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# Rheumatoid arthritis associated with methotrexate-induced pneumonitis: Improvement with i.v. cyclophosphamide therapy

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**ABSTRACT**

*Pneumonitis is one of the most serious adverse effects associated with low-dose weekly methotrexate (MTX) therapy. Immediate cessation of MTX, and the introduction of oxygen therapy and glucocorticoids usually results in a dramatic improvement in the pulmonary toxicity. We report here a case of MTX-induced pneumonitis in a patient with rheumatoid arthritis (RA). Severe hypoxemia and interstitial infiltration in both lung fields did not respond to the withdrawal of MTX and the administration of oxygen and steroid pulse therapy. When intravenous cyclophosphamide (CYC) pulse therapy was initiated, however, rapid physiologic and radiographic improvement was seen. Our case suggests that CYC treatment may have a beneficial effect on MTX-induced pneumonitis that is resistant to steroid therapy.*

## Introduction

Low-dose pulse methotrexate (MTX) is now widely used in the treatment of rheumatoid arthritis (RA) (1, 2). MTX-induced pneumonitis is a serious adverse drug effect seen during the treatment of RA (3-5). Although fatal outcomes have been described, the pneumonitis usually responds rapidly the withdrawal of MTX and to the introduction of glucocorticoid therapy (5-7). We describe here a patient with RA who developed MTX-induced pneumonitis that responded to intravenous cyclophosphamide (CYC) pulse therapy.

## Case report

In January 1994 a 66-year-old woman developed polyarthritis. Hand roentgenograms showed periarticular demineralization and marginal erosions. A diagnosis of RA was made, and treatment with auranofin was attempted but abandonned due to adverse side effects. Treatment with salazosulfapyridine and mizoribine was also ineffective. The patient was maintained on a regimen of diclofenac 75 mg/day and prednisolone (PSL) 5 mg/day. Starting on 3 September 1997, MTX (5 mg/week) was administered orally. After 3 weeks the MTX dose was increased to 7.5 mg/week.

On September 30 the patient developed progressive dyspnea on exertion, a non-productive cough, and low-grade fever. MTX (total cumulative dose 22.5 mg) was immediately discontinued, and the patient was admitted to Tokyo Metropolitan Ohtsuka Hospital. Her case was complicated by diabetes mellitus for which she had been taking glibenclamide for one year. There were no sicca symptoms nor salivary gland enlargement. She did not smoke, had no history of toxic gas inhalation or pulmonary disease, and had normal findings on chest roentgenogram one year before her admission.

Examination revealed an ill-appearing, confused woman in severe respiratory distress. Vital signs were as follows: blood pressure 150/90 mmHg; pulse rate 92 per min; respiration 30 per min; temperature 38.0°C. Dry inspiratory crackles were heard in both lungs. Findings from the cardiovascular examination were normal. Musculoskeletal examination demonstrated mild synovitis.

Laboratory findings included an ESR of 71 mm/hr (Westergren); urinalysis normal; white blood cell count 6,100/$mm^3$ (eosinophils 366/$mm^3$); red blood cell count 334 x $10^4$/$mm^3$; platelet count 30.4 x $10^4$/$mm^3$; fibrinogen 351 mg/dl (normal < 400); D-D dimer 272 ng/ml (normal < 150); albumin 2.9 g/dl (normal > 3.8); blood urea nitrogen 18 mg/dl (normal < 23); creatinine 6 mg/l (normal < 12); lactic dehydrogenase 241 IU/L (normal < 220); glucose 128 mg/dl (normal < 110); HbA1 8.5% (normal < 8.0); $HbA_1C$ 6.3% (normal < 6.0); C-reactive protein, 6.3 mg/dl (normal < 0.4); and orosomucoid 163 mg/dl (normal < 90). An antinuclear antibody study was negative, and antibodies to SS-A/Ro and SS-B/La were not detected. The rheumatoid factor was 27 IU/mL (normal < 10). Immunoglobulins were normal. Serologic tests were negative for herpes simplex virus, herpes zoster virus, and cytomegalovirus. Candida albicans antigen was not detected in a blood sample. HLA-class II DNA typing indicated DRB1* 0101/*1406. Arterial blood gases in room air showed $PO_2$ 54 mmHg, $PCO_2$ 34 mmHg, and pH 7.45. Gram stain and cultures of sputum showed only normal flora.

