Hospital, Tokyo, Japan

Present address:
[1] Department of Rheumatology, Kameda Medical Center, 929 Higashi-cho, Kamogawa 296-8602, Japan
Tel. +81-470-92-2211; Fax +81-470-93-0420
e-mail: kintarou@yc5.so-net.ne.jp

This treatment regimen resulted in amelioration of the polyarthritis, with the C-reactive protein (CRP) levels remaining around 2 mg/dl after SASP administration. In 2002, the chest radiograph revealed pleural thickening of the right lower lung field that was more prominent than the pleural thickening evident in 1994. In addition, there was no evidence of a pleural effusion in 2002. Folic acid was not administered during this time.

The patient's vital signs on admission included a temperature of 37.2°C, regular heart rate of 86 beats/min, and blood pressure of 154/94 mmHg. Physical examination revealed coarse crackles and dullness to percussion in the right dorsal lower thorax. Deformities of the hands included boutonnière's deformity and ulnar deviation. However, clinically, the right ankle was the only slightly swollen, tender joint. There was no history of morning stiffness, and skin lesions and rheumatoid nodules were absent. Yellow nails, ungual dystrophy, and oral ulceration were not detected. Mild pitting edema of the lower limbs was observed, but there was no neuropathy evident.

Laboratory findings were as follows: white blood cell count (WBC), 6.6 $\times$ 10^3/μl; hemoglobin, 10.0 g/dl; platelet count, 160 $\times$ 10^3/μl; total protein, 6.7 g/dl; albumin, 2.7 g/dl; total bilirubin, 0.4 mg/dl; serum urea nitrogen, 26 mg/dl; creatinine, 1.1 mg/dl; uric acid, 6.6 mg/dl; sodium, 145 mmol/l; potassium, 3.9 mmol/l; chloride, 110 mmol/l; calcium, 4.0 mEq/l; phosphorus, 3.1 mg/dl; aspartate aminotransferase (AST), 20 U/l; alanine aminotransferase (ALT), 10 U/l; lactic dehydrogenase (LDH), 134 U/l; alkaline phosphatase (ALP), 203 U/l; amylase, 64 U/l; creatine phosphokinase (CPK), 87 U/l; CRP, 17.5 mg/dl; ferritin, 215 ng/dl (normal 50–80 ng/dl); angiotensin-converting enzyme (ACE), 12.4 U/l (normal 8.3–21.4 U/l); KL-6, 300 U/ml (normal $<$ 500 U/ml). The serum matrix metalloproteinase-3 (MMP-3) level was normal at 78.4 μg/l (normal 36.9–121 μg/l). Serological findings were as follows: immunoglobulin G (IgG), 1440 mg/dl; IgA, 299 mg/dl; IgM, 94.7 mg/dl; C3, 120 mg/dl; C4, 19 mg/dl; CH_{50}, 60 U/ml; rheumatoid factor (RF), 40 U/ml (normal $<$ 10 U/ml); IgG-RF, 1.6 (normal $<$ 2); immune complex (C1q), 1.4 μg/ml (normal $<$ 3 μg/ml); antinuclear antibody (ANA) titer, 1:20; anti-double-stranded DNA antibody, 0.5 U/ml (normal $<$ 10 U/ml); anti-Ro (SS-A) and anti-La (SS-B) antibodies were negative; MPO-ANCA, 10 EU (normal $<$ 20 EU); PR3-ANCA, 10 EU (normal $<$ 20 EU). Cytomegalovirus (CMV) studies in blood and serum β-D-glucan were negative. The findings of blood gas analysis on room air were as follows: pH, 7.43; PCO_2, 40 mmHg; PO_2, 80 mmHg. Hand radiographs revealed joint erosion, narrowing of the joint spaces, and incomplete joint dislocations of the bilateral distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints. Cervical spine radiographs revealed horizontal atlantoaxial subluxation. Chest radiographs demonstrated bilateral pleural effusions and pleural thickening of the right lower lung field (Fig. 1A) comparable to that evident in 2002. A chest computed tomography (CT) scan revealed marked bilateral pleural thickening with pleural effusions together with pericardial thickening and a faint pericardial effusion (Fig. 2A). Abdominal ultrasonography did not reveal the presence of ascites, and there was no clinical or radiological evidence of cardiac tamponade.

