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# Methotrexate-Induced Pneumonitis in Patients with Rheumatoid Arthritis and Psoriatic Arthritis: Report of Five Cases and Review of the Literature

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*Summary* **Pneumonitis is emerging as one of the most unpredictable and potentially serious, adverse effects of treatment with MTX. Its prevalence in rheumatoid arthritis (RA) has been estimated from several retrospective and prospective studies to range from 0.3% to 18%. On the other hand, MTX-induced pneumonitis seems to be very rare in psoriatic arthritis (PsA).**

**Our review of 194 RA patients and 38 PsA patients receiving MTX has identified four RA patients and one PsA patient with MTX-induced pneumonitis, giving a prevalence of 2.1% and 0.03%, respectively. Diagnosis was suggested by clinical history and radiographic findings, but the bronchoalveolar lavage plays an important role both in excluding infectious agents and in providing information for understanding the pathogenesis of lung injury. The presence of a lymphocyte alveolitis with a predominance of CD4+ T cells in 3 RA patients and CD8+ T cells with a concomitant increase in neutrophils in another case suggests that immunologically mediated reactions may be one damage mechanism in MTX-induced pneumonitis. Although risk factors for MTX-induced pulmonary toxicity are poorly understood, the presence in 3 out of 5 of our patients of pre-existing lung disease, represented by diffuse interstitial changes on chest X-ray, and mild bronchial asthma in two RA patients and by pulmonary silicosis in the patient with PsA may account for a predisposition to the development of MTX pneumonitis.**

*Key words* **Methotrexate, Pneumonitis, Rheumatoid Arthritis, Psoriatic Arthritis, Bronchoalveolar Lavage.**

## INTRODUCTION

The value of low dose methotrexate (MTX) in the treatment of refractory rheumatoid arthritis (RA) (1-6) and severe and disabling psoriatic arthritis (PsA) is well established (7).

Pneumonitis is emerging as one of the most unpredictable and potentially serious adverse effects of treatment with MTX (1-5,819). The prevalence in RA has been estimated from several retrospective and prospective studies to range from 0.3% (20) to 18% (21). On the other hand, MTX-induced pneumonitis seems to be very rare in PsA. The clinical manifestations of this disorder have been described in detail, (8,10,11,15,22-26), but the mechanism of lung injury is unknown. Moreover, the diagnosis remains difficult to establish since no pathognomonic clinical, laboratory or radiological features which allow differentation between infectious and non-infectious pulmonary disease (except for the isolation of a pathogenic micro-organism) have been described. Although no predisposing factors for the development of MTX pneumonitis are known, abnormalities on chest radiographs or preexisting pulmonary disease, smoking, use of acetylsalycilic acid and abnormal renal function have been suggested to increase the risk of pulmonary toxicity (11,21,24,27-29).

Our aims were to describe five additional patients with MTX pneumonitis, estimate the prevalence and identify risk factors. Further, to help clarify the pathogenesis of lung injury in this disorder, we used bronchoalveolar lavage (BAL) to study the immune response of the low-

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er respiratory tract in these patients compared to a control group of RA patients receiving MTX without evidence of pulmonary toxicity (MTX controls).

## METHODS

Between 1989 and 1995, 194 patients with RA as defined by the 1987 ARA criteria (30) and 38 with psoriatic arthritis (PsA) diagnosed according to the criteria suggested by Moll and Wright (31) began MTX therapy (5-15 mg/week). Treatment was conducted at the Department of Rheumatology, University of Ancona (108 patients with RA and 22 with PsA) and at the Rheumatic Disease Unit, University of Parma (86 patients with RA and 16 with PsA). They were monitored at regular intervals by their primary care physician and reviewed on a six month basis by a rheumatologist (FS, PM). During this period, five patients (4 with RA and 1 with PsA) were hospitalised with a syndrome consistent with MTX pneumonitis. For this study, we used the diagnostic criteria advocated by Searles and McKendry (11): 1) acute onset of shortness of breath; 2) fever > 38°C; 3) tachypnoea ≥ 28/min and a non-productive cough; 4) radiological evidence of pulmonary interstitial or alveolar infiltrates; 5) white cell count ≤ $15.0 \times 10^{12}$/l; 6) negative blood and sputum cultures; 7) pulmonary function tests (PFT) showing restrictive pulmonary function with decreased diffusion capacities; 8) $PaO_2$ < 55 mmHg on room air at time of admission; and 9) histopathology consistent with bronchiolitis or interstitial pneumonitis. The diagnosis is definite if ≥ 6/9 criteria are present, probable if 5/9 are present and possible if 4/9 are present. In all cases, BAL was performed as previously described (32). The BAL was performed also in 16 RA patients (mean age: 60.4 ± 6.8 years) treated with MTX, but without interstitial pneumonitis (MTX controls). All patients gave their informed consent to the BAL before entry into the study, approval for which was obtained from local ethical committees.