A chest roentgenogram revealed bilateral, diffuse alveolar and interstitial in-

filtrates most prominent in the lower lobes. Computed tomography of the chest showed heterogeneous ground glass opacities (Fig. 1A). A gallium-67 scan showed increased uptake in the bilateral lungs. Fiberoptic bronchoscopy was performed on the day of admission and the findings were normal. Bronchoalveolar lavage (BAL) was carried out in the right middle lobe (50 ml aliquots 3 times); the cell count was 530 x $10^3$/ml with 44% lymphocytes. The T-cell subpopulation revealed CD3 96%, CD4 66%, and CD8 22% (CD4:CD8 ratio 3.0). Stains and cultures for bacteria, acid-fast organisms, and *Pneumocystis carinii* were negative. A transbronchial lung biopsy (TBLB) was performed in the left middle and lower lobes. Histologic examination revealed interstitial fibrotic thickening of the alveolar septa with mononuclear cell infiltration (Fig. 2).

The histological findings, together with the absence of any positive evidence for an infective cause, were felt to be consistent with an acute pneumonitis related to MTX use. Supportive oxygen therapy was started on admission. The patient initially received methylprednisolone (1,000 mg i.v.) for 3 days, followed by oral prednisolone (PSL) 30 mg/day. A second course of therapy was administered a week later. Despite aggressive therapy, she developed progressively increasing dyspnea on exertion and a non-productive cough. Serum level of glucose rose to 184 mg/dl. Arterial blood gases in room air showed a $PO_2$ 34 mmHg, $PCO_2$ 35 mmHg, and pH 7.45 on December 24.

Immunosuppressive therapy was instituted with 500 mg of CYC intravenously in addition to 10 mg daily of PSL. Within 3 weeks after the initiation of CYC, the patient's dyspnea and cough lessened. After 4 weeks, 500 mg of CYC was given again intravenously. Serum levels of acute-phase proteins became normal or decreased markedly. Chest roentgenogram and computed tomography of the chest showed gradual improvement in the diffuse interstitial infiltration over both lung fields (Fig. 1B). A gallium-67 scan gave negative results. Arterial blood gases in room air showed $PO_2$ 77 mmHg, $PCO_2$ 39 mmHg, and pH 7.41 on 3 March 3 1998. The patient was discharged on tapering doses of PSL on March 20 without any clinically relevant adverse events, and was still well 16 weeks after her discharge.

**Discussion**

The proposed diagnostic criteria for MTX-induced pneumonitis include: (i) acute onset of dyspnea; (ii) fever (> 38.0° C); (iii) tachypnea and non-productive cough; (iv) WBC count ≤ 15,000/$mm^3$ (with or without eosinophilia); (v) $PO_2$ < 55 mmHg at admission; (vi) negative blood and sputum cultures; (vii) pulmonary interstitial or alveolar infiltrates on chest radiograph; (viii) restrictive pulmonary function with decreased diffusion; and (ix) histologic evidence of parenchymal lung disease developing during MTX therapy (8). The clinical features in this patient were consistent with the above criteria except for the results of pulmonary function tests.