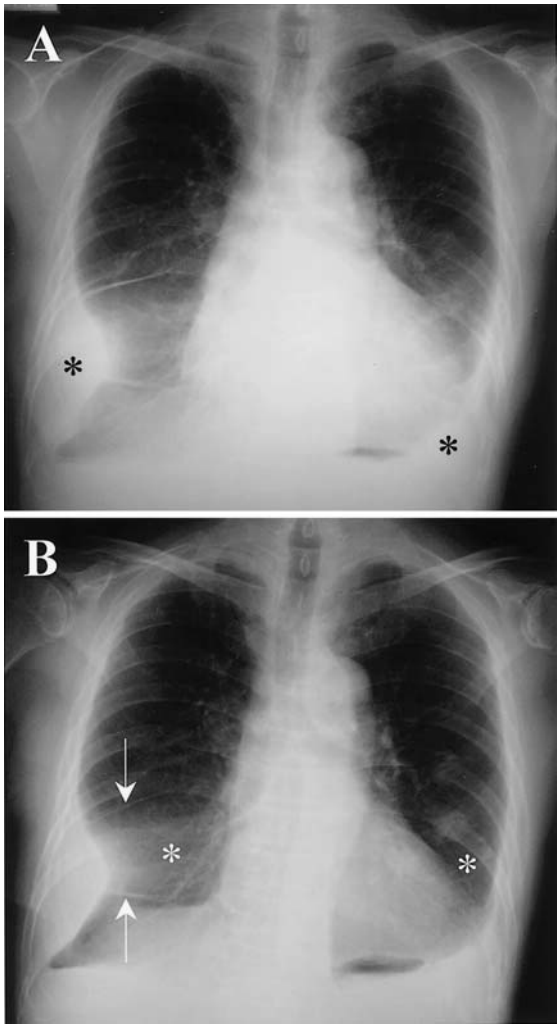

Fig. 1. A Chest radiograph obtained on admission. Thickening of the pleurae is prominent (*asterisks*). In addition, bilateral pleural effusions are evident. **B** Radiograph obtained on day 52 [10 days after start of prednisolone (PSL) and cyclosporine A (CyA) treatment]. The right interlobular pleural effusions (*arrows*) and the bilateral lower pleural effusions (*asterisks*) are decreased compared to that seen at admission

Thoracentesis was performed, and analysis of the yellow cloudy pleural effusion was as follows: specific gravity, 1.018; total protein, 4.8 g/dl; Rivalta's reaction, positive; LDH, 109 U/l; glucose level, 116 mg/dl; RF level, 68 U/ml (higher than the serum level of 40 U/ml); ACE level, 9.9 U/ml; no evidence of infectious organisms or neoplastic cells. These findings indicated that the fluid was an exudate with an elevated RF level. The physical, laboratory, and radiographic findings were consistent with long-standing RA with remitted articular manifestations (Steinbrocker class 2, stage III) and did not suggest the occurrence of any other collagen disease.

On day 8 of admission, the WBC count decreased to 2.8 $\times$ 10^3/μl. MTX therapy was discontinued but SASP continued to be given. On day 12, the WBC count was normal at 7.9 $\times$$10^3$/μl, and MTX-induced leukocytopenia was diag-