### Statistical analysis

When applicable, data is expressed as the mean ± standard error of the mean (SEM). Statistical comparison was carried out using the nonparametric Mann-Whitney U-test for absolute values and Yates's corrected of the chi-square test for proportions. Any P values less than 0.05 were considered significant. Calculations were performed using Stat View 4.0© (Abacus Concepts Inc., 1992) for Macintosh.

## CASE REPORTS

### Case 1

A 66-year-old woman with a 6-year history of seropositive RA, previously treated with aurothiomalate and sulphasalazine, was maintained on diclofenac 100 mg daily and prednisone 5 mg daily. In January 1992, oral MTX was initiated at 7.5 mg weekly with significant clinical improvement. After 43 weeks, the patient was hospitalised because of increasing dyspnoea, non-productive cough, fever, headache and general malaise. Upon admission, her respiratory rate was 32/min; blood pressure, 140/90 mm Hg; pulse rate, 112/min and axillary temperature, 38.4 °C. Rare midinspiratory bilateral rales were heard. A chest X-ray demonstrated diffuse alveolar and interstitial pulmonary infiltrates, most prominent in the lower lobes (Figure 1A) and the computed tomography scan showed heterogeneous ground glass opacities and septal lines (Figure 1B). PFT were consistent with a restrictive ventilatory defect and a reduced diffusion capacity for carbon monoxide (DLCO, 58% predicted). Laboratory tests showed haemoglobin 11.1 g/dl, white blood cells (WBC) 9,200/$mm^3$ (neutrophils 75%, lymphocytes 15%; monocytes 6%, eosinophils 4%), erythrocyte sedimentation rate (ESR) 33 mm/h. Arterial blood analysis revealed $PaO_2$ of 46 mm Hg, $PaCO_2$ of 39 mm Hg and pH of 7.56 on room air. MTX was discontinued, and the patient was treated with prednisone 60 mg daily and supplemental oxygen with significant improvement. She was discharged after 12 days with prednisone 25 mg daily which was tapered over the following month. One month later, arterial blood gas analysis showed $PaO_2$ of 71 mm Hg, $PaCO_2$ of 29 mm Hg and pH of 7.45 on room air. The patient remained free of respiratory symptoms during a 6-month follow-up. MTX was reinstituted at a dose of 7.5 mg weekly due to a severe flare of RA. The patient did not complain of pulmonary symptoms over a 14 month follow-up.

### Case 2

A 57-year old woman with a 11-year history of seropositive RA unresponsive to aurotiomalate, hydroxychloroquine and sulphasalazine, began in March 1993, MTX 10 mg/week and prednisone 5 mg daily with significant clinical improvement. After approximately 8 months the patient complained of shortness of breath, non-productive cough, general malaise and fever. Upon admission, her respiratory rate was of 30/min, blood pressure of 105/70 mm Hg, heart rate of 100/min and axillary temperature of 38.7°C. Physical examination revealed inspirato-

