Low dose methotrexate pneumonitis in rheumatoid arthritis

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The antimetabolite drug methotrexate has recently been used in the treatment of rheumatoid arthritis refractory to conventional antirheumatic drugs.¹⁻³ The doses of methotrexate used in such cases are much lower than those used in the treatment of malignancy or skin disorders. Instances of diffuse interstitial pneumonitis apparently related to the use of methotrexate in such low doses are uncommon.^{4,5} We report a case in which diffuse pneumonitis developed after low weekly and low accumulative doses of methotrexate and which showed spontaneous resolution after the drug had been discontinued.

Case report

In 1975, a 64 year old woman, a former smoker, developed severe rheumatoid arthritis. Drug treatment initially consisted of salicylates and prednisone. In 1977 she had a hypersensitivity reaction to a trial of gold treatment. She then received ibuprofen and prednisone until August 1983, when the latter was discontinued. Fusion of the metacarpophalangeal joints of both thumbs was carried out in 1978, left hip replacement in January 1982, and right shoulder replacement in January 1983. Chronic deformities were present in many other joints. In April 1984 methotrexate was started, with an initial dose of 2.5 mg followed by 7.5 mg orally each week. Methotrexate was discontinued 10 October 1984 after a cumulative dose of 137.5 mg because of raised serum aspartate transaminase activity to 68 U/l (normal 10-45 U/l). She continued to take oral ibuprofen 600 mg four times daily. On 17 October she complained of a cough, dyspnoea on exertion, and right sided pleuritic chest pains, which had been present during the last month. She was afebrile but had bilateral basilar crackles on auscultation of the chest. The white blood count was $9.5 \times 10^9/l$. The arterial oxygen tension (P_{aO_2}) during the breathing of air was 66 mm Hg (8.8 kPa) and the arterial carbon dioxide tension (P_{aCO_2}) 32 mm Hg (4.3 kPa), and the arterial pH was 7.43. A chest radiograph showed emphysematous changes and a bilateral interstitial pattern of the reticulonodular type. She was given ampicillin 250 mg four times daily for presumed bronchitis.

She was admitted to hospital on 23 October 1984 with increasing breathlessness and worsening pleuritic chest pains. She was afebrile and tachypnoeic (30 breaths/min). There was dullness to percussion and crackles on auscultation.

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Accepted 7 January 1986

tation over the lower half of the right thorax. There was no evidence of congestive heart failure, finger clubbing, or subcutaneous nodules. While she was breathing room air P_{aO_2} was 51 mm Hg (6.8 kPa), P_{aCO_2} 31 mm Hg (4.1 kPa), and arterial pH 7.46. The white blood count was $14.4 \times 10^9/l$ with 6% band forms, 54% neutrophils, 31% lymphocytes, 5% monocytes, and 4% eosinophils. A peripheral eosinophilia of 7-8% developed and persisted during her stay in hospital. The erythrocyte sedimentation rate (Westergren) was 53 mm in one hour. Results of liver function tests, including serum bilirubin concentration and serum aspartate transaminase and alkaline phosphatase activities, were normal. A chest radiograph showed diffuse interstitial changes and patchy infiltrates in the right lower lobe and left upper lobe (Fig A).

Chest radiographs of the patient (A) on 23 October 1984 and (B) on 28 November 1984

The patient was given oxygen and completed her course of negative ampicillin. Blood cultures yielded no growth and a range of serological tests gave negative results. Pulmonary function testing on 26 October 1984 indicated a mild restrictive ventilatory defect with evidence of small airways obstruction (table). Transfer factor was considerably reduced. Fibreoptic bronchoscopy with bronchoalveolar lavage, transbronchial biopsy, and a trial of steroids were considered but deferred when clinical improvement was observed. She was discharged from hospital on 29 October 1984.

A month later her symptoms had improved greatly, her

Pao₂ while she was breathing room air had increased to 73 mm Hg, and the pulmonary infiltrates had disappeared, the appearances being the same as those noted in 1982 (fig B). The results of pulmonary function tests had returned to normal by March 1985 (table).