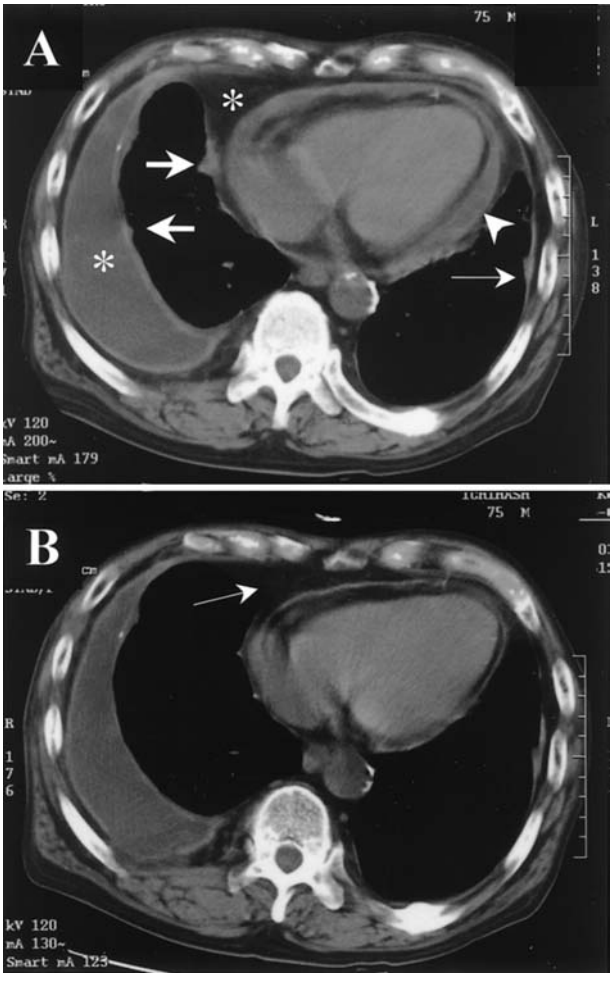

Fig. 2. **A** Chest computed tomography (CT) scan obtained on admission. The pleural effusion (*asterisks*) in the right lower thorax is surrounded by the markedly thickened parietal and visceral pleurae (*thick arrows*). The pleural thickening is also detected in the left thorax (*thin arrow*). The thickened pericardium (*arrowhead*) with faint pericardial effusion is shown. **B** Scan obtained on day 52 (10 days after the start of PSL and CyA treatment). Note the reduction in pleural and pericardial thickening. In addition, the right ventral lower thoracic pleural effusion is markedly decreased (*arrow*)

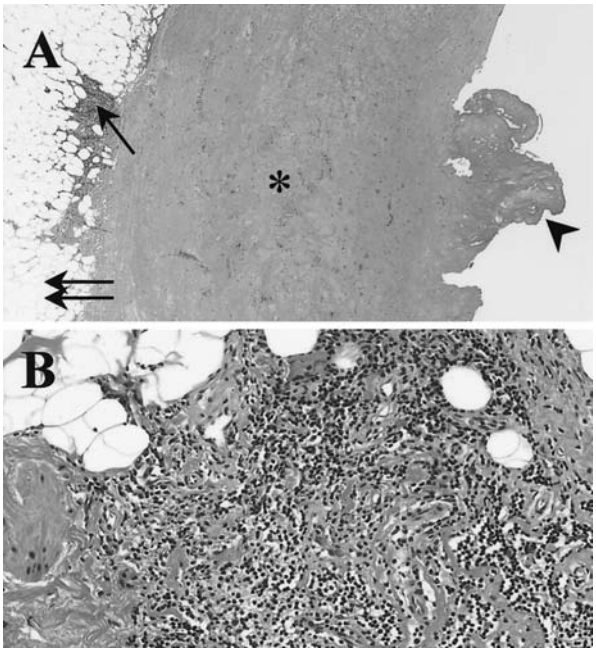

Fig. 3. Histology of the parietal pleural biopsy. **A** Superficial fibrinoid deposit (*arrowhead*), hyalinization of the markedly thickened pleura (*asterisk*), and lymphocytic infiltration (*arrow*) at the boundary between the pleura and the subjacent adipose tissue (*double arrows*). The right is the inner side and the left is the outer side of the thoracic cavity. Angiogenesis is occasionally observed in the hyalinized pleura. **B** Lymphocytic infiltration shown in **A**. A few plasma cells are also observed. Giant cells are not observed in the sample. (**A** H&E, ×40. **B** H&E, ×200)

nosed. On day 19, the CRP level had fallen to 6.3 mg/dl. However, the pleuritic symptoms and the moderately elevated CRP level (about 10 mg/dl) persisted. Thoracoscopic biopsy of the right parietal pleura was performed on day 35. Histological analysis revealed an extremely thickened hyalinized parietal pleura with fibrinoid deposits in the superficial pleura and lymphocytic infiltration at the boundary between the pleura and the subjacent adipose tissue. There was no evidence of malignancy (Fig. 3). The drug-induced lymphocyte stimulation test (DLST) against MTX was positive, with a stimulation index of 276% (normal < 180%).