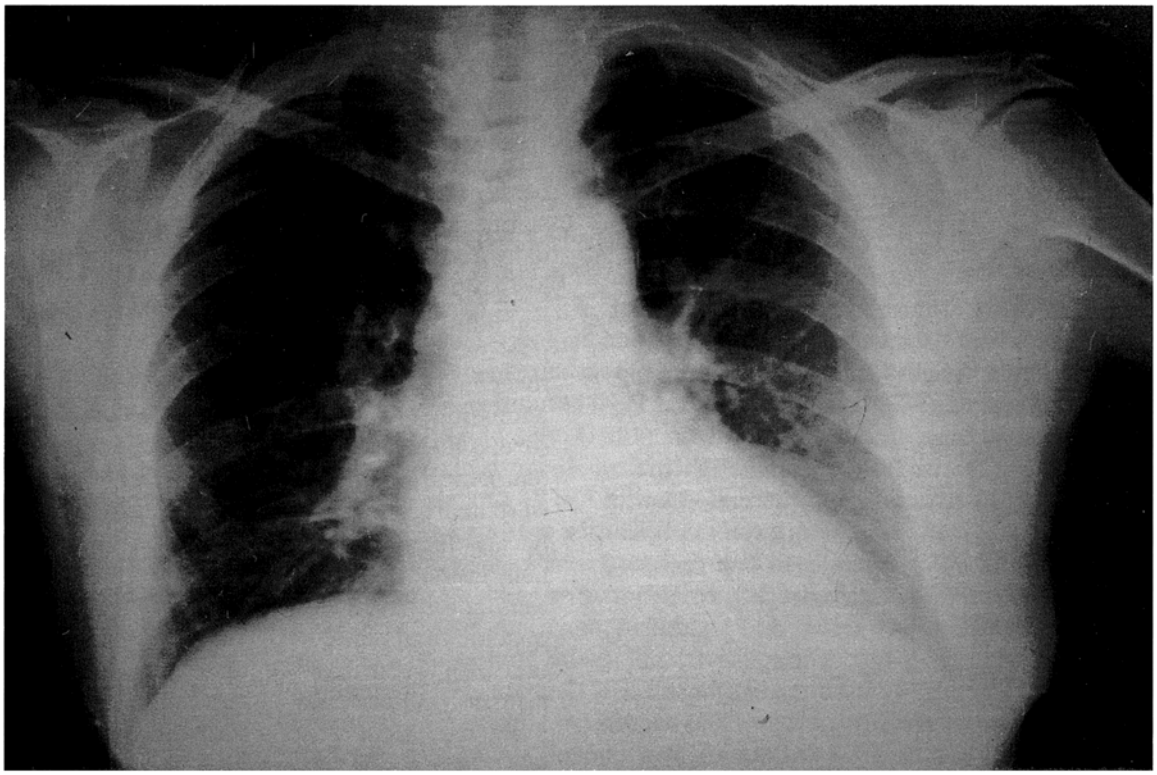

*Fig. 1a*

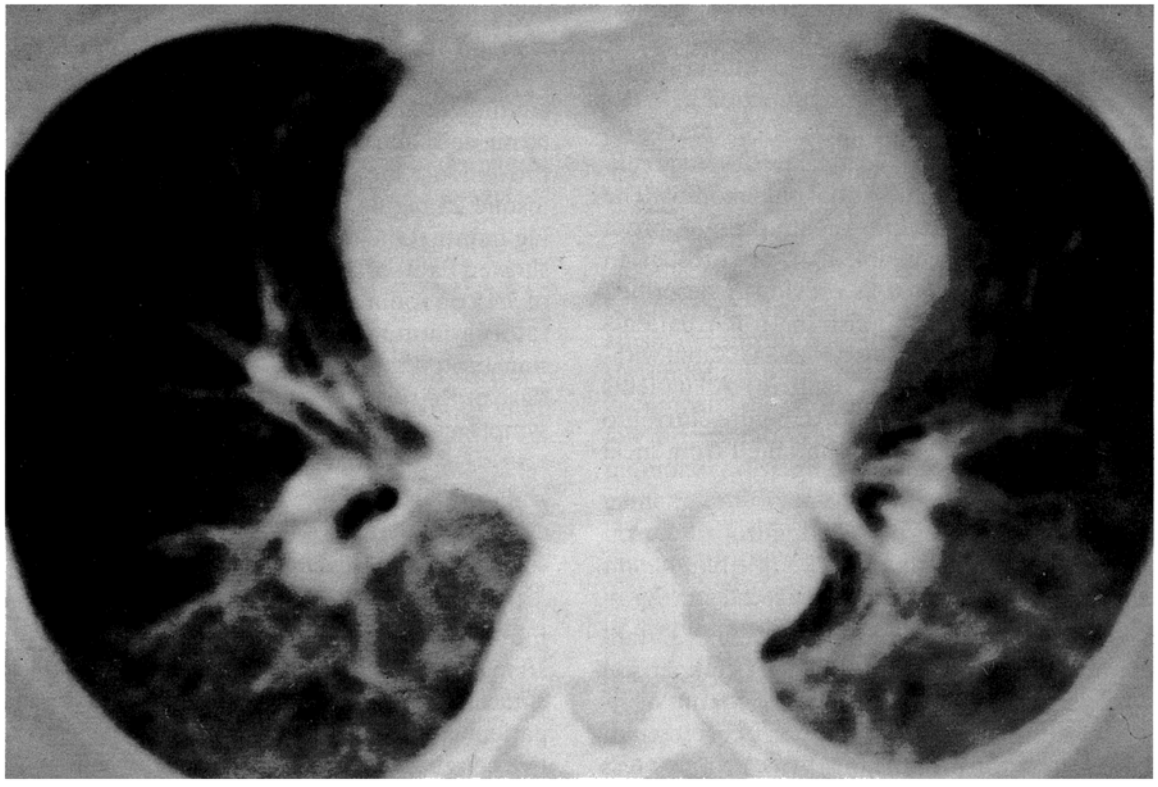

*Fig. 1b*

*Fig. 1:* Chest radiograph showing diffuse alveolar and interstitial infiltrates, most prominent in the lower lobes (Figure 1A). Computed tomography scan showing heterogeneous ground glass opacities and septal lines (Figure 1B).