The risk factors for MTX-induced pneumonitis include advanced age, pre-existing rheumatoid pleuropulmonary involvement, previous use of disease-modifying anti-rheumatic drugs (DMARDs), adverse reactions to DMARDs, a low serum albumin level, and diabetes mellitus (9, 10). Our patient had all of these risk factors except for pre-existing rheumatoid pleuropulmonary involvement. It has been mentioned that an immunogenetic factor might contribute to the occurrence of MTX-induced pneumonitis

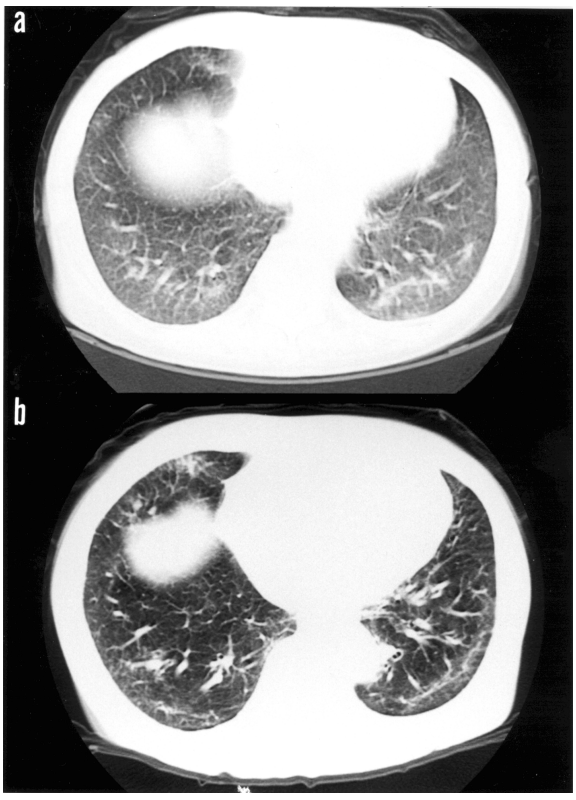


**Fig. 1.** (**a**) Heterogenous ground glass opacities on computed tomography of the chest upon admission; (**b**) resolution two months after the initiation of cyclophosphamide therapy.

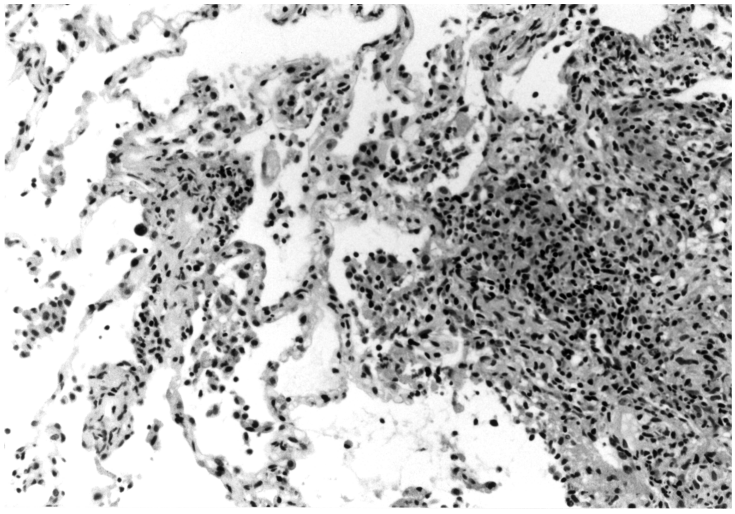

**Fig. 2.** Transbronchial lung biopsy specimen showing thickening of the alveolar septa with lymphocytic interstitial infiltrate (hematoxylin & eosin staining, x 200).

(7). A possible relationship between an increased risk of pulmonary toxicity and certain HLA haplotypes such as A2, 24, DRw3, and DR4 has been previously shown, although our patient did not have those haplotypes (7).

The mechanism of MTX-induced pneumonitis remains unclear (7), but several findings suggest that MTX-related pulmonary toxicity occurs due to a hypersensitivity reaction, i.e.: a relatively short duration of MTX use, peripheral eosinophilia, interstitial pneumonitis and granuloma formation in TBLB, and increased lymphocytes with a reversed CD4/CD8 ratio in BAL (7). In our case, the pulmonary toxicity occurred with the administration of a low dose of MTX for only one month (5 - 7.5 mg/week, total dose 22.5 mg). Although the patient did not have eosinophilia, she did exhibit characteristic findings on TBLB and BAL, thus supporting the hypothesis.