On day 42, a diagnosis of rheumatoid pleurisy and pericarditis was made, and daily treatment with 10 mg of prednisolone (PSL) and 100 mg of cyclosporine A (CyA) commenced. Immediately after the start of the treatment, the pleuritic symptoms dramatically resolved. On day 52, the chest radiograph revealed a reduction in the pleural effusions (Fig. 1B), and the chest CT scan revealed some resolution of the pleural and pericardial thickening and a reduction in the pleural effusions (Fig. 2B). In addition, the CRP level had decreased to 0.4 mg/dl, and the vital capacity (VC) had increased from 1.61 to 2.01 (74% of the predicted value). After discontinuing MTX therapy, there was no relapse of rheumatoid symptoms including polyarthritis and morning stiffness.

Discussion

The efficacy of low-dose weekly MTX therapy for the articular symptoms of RA was confirmed by randomized controlled clinical trials during the 1980s.[8–10] Furthermore, the long-term efficacy and tolerability of the treatment were demonstrated during the early 1990s.[5,6] On the other hand, adverse events such as interstitial pneumonitis, hematological toxicity, liver fibrosis, opportunistic infection, and the new development of rheumatoid nodules (nodulosis) are also reported.[4,5] Interestingly, nodulosis, an extraarticular manifestation of RA, may be triggered by MTX therapy despite resolution of the polyarthritis.[4,11]

In our case, although the polyarthritis was in remission according to clinical criteria and other parameters such as the serum MMP-3 level,[12] the patient developed rheuma-

toid pleurisy during MTX therapy. This suggests that the markedly elevated CRP level on admission reflected the activity of rheumatoid pleurisy rather than the polyarthritis. The diagnosis of rheumatoid pleurisy was made by exclusion in our case, although the elevated RF level of the pleural fluid supports the diagnosis, as this finding is a specific characteristic of rheumatoid pleurisy and suggests local production of RF in the affected pleura.[13] Abu-Shakra et al. reported a similar case in which rheumatoid nodules, rheumatoid pleurisy, and pericarditis developed during MTX therapy despite achieving clinical remission of the polyarthritis.[7] They speculated that MTX therapy might also trigger the development of rheumatoid pleurisy because the development of the pleurisy was accompanied by deterioration of the rheumatoid nodules and resolved after discontinuation of MTX therapy concomitant with PSL administration.[7] In our case, findings such as MTX-induced leukocytopenia concomitant with the development of the pleurisy and reduced CRP level following discontinuation of the MTX therapy are strongly suggestive of a causal relation between the development of pleurisy and MTX therapy. MTX toxicity is enhanced in the case with pleural effusion because MTX may be stored in the effusion and serum MTX concentration may increase.[14] In our case, once the pleural effusion due to rheumatoid pleurisy developed concomitantly with exertional dyspnea, serum MTX concentration might increase and the pleurisy might deteriorate progressively, accompanied by the leukocytopenia induced by MTX. Although the positive result in the DLST against MTX may be another finding of MTX-induced pleurisy, DLST is not a reliable system during MTX therapy.[15] Because MTX deprives thymidilate synthetase, de novo synthesis of thymidine is prevented. The intracellular pools of thymidine then decrease and MTX-treated cells rely on exogenous (i.e., radiolabeled) thymidine. As a result, DLST can become positive during MTX treatment even when the lymphocytic response to the mitogen-stimulation is absent.[15]