ry rales over both lower lung fields. A chest X-ray demonstrated a diffuse and bilateral opacification with an interstitial pattern. Diffuse interstitial changes, predominantly at the lung bases, were noted on a chest roentgenogram obtained two years before. Laboratory tests showed haemoglobin 12.1 g/dl, WBC 7,100/$mm^3$ (neutrophils 78%, lymphocytes 14%, monocytes 6%, basophils 2%) and ESR 55 mm/h. Arterial blood gas analysis revealed $PaO_2$ of 48 mm Hg, $PaCO_2$ of 28 mm Hg and pH of 7.54 on room air. PFT showed a restrictive ventilatory defect and reduced DLCO (51% predicted). MTX was withdrawn and the patient was treated with nasal oxygen and i.v. erythromycin. Since her clinical conditions did not improve in the following 48 hours, corticotherapy with methylprednisolone 2 mg/kg/d, was started with clinical improvement within 48 hours. The patient was discharged after 15 days taking prednisone 10 mg daily, which was tapered over the following two months. When reviewed three months later she was asymptomatic, $PaO_2$ was 78 mm Hg on room air, and a chest- X-ray showed a complete resolution of pulmonary opacification. The patient did not complain of respiratory symptoms during a 18-month follow-up.

**Case 3**

A 65-year-old male with a 3-year history of seropositive RA, unresponsive to hydroxychloroquine and sulphasalazine, was treated with ibuprofen 1200 mg daily and methylprednisolone 4 mg daily. In November 1993, he started MTX 10 mg weekly with significant clinical improvement. He admitted to smoking a packet of cigarettes daily for 40 years, but denied significant respiratory symptoms. After approximately 9 months, the patient complained of nonproductive cough and low-grade fever and was treated with amoxicillin by his family physician. He rapidly deteriorated and 1 week later was hospitalised for fever, chest pain, marked dyspnoea at rest, tachypnea and cyanosis. Diffuse rales were heard over both lungs and arterial blood gas analysis revealed a $PaO_2$ of 39.3 mm Hg, $PaCO_2$ of 29.5 mm Hg, and pH of 7.46 on room air. The WBC count was 10,900/$mm^3$ (neutrophils 68%, lymphocytes 14%, monocytes 3%, eosinophils 5%), haemoglobin 13.7 g/dl and ESR 65 mm/h. A chest X-ray demonstrated bilateral diffuse interstitial infiltrates in the lower lobes. PFT showed a restrictive ventilatory defect and decreased DLCO (51% predicted). MTX and ibuprofen therapy were discontinued and i.v. erythromycin and cefotaxime were given. The patient was transferred to the intensive care unit, where he received ventilatory support. Corticosteroid therapy with methylprednisolone 250 mg was administered, intravenously every 8 hours for two days, reduced in the following 5 days and then converted to prednisone 60 mg daily. A dramatic clinical improvement was noted within 24 hours from the start of the corticosteroid treatment. At discharge, one month later, prednisone was decreased to 40 mg daily and withdrawn over two months. When reviewed six months later he was free of respiratory complaints.

**Case 4**

A 60-year-old woman with a 5-year history of seropositive RA previously unresponsive to auranofin and D-penicillamine, was maintained on a regimen of indomethacin 100 mg daily and methylprednisolone 4 mg daily. In July 1994, she began oral MTX 7.5 mg/week, increased to 15 mg/week after 8 weeks. She had never smoked but had a history of mild bronchial asthma controlled by regular use of salbutamol. After 24 weeks, the patient developed shortness of breath and non-productive cough. She had no fever. Upon admission she was dyspnoeic at rest, her pulse rate was 92/min, respiratory rate 30/min and blood pressure 130/85 mm Hg. Scattered inspiratory rales were heard at both bases. A chest X-ray showed diffuse interstitial infiltrates in both lungs with patchy confluent lesions in the upper lobes. While she received oxygen (2L/min), the $PaO_2$ was 56 mm Hg, PaCO2,30.1 mm Hg and pH, 7.51. The WBC count was 10,200/$mm^3$ (neutrophils 79%, lymphocytes 8%, monocytes 6%, eosinophils 6%) and ESR, 86 mm/h. PFT indicated a moderate restrictive ventilatory impairment. Stains and cultures of BAL fluid showed the presence of a few colonies ($2\times10^3$/ml) of Haemophilus influenzae. MTX was withdrawn and the patient was treated with i.v. trimethoprim 8 mg/kg/daily and sulfamethoxazole 40 mg/kg/daily, nasal oxygen and nebulised salbutamol. Corticotherapy with methylprednisolone 2 mg/kg/daily was started because of persistent hypoxemia. The patient rapidly improved, the lung infiltrates resolved and, at discharge, arterial blood gases with the patient breathing room air were: $PaO_2$ 75 mm Hg, $PaCO_2$ 28 mm Hg and pH 7.46. Prednisone, which had been decreased to 30 mg daily, was subsequently tapered at a rate of 5 mg/week. Five months later she was asymptomatic and her chest radiograph was normal.