The initial step for the treatment for MTX-induced pneumonitis is the immediate cessation of MTX and the introduction of supportive oxygen therapy (7). Steroids have been advocated for the treatment of MTX-induced pneumonitis and usually dramatically improve the symptoms and signs relating to pulmonary toxicity (7, 11). Although some patients have recovered without steroid therapy, it is considered that steroids can hasten the recovery and high doses are recommended until clinical improvement is evident (6, 7, 11, 12). A review of previous reports showed only one report of the efficacy of a drug other than steroids for MTX-induced pneumonitis; treatment with daunorubicine proved effective in 3 leukaemia patients with MTX-induced pneumonitis (13).

CYC is an immunosuppressive agent with important effects on the immune system, such as the inhibition of immunoglobulin production from B lymphocytes and the modulation of T lymphocyte activation (14). CYC has proven efficacious in the treatment of the severe manifestations of systemic lupus erythematosus, such as proliferative glomerulonephritis, central nervous system involvement, severe thrombocytopenia, and pneumonitis (14-20). CYC may have a beneficial effect on pulmonary fibrosis in patients with systemic sclerosis and elevated levels of acute-phase proteins (21). Steen *et al.* (22) also reported that CYC produced a more significant improvement in pulmonary function than did high-dose PSL, D-penicillamine, or other immunosuppressive agents to treat interstitial lung disease in systemic sclerosis. Because two courses of high-dose steroid therapy were not effective and prolonged steroid therapy might have worsened the diabetes mellitus in our patient, CYC was administered intravenously in association with PSL and improvement in the symptoms and laboratory findings was observed. It is unclear why this patient showed a poor response to high-dose steroid therapy.

The present case suggests that CYC therapy may be useful in the treatment of MTX-induced pneumonitis that is unresponsive to steroid therapy and in which steroid administration is contraindicated because of its adverse effects. It is possible that a combination of CYC and PSL may be more effective than PSL alone or CYC alone. CYC is known to cause several severe adverse drug effects (14). Furthermore, interstitial pneumonitis induced by CYC also has been reported (23-25). Therefore, it is necessary to administer CYC cautiously and to carefully monitor its effects.