Although rheumatoid pleurisy has been diagnosed by exclusion, some reports propose that it is accompanied by specific pathological features: (1) a superficial layer of fibrinoid and necrotic debris; (2) a subjacent palisading layer (pseudostratified layer of epithelioid cells); and (3) profound granulation tissue with lymphocytes, plasma cells, and occasional giant cells.[16–18] Champion et al. noted that the appearance of rheumatoid pleurisy may be likened to that of an "opened out" rheumatoid nodule, exposing the fibrinoid zone to the thoracic cavity.[16] In our case, the histological findings of the affected parietal pleura are not fully consistent with the appearance of rheumatoid pleurisy reported previously. However, the superficial fibrinoid deposition and the profound lymphocytic infiltration resemble the histological appearance of rheumatoid pleurisy, except the palisading layer. Furthermore, although the hyalinization and marked thickening of the pleura observed in our case are nonspecific findings, they may be consistent with prolonged active inflammation.[19] In addition, it is suggested that the pleural thickening of the right lung had persisted since 1994 according to the findings of the previous chest radiographs. These findings may be compatible with the result of long-standing active rheumatoid pleurisy augmented by MTX therapy over a period of 9 years. In fact, the typical histological findings of the pleurisy are observed only in the early phase (less than 4 months after the onset of the pleurisy).[16] Because the histological findings of long-standing rheumatoid pleurisy are not available, the histological findings observed in our case may represent the typical appearance of long-standing rheumatoid pleurisy.

In view of the histological similarities between the rheumatoid pleural membrane and rheumatoid nodules, a similar pathological process may underlie both of these extraarticular manifestations. In rheumatoid nodules, monocytes continue to be recruited and migrate from the outer vascular zone toward the palisading and central necrotic area, with maturation of the cells taking place during migration.[20] Thus, activation of monocytes may play a crucial role in the development of rheumatoid nodules. Although the pathological process of rheumatoid pleurisy is unclear, it is likely that monocyte activation is also involved actively in the development of rheumatoid pleurisy. The anti-inflammatory effects of MTX on the articular synovitis of RA are mediated by an increased extracellular concentration of adenosine, which binds to adenosine A2 receptors.[21,22] On the other hand, Merrill et al. demonstrated that monocyte activation is markedly increased by MTX through adenosine A1 receptors and not adenosine A2 receptors, such that MTX can accelerate the formation of rheumatoid nodules.[23] In our case, the different signal pathways of MTX, through adenosine A1 or A2 receptors, may account for the discrepancy between the active pleurisy and the polyarthritis that underwent resolution during MTX therapy. Indeed, the extremely thickened pleurae evident in our case may result from prolonged stimulation of MTX through adenosine A1 receptors, resulting in continuous activation of monocytes in the affected regions.

In our case, SASP is not thought to have caused the pleurisy, as it improved without discontinuing SASP. SASP-induced pulmonary toxicity is rare, but eosinophilic pneumonia and interstitial pneumonia have been reported as being SASP-induced lung diseases.[24] In addition, chest pain suggesting the occurrence of pleurisy is not a consistent finding of SASP-induced pulmonary disease.[24]

Finally, the findings in our case suggest that MTX therapy may be ineffective in the treatment of rheumatoid pleurisy and may actually augment it. Hence, MTX therapy should be carefully evaluated before using it to treat RA patients with concomitant rheumatoid pleurisy.

Acknowledgment The authors thank Dr. T. Kono for the excellent surgical procedure used for the further investigation of this patient.

References

1. Blackburn WD Jr, Chatham WW. Laboratory findings in rheumatoid arthritis. In: Koopman WJ, ed. Arthritis and allied condition. 14th ed. Philadelphia: Lippincott; 2001. p. 1202–22.