**Case 5**

A 62-year-old man with polyarticular psoriatic arthritis unresponsive to i.m. gold salts (aurothiomalate), etretinate and sulphasalazine, began in September 1989, MTX, 15 mg/week orally, and flurbiprofen 200 mg daily. He also had a 23-year history of pulmonary silicosis, but de-

Table I: *Clinical features and profile of possible risk factors in patients with acute pneumonitis during treatment of RA and PsA with methotrexate (at time of hospital admission)*

| | | | | | | | Arterial PO2 mmHg | | | | Methotrexate therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt. | Age/Sex | Underlying disease | Disease duration (yr.) | Symptoms* | Respir. rate/min | Rales | WBC ($\times 10^9$) | Acute | Follow-up | Abnormal CXR** | Pre-existing lung disease | Duration (weeks) | Total dose (mg) |
| 1 | 66/F | RA | 6 | D,F,C,H,M | 32 | + | 9.1 | 46 | 75 | + | 0 | 43 | 320 |
| 2 | 57/F | RA | 11 | D,F,C,M | 30 | + | 7.1 | 48 | 78 | + | Diffuse interstitial changes | | |
| 3 | 65/M | RA | 3 | D,F,C,CP,Cy | 38 | + | 10.9 | 39 | ND | + | 0 | 108 | 1080 |
| 4 | 60/F | RA | 5 | D,C | 30 | + | 10.2 | 56 | 72 | + | Bronchial asthma | 24 | 420 |
| 5 | 62/M | PsA | 23 | D,C,F,M | 32 | + | 6.6 | 59 | 80 | + | Silicosis | 16 | 240 |

* D = Dyspnoea, C = Cough, F = Fever (>38°C), H = Headache, M = General malaise, Cy = Cyanosis, CP = Chest pain;
** CXR = Chest radiograph.

nied significant respiratory symptoms and tobacco use. In January 1990, the patient was hospitalised because of a sudden and increasing dyspnoea, fever, general malaise and non-productive cough. At the time of hospital admission, his respiratory rate was 32/min, blood pressure 120/80 mm Hg, heart rate 102/min and axillary temperature 39°C. Bibasilar inspiratory rales were heard. Laboratory tests showed ESR 43 mm/h, WBC 6,680/mm$^3$ (neutrophils 62%, lymphocytes 27%, monocytes 5%, eosinophils 6%). Arterial blood gas analysis revealed a $PaO_2$ of 59.6 mmHg, Pa $CO_2$ of 37 mmHg and pH of 7.42 on room air. The chest X-ray showed bilateral and diffuse interstitial infiltrates, broader in the upper right lobe, and 67-Gallium lung scan a pattern of bilateral and diffuse uptake. PFT demonstrated a restrictive ventilatory defect and a reduced DLCO (37% predicted). MTX was withdrawn and i.v. bethametasone 8 mg daily, was begun. Clinical and roengenographic improvement occurred after 48 hours, and the patient was discharged after two weeks. At that time, arterial blood gas analysis showed $PaO_2$ of 80 mmHg and $PaCO_2$ of 30.3 mmHg on room air, ESR values were reduced to 4 mm/h, and a marked reduction of both the pulmonary interstitial infiltrates and the 67-Gallium uptake at chest X-ray and lung scan, respectively, was shown. Corticosteroid therapy was tapered and then withdrawn in the following two months. During a 5-year follow-up, the patient did not complain of respiratory symptoms.