Discussion

Evidence is accumulating that low dose methotrexate is effective in controlling rheumatoid arthritis refractory to more conventional treatment.¹⁻³ Common adverse reactions from low dose methotrexate include increase in serum transaminase activity, nausea, diarrhoea, leucopenia, and pancytopenia.¹⁻³ In most cases in which methotrexate has been associated with a diffuse, non-infectious pneumonitis large cumulative doses of methotrexate have been used, for treating haematological malignancies and dermatological disorders.⁶ There are, however, three reported cases of diffuse pneumonitis apparently secondary to low dose methotrexate treatment for rheumatoid arthritis.⁴⁻⁵

Drug induced lung disease is often insidious and non-specific in its presentation. Dry cough, dyspnoea, crackles, hypoxaemia, and reduction in lung volumes and transfer factor are common features of interstitial lung disease from any cause. Distinguishing a drug reaction from underlying disease and superimposed infection is essential. Infectious pneumonia was reasonably excluded in our patient without lung biopsy. Any clinical deterioration during her stay in hospital would have prompted fiberoptic bronchoscopy or even open lung biopsy to establish the diagnosis. The absence of any reduction in lung volumes before treatment with methotrexate and the return of pulmonary function abnormalities to baseline argues against severe rheumatoid lung disease (table). The temporal association, peripheral eosinophilia, and clinical improvement after the drug was stopped further implicate methotrexate as the offending agent. Our patient's recovery without high dose steroid treatment contrasts with previous case reports and illustrates the variable clinical course of methotrexate pneumonitis.⁶

Although methotrexate pneumonitis has been often attributed to a non-cytotoxic, hypersensitivity reaction,⁴⁻⁶ the mechanism of lung injury remains unproved and controversial.⁶ Bronchoalveolar lavage in six patients with methotrexate pneumonitis showed a considerable increase in the total cells retrieved and the proportion of lymphocytes in the fluid.⁷ The T lymphocyte helper:suppressor ratio was found by the monoclonal antibody method to be increased in three patients. These findings suggest that methotrexate pneumonitis is a predominantly helper T cell lymphocyte alveolitis.

Results of pulmonary function tests*

Date:	25 Jan 1982	26 Oct 1984	21 Nov 1984	27 Mar 1985
FEV ₁ (l)	2.16 (119)	1.48	1.44	1.92
FVC (l)	3.09 (122)	1.84	1.84	2.80
TLC (l)	5.10 (120)	3.02	3.48	4.47
RV (l)	2.01 (117)	1.17	1.60	1.67
TLCO (ml min ⁻¹ /mm Hg ⁻¹)	5.26 (28)		7.39	10.09
Pao ₂ (mm Hg)	76	59	73	93
Paco ₂ (mm Hg)	40	34	37	36
pH	7.43	7.44	7.31	7.36

*Numbers in parentheses indicate percentage of predicted normal values.

FVC—forced vital capacity; TLC—total lung capacity; RV—residual volume; TLCO—transfer factor (diffusing capacity); Pao₂—arterial oxygen tension during breathing of air; Paco₂—arterial carbon dioxide tension.

Conversion of traditional to SI units—Blood gas tensions: 1 mm Hg ≈ 1.33 kPa.

Methotrexate pneumonitis has been reported after doses ranging from 40 to 6500 mg and, although not dose related, the occurrence of pneumonitis is rare in patients taking less than 20 mg weekly.⁶ As experience accumulates with methotrexate in rheumatoid arthritis, the incidence of pulmonary complications will become more evident. The low weekly and cumulative doses in our case and in the three previously reported patients with rheumatoid arthritis suggest the possibility that rheumatoid arthritis may exert an additive or synergistic effect in the pathogenesis of methotrexate pneumonitis. The occurrence of fibrosing alveolitis in cases of rheumatoid arthritis is well known and pulmonary function may be abnormal despite an apparently normal chest radiograph.⁸ The very low incidence of pulmonary toxicity in patients receiving high dose methotrexate for osteogenic carcinoma⁹ and breast carcinoma¹⁰ also supports the concept of selective synergistic effects in certain underlying diseases.

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