2. Harris ED. Clinical features of rheumatoid arthritis. In: Ruddy S, Harris ED, Sledge CB, eds. Kelly's textbook of rheumatology. 6 ed. Philadelphia: Saunders; 2001. p. 967–1000.
3. Lehuédé G, Toussirot E, Despaux J, Michel F, Wendling D. Yellow nail syndrome associated with thiol compound therapy for rheumatoid arthritis: two case reports. Joint Bone Spine 2002;69:406–8.
4. Graciela SA. Methotrexate: its use for the treatment of rheumatoid arthritis and other rheumatic disorders. In: Koopman WJ, ed. Arthritis and allied condition. 14th ed. Philadelphia: Lippincott. 2001. p. 734–68.
5. Weinblatt ME, Weissman BN, Holdsworth DE, Fraser PA, Maier AL, Falchuk KR, et al. Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis, 84-month update. Arthritis Rheum 1992;35:129–37.
6. Weinblatt ME, Laplan H, Germain BF, Black S, Solomon SD, Merriman RC, et al. Methotrexate in rheumatoid arthritis: a five-year prospective multicenter study. Arthritis Rheum 1994;37: 1492–8.
7. Abu-Shakra M, Nicol P, Urowitz MB. Accelerated nodulosis, pleural effusion and pericardial tamponade during methotrexate therapy. J Rheumatol 1994;21:934–7.
8. Andersen PA, West SG, O'Dell JR, Via CS, Claypool RG, Kotzin BL. Weekly pulse methotrexate in rheumatoid arthritis: clinical and immunologic effects in a randomized, double-blind study. Ann Intern Med 1985;103:489–96.
9. Williams HJ, Willkens RF, Samuelson CO Jr, Alarcon GS, Guttadauria M, Yarboro C, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 1985;28:721–30.
10. Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth ED, Glass DN, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 1985;28:818–22.
11. Kerstens PJSM, Boerbooms AMT, Jeurissen MEC, Fast JH, Assmann KJM, van de Putte LBA. Accelerated nodulosis during low dose methotrexate therapy for rheumatoid arthritis, an analysis of ten cases. J Rheumatol 1992;19:867–71.
12. Katrib A, Smith MD, Ahern MJ, Slavotined J, Stafford L, Cuello C, et al. Reduced chemokine and matrix metalloproteinase expression in patients with rheumatoid arthritis achieving remission. J Rheumatol 2003;30:10–21.
13. Halla JT, Koopman WJ, Schrohenloher RE, Darby WL, Heck LW. Local synthesis of IgM and IgM rheumatoid factor in rheumatoid arthritis. J Rheumatol 1983;10:204–9.
14. Evans WE, Pratt CB. Effect of pleural effusion on high-dose methotrexate kinetics. Clin Pharmacol Ther 1978;23:68–72.
15. Afane M, Ramos F, Chassagne J, Dubost JJ, Galtier B, Sauvezie B. Discrepancy between ^{3}H-thymidine uptake and cell cycle studies in stimulated lymphocyte cultures treated with methotrexate. Clin Exp Rheumatol 1989;7:603–8.
16. Champion GD, Robertson MR, Robinson RG. Rheumatoid pleurisy and pericarditis. Ann Rheum Dis 1968;27:521–30.
17. Faurschou P, Francis D, Faarup P. Thoracoscopic, histological, and clinical findings in nine cases of rheumatoid pleural effusion. Thorax 1985;40:371–5.
18. Aru A, Engel U, Francis D. Characteristic and specific histological findings in rheumatoid pleurisy. Acta Pathol Microbial Immunol Scand A 1986;94:57–62.
19. Cellular pathology. II. Adaptations, intracellular accumulations and cell aging. In: Cotran RS, Kumar V, Collins T, eds. Robbins pathologic basis of disease. 6th ed. Philadelphia:Saunders; 1999. p. 31–49.
20. Palmer DG, Hogg N, Highton J, Hessian PA, Denholm I. Macrophage migration and maturation within rheumatoid nodules. Arthritis Rheum 1987;30:728–36.
21. Cronstein BN, Naime D, Ostad E. The anti-inflammatory mechanism of methotrexate. J Clin Invest 1993;92:2675–82.
22. Cronstein BN, Eberle MA, Gruber HE, Levin RI. Methotrexate inhibits neutrophil function by stimulating adenosine release from connective tissue cells. Proc Natl Acad Sci USA 1991;88:2441–5.
23. Merrill JT, Shen C, Schreibman D, Coffey D, Zakharenko O, Fisher R, et al. Adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes. Arthritis Rheum 1997;40:1308–15.
24. Parry SD, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. Eur Respir J 2002;19:756–64.