## RESULTS

The clinical features and the profile of possible risk factors of these patients with MTX pneumonitis are summarised in Table I. All four RA patients were positive for IgM rheumatoid factor (mean ± SD titre = 312.7 ± 127.8 UI/ml) and one (n. 2) had subcutaneous nodules. The duration of RA ranged from 3 to 11 years; the PsA patient had a longstanding disease (23 years). Pre-existing lung disease was present in three, represented by diffuse interstitial lung changes at chest X-ray and mild bronchial asthma in two RA patients and silicosis in the patient with PsA. Only one patient (n. 3) was a smoker. The duration of MTX therapy ranged from 16 to 108 weeks (median, 57.4 weeks). Non-steroidal antiinflammatory drugs and low-doses of corticosteroids (prednisone or equivalent 5 mg/d) were additional therapy in four patients. The diagnosis of MTX pneumonitis was definite in all patients according to the Searles and McKendry criteria (11). Respiratory symptoms such as dyspnoea and nonproductive cough were present in all, whereas other clinical features, such as fever and general malaise, were detected in three patients. Headache, chest pain and cyanosis were each present in one patient. The WBC count was slightly elevated in three patients and a mild eosinophilia was seen in two cases. In all patients arterial blood gas analysis showed significant hypoxemia, chest X-ray interstitial infiltrates and PFT a restrictive ventilatory defect and decreased DLCO. The data for the differential cell count of BAL in the MTX controls and in patients with MTX pneumonitis are shown in Table II. There was a significant increase in the total number of calls of BAL fluid recovered in the MTX pneunonitis group compared with that in MTX controls (246.6 ± 29.3 vs 140.1 ± 18.2; $p < 0.01$). An abnormal differential cell count was seen in all patients. A pure lymphocyte alveolitis was present in 3 RA patients and a neutrophil and lymphocyte alveolitis in 1 RA patient. In the PsA patient the increase in lymphocytes was associated with that in neutrophils and eosinophils. CD4+ cells were the predominant T-cell subset in patients with RA and the mean CD4:CD8 ratio was normal compared with MTX controls (1.9 ± 0.4 vs 1.9 ± 0.6, p = n.s.). In contrast, the patient with neutrophil alveolitis demonstrated a marked increased percentage of CD8+ T cells (63%).

In each patient MTX was stopped. Two patients were unsuccessfully treated with antibiotic therapy. In all cases corticosteroid treatment resulted in a rapid clinical and radiological improvement. In addition, arterial gas analysis showed a significant increase in the $PaO_2$ val-

Table II: *Differential cell count of BAL in MTX controls (16 patients) and in five patients with methotrexate pneumonitis. Alveolar macrophages, lymphocytes, neutrophils, eosinophils and lymphocyte subpopulations are expressed as absolute values ($\times 10^3$/ml) or as percentage of total cell count.*

| | Methotrexate controls (n=16) | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|---|
| Total cell count ($\times 10^3$/ml) | 140.1± 18.2 | 208 | 178 | 345 | 276 | 226 |
| Alveolar macrophages ($\times 10^3$/ml) | 109.2±14.06 | 104 | 99.6 | 155.2 | 165.6 | 113 |
| % | 78.0± 2.1 | 50 | 56 | 45 | 60 | 50 |
| Lymphocytes ($\times 10^3$/ml) | 23.8± 6.6 | 93.6 | 69.4 | 138 | 93.8 | 72.3 |
| % | 17.0± 2.1 | 45 | 39 | 40 | 34 | 32 |
| Neutrophils ($\times 10^3$/ml) | 4.7± 1.3 | 6.2 | 5.3 | 48.3 | 11.1 | 22.6 |
| % | 3.4± 0.6 | 3 | 3 | 14 | 4 | 10 |
| Eosinophils ($\times 10^3$/ml) | 2.4± 0.9 | 4.1 | 3.5 | 3.4 | 5.5 | 40.7 |
| % | 1.6± 0.3 | 2 | 2 | 1 | 2 | 18 |
| CD4+ lymphocytes ($\times 10^3$/ml) | 11.4± 2.0 | 62.7 | 50.6 | 46.9 | 51.5 | ND |
| % | 47.7± 2.4 | 67 | 73 | 34 | 55 | ND |
| CD8+ lymphocytes ($\times 10^3$/ml) | 5.8± 1.1 | 25.3 | 16.6 | 86.9 | 30.9 | ND |
| % | 24.6± 1.7 | 27 | 24 | 63 | 33 | ND |
| CD4/CD8 ratio | 1.9± 0.4 | 2.5 | 3.1 | 0.5 | 1.6 | ND |

Results for MTX controls are expressed as the mean with standard error of the mean (SEM).
*ND = Not done

ues. In the PsA patient a marked reduction in the pulmonary 67-Gallium uptake was also seen. MTX was reintroduced in a RA patient (case 1) with no recurrence of pulmonary symptoms during a 14-month follow-up period.