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**References**

1. WEINBLATT ME, WEISSMAN BN, HOLDSWORTH DE *et al.*: Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1992; 35: 129 -37.
2. KREMER JM, PHELPS CT: Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis: Update after a mean of 90 months. *Arthritis Rheum* 1992; 35: 138-45.
3. CANNON GW, WARD JR, CLEGG DO, SAMUELSON CO JR, ABBOTT TM: Acute lung disease associated with low-dose pulse methotrexate therapy in patients with rheumatoid arthritis. *Arthritis Rheum* 1983; 26: 1269-74.
4. ENGELBRECHT JA, CALHOON SL, SCHERRER JJ: Methotrexate pneumonitis after low-dose therapy for rheumatoid arthritis. *Arthritis Rheum* 1983; 26: 1275-8.
5. ST CLAIR EW, RICE JR, SNYDERMAN R: Pneumonitis complicating low-dose methotrexate therapy in rheumatoid arthritis. *Arch Intern Med* 1985; 145: 2035-8.
6. GISPEN JG, ALARCON GS, JOHNSON JJ, ACTON RT, BARGER BO, KOOPMAN WJ: Toxicity to methotrexate in rheumatoid arthritis. *J Rheumatol* 1987; 14: 74-9.
7. BARRERA P, LAAN RFJM, VAN RIEL PLCM, DEKHUIJZEN PNR, BOERBOOMS AMTH, VAN DE PUTTE LBA: Methotrexate-related pulmonary complications in rheumatoid arthritis. *Ann Rheum Dis* 1994; 53: 434-9.
8. SEARLES G, MCKENDRY RJR: Methotrexate pneumonitis in rheumatoid arthritis: potential risk features. Four case reports and a review of literature. *J Rheumatol* 1987; 14: 1164-71.
9. ALARCON GS, KREMER JM, MACALUSO M *et al.*: Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis: A multicenter, case control study. *Ann Intern Med* 1997;127:356-64.
10. OHOSONE Y, OKANO Y, KAMEDA H *et al.*: Clinical characteristics of patients with rheumatoid arthritis and methotrexate induced pneumonitis. *J Rheumatol* 1997; 24:2299-303.
11. SOSTMAN HD, MATTHAY RA, PUTNAM CE, SMITH GJ: Methotrexate-induced pneumonitis. *Medicine* 1976; 55: 371-88.
12. CLARYSSE AM, CATHEY WJ, CARTWRIGHT GE, WINTROBE MM: Pulmonary disease complicating intermittent therapy with methotrexate. *JAMA* 1969; 209: 1861-4.
13. PASQUINUCCI G, FERRARA P, CASTELLARI R: Daunorubicine treatment of methotrexate pneumonia. *JAMA* 1971; 216: 2017.
14. FOX DA, MCCUNE WJ: Immunosuppressive drug therapy of systemic lupus erythematosus. *Rheum Dis Clin North Am* 1994; 20: 265-99.
15. BALOW JE, AUSTIN HA, TSOKOS GC, ANTONOVYCH TT, STEINBERG AD, KLIPPEL JH: NIH Conference: lupus nephritis. *Ann Intern Med* 1987; 106: 79-94.
16. NEUWELT CM, LACKS S, KAYE BR, ELLMAN JB, BORENSTEIN DG: Role of intravenous cyclophosphamide in the treatment of severe neuropsychiatric systemic lupus erythematosus. *Am J Med* 1995; 98: 32-41.
17. BOUMPAS DT, AUSTIN HA, VAUGHN EM *et al.*: Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; 340: 741-5.
18. BOUMPAS DT, BAREZ S, KLIPPEL JH, BALOW JE: Intermittent cyclophosphamide for the treatment of autoimmune thrombocytopenia in systemic lupus erythematosus. *Ann Intern Med* 1990; 112: 674-7.
19. SCHROEDER JO, EULER HH, LOFFLER H: Synchronization of plasmaphresis and pulse cyclophosphamide in severe lupus erythematosus. *Ann Intern Med* 1987; 107: 344-6.
20. FUKUDA M, KAMIYAMA Y, KAWAHARA K, KAWAMURA K, MORI T, HONDA M: The favorable effect of cyclophosphamide pulse therapy in the treatment of massive pulmonary hemorrhage in systemic lupus erythematosus. *J Pediatr* 1994; 153: 167-70.
21. AKESSON A, SCHEJA A, LUNDIN A, WOLLHEIM FA: Improved pulmonary function in systemic sclerosis after treatment with cyclo-

phosphamide. *Arthritis Rheum* 1994; 5: 729-35.
22. STENN VD, LANZ JK JR, CONTE C, OWENS GR, MEDSGER TA JR: Therapy for severe interstitial lung disease in systemic sclerosis: A retrospective study. *Arthritis Rheum* 1994; 8: 1290-6.
23. MAHENDRA P, HOOD IM, LEE MA *et al.*: Interstitial pneumonitis as a late complication of high dose therapy with cyclophosphamide/thiotepa and peripheral blood progenitor cell rescue for carcinoma of the breast. *Clin Oncol* 1996; 8: 198-200.
24. MALIK SW, MYERS JL, DEREMEE RA, SPECKS U: Lung toxicity associated with cyclophosphamide use: Two distinct patterns. *Am J Respir Crit Care Med* 1996;154:1851-6.
25. HARIGAYA H, MATSUBARA K, NIGAMI H, BABA K: Interstitial pneumonitis probably induced by cyclophosphamide in nephrosis. *Acta Paediatr Jpn* 1997; 39: 364-7.