## DISCUSSION

Low-dose weekly MTX therapy is an effective treatment for RA (1-6) and PsA (7). MTX-induced pneumonitis is a well recognised complication of therapy with this cytotoxic agent, not only in patients receiving high doses for malignant disorders (8), but also in RA patients treated with low weekly doses (1-5,9-19,33). The prevalence of MTX pneumonitis in RA ranges from 0.3% (20) to 18% (21), with mean prevalence of 3.3% (Table III). In the present, MTX pneumonitis was seen in 4 out of 194 RA patients (2.1%). On the other hand, MTX-induced pneumonitis is very rare in PsA. To our knowledge, it has been previously reported in only one patient with psoriasis-associated polyarthritis (34). Thus, our patient represents the second case of MTX-induced pneumonitis in PsA. One can speculate that the difference in the prevalence of MTX pneumonitis in RA and PsA might reflect a different propensity of these inflammatory arthropathies to develop such a complication of MTX therapy. Similarly, a different prevalence of MTX-induced pneumonitis has been reported in patients with chronic cholestatic liver diseases, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). In fact, MTX pneumonitis was found in 14% of PBC patients, whereas approximately only 1% of PSC developed this complication of low-dose pulse MTX therapy (35).

The clinical picture of MTX-induced lung disease seen in our series was similar to that described in other ones (9,12,21,26). Dyspnoea and dry cough were reported by all our patients; three patients also complained of constitutional symptoms such as fever and general malaise; headache and chest pain were each reported by one patient. At physical examination, tachypnoea, rales or inspiratory crackles and cyanosis are the most common findings (10,11,24,25). Upon admission, tachypnoea and rales were noted in all our patients, whereas cyanosis was present in only one. In MTX pneumonitis laboratory investigations show marked arterial hypoxemia in almost all cases (10,11,23,36). The WBC count may be normal (8,11) or show moderate leukocytosis without left shift (10). Slight increases in blood eosinophils (8,25) and lactate dehydrogenase (10,22,36) have also been reported. Upon admission, arterial blood gas analysis showed hypoxemia in all our patients; mild leukocytosis was present in two patients and slight eosinophilia in one. The chest roentgenogram may be normal, but more commonly it reveals bilateral interstitial or mixed, interstitial and alveolar infiltrates with a predilection for the bases and midlung fields (8,10,36,37). A reticulonodular pattern (12) and more rarely transient hilar or mediastinal lymphadenopathy (8) and pleural effusion (8,38) have also been described. An abnormal chest roentgenogram, characterised by bilateral interstitial or mixed infiltrates, was found in all our patients. In addition, bilateral and diffuse uptake of Gallium-67 was found in the PsA patient

Table III: *Prevalence of pneumonitis in patients with rheumatoid arthritis receiving methotrexate*

| Reference | Publication year | Study design | Observation years | Number case/Number patients at risk | Prevalence |
|---|---|---|---|---|---|
| Sostman et al. (8) | 1976 | retrospective | 7 | 7/92 | 7.6% |
| Cannon et al. (15) | 1984 | retrospective | not mentioned | 5/127 | 3.9% |
| St Clair et al. (9) | 1985 | retrospective | not mentioned | 3/95 | 3.1% |
| Boh et al. (16) | 1986 | prospective | 2 | 3/59 | 5.1% |
| Carson et al. (10) | 1987 | retrospective | 8 | 9/163 | 5.5% |
| Gispen et al. (12) | 1987 | retrospective | 3 | 1/72 | 1.4% |
| Searles and McKendry (11) | 1987 | retrospective | 8 | 4/73 | 5.5% |
| Bell et al (21) | 1987 | prospective | 3 | 4/22 | 18.1% |
| Andersen et al. (17) | 1987 | prospective | not mentioned | 1/40 | 2.5% |
| Haranhan et al. (2) | 1989 | prospective | 4 | 1/128 | 0.8% |
| Alarcòn et al. (1) | 1989 | retrospective | 5 | 2/152 | 1.3% |
| Drosos et al. (3) | 1990 | prospective | 2 | 1/137 | 0.7% |
| Scully et al. (13) | 1991 | retrospective | 5 | 11/124 | 8.9% |
| Hargreaves et al. (23) | 1992 | retrospective | 3 | 5/43 | 11.6% |
| Kremer and Phelps (4) | 1992 | prospective | 7.5 | 2/29 | 6.9% |
| Weinblatt et al. (5) | 1992 | prospective | 7 | 2/26 | 7.7% |
| Shergy et al. (14) | 1992 | retrospective | not mentioned | 13/594 | 2.2% |
| Buchbinder et al. (20) | 1993 | retrospective | 5 | 3/587 | 0.3% |
| McKendry and Dale (18) | 1993 | retrospective | 13 | 5/144 | 3.5% |
| Barrera et al. (25) | 1994 | retrospective | not mentioned | 13/220 | 5.9% |
| Golden et al. (29) | 1995 | prospective | 9 | 9/125 | 7.2% |
| Cottin et al. (39) | 1996 | prospective | 2 | 4/124 | 3.2% |
| Hilliquin et al. (26) | 1996 | retrospective | 6 | 4/130 | 3.0% |
| Our data | 1997 | retrospective | 6 | 4/194 | 2.1% |
| Total | | | | 116/3500 | 3.3% |

at lung scintigraphy. PFT revealed a restrictive ventilatory defect and a reduced diffusion capacity for carbon monoxide, in agreement with previous reports (8,11,24,39).

In patients with suspected MTX pneumonitis, BAL plays an important role either in excluding infectious agents, mainly Pneumocystis carinii, fungi and mycobacteria, or in giving information to understand the pathogenesis of lung injury. In this regard, a lymphocyte alveolitis with predominance of T CD4+ (36,40,41) or T CD8+ cells (42) has been reported, suggesting an immune-mediated damage mechanism in MTX pneumonitis. Further evidence of an immunological mechanism is provided by the reported release of a lymphokine, the leukocyte inhibitory factor, by peripheral blood lymphocytes from patients with MTX-induced pneumonitis after in vitro incubation with the drug (43). Other BAL cell profile alterations include an increase in eosinophilis (36,40) or neutrophils (36,42). In some cases, the increase in BAL neutrophilis is so marked that it characterises a neutrophilic alveolitis (44). Interestingly, a discrepancy between BAL neutrophilia and the histological findings of interstitial lymphocyte infiltrate with granulomas at transbronchial biopsy, has been reported (44). BAL results in our series confirmed the presence of a lymphocyte alveolitis with a predominance of CD4+ T cells in three RA patients and CD8+ with an concomitant increase in neutrophils in another. An increase in lavage eosinophils associated with lymphocytosis and neutrophilia was also seen in the PsA patient.

Risk factors for MTX-induced pneumonitis are poorly understood. There is no relationship between age, sex, disease duration (10,39), extraarticular manifestations of RA (29), and weekly or cumulative dose of the drug (10). Renal function impairment and concomitant use of antiinflammatory drugs have been suggested as provoking a predisposition to MTX toxicity in some studies (10,11,45), but not in others (24,29). MTX lung disease may occur either after small doses of the drug, such as 12.5 mg (33), or after discontinuation of treatment (41,46,47). Cigarette smoking (11), pre-existing lung disease (11,21,29) and abnormal PFT (28) have been suggested to increase the risk of developing MTX pneumonitis in RA patients. Carson et al. (10), however, found the prevalence of smoking history, previous pulmonary disease and abnormal chest X-ray to be the same in pa-

tients with and without pneumonitis. No predisposing factors for MTX pneumonitis were found in a recent report by Cottin et al. (39). On the other hand, in our series, 3 out of 5 patients had lung disease before the beginning of MTX, represented by diffuse interstitial changes at chest X-ray and mild bronchial asthma in two RA patients and by pulmonary silicosis in the patient with PsA. This suggests that pre-existing lung disease might have had a role in the development of MTX pneumonitis in our cases. Interestingly, MTX-induced pneumonitis has been described in a patient with steroid-dependent bronchial asthma (48).

The diagnosis of MTX-induced pneumonitis is difficult since there are no pathognomonic findings and it may imitate other pulmonary diseases (25). In particular, great care must be taken to rule out Pneumocystis carinii pneumonia which may complicate low-dose MTX therapy (49,50) and have a similar presentation (50).

The mainstay of therapy is the withdrawal of MTX, however, in some cases pneumonitis resolved despite continued MTX use (51). Besides withdrawal of MTX and supportive care, corticosteroids appear to hasten the complete recovery (8,10). In some cases, additional antibiotic treatment may be required in view of the difficulty in excluding some pulmonary infections (25).

The prognosis of acute MTX-induced pulmonary disease is usually favourable, but occasionally the outcome may be fatal, even for a short course of low dose MTX (8,9,12,19,26,52). In all our cases, MTX was withdrawn and corticosteroid therapy resulted in a rapid clinical and radiological improvement and no recurrence of the pulmonary symptoms in the follow-up was seen. The reintroduction of the drug after MTX pneumonitis may sometimes be safe, without recurrence of the pulmonary toxicity, as shown in previous series (10,11,53) and in one of our cases. However, patients who resume MTX after an episode of acute lung disease are a high risk group and, therefore, reinstitution of the drug should be reserved to those with severe disease refractory to other second-line drugs.

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