Case report

Life threatening acute pneumonitis during low dose methotrexate treatment for rheumatoid arthritis: a case report and review of the literature

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SUMMARY A patient is described with definite rheumatoid arthritis (RA) who developed life threatening acute pneumonitis after receiving a total dose of only 12.5 mg methotrexate (MTX). This complication has been previously described, but this is probably the lowest reported dose before development of pneumonitis in a patient with RA. The possible significance of this case is discussed in the light of recent reports suggesting an increased susceptibility of patients with RA to the pulmonary toxicity of MTX.

Key words: drug sensitivity.

Methotrexate pneumonitis (MP) can take two forms. Firstly, a diffuse chronic interstitial fibrosis associated with chronic therapy and, secondly, an acute pneumonitis.¹ Neither appears to be directly related to the total cumulative dose of MTX. The acute pneumonitis may be related to peak dosage, however, and is well recognised as a complication of cancer chemotherapy.²⁻⁴

A number of controlled studies demonstrating the usefulness of low dose intermittent MTX in the treatment of RA resistant to conventional second line therapy⁵⁻⁷ has resulted in an increased use of the drug, particularly in the USA. Subsequent reports of pulmonary toxicity complicating low dose MTX treatment in RA⁸⁻¹⁰ have been followed by other studies, which have suggested the possibility of an increased susceptibility in some patients with RA to MTX pulmonary toxicity.¹¹ A patient with RA is described who developed life threatening acute pneumonitis after a total dose of only 12.5 mg MTX, a smaller dose than has been previously associated with this complication.

Case report

An Indian woman presented in 1981 aged 46 with an 18 month history of a symmetrical polyarthritis involving the proximal interphalangeal joints, the metacarpophalangeal joints, knees, ankles, and metatarsophalangeal joints. Her mother had RA and diabetes mellitus.

On examination there was evidence of active synovitis with early swan neck and boutonnière deformities in both hands. Investigation showed haemoglobin (Hb) 102 g/l, erythrocyte sedimentation rate (ESR) 63 mm/h, latex screen positive Rose-Waaler test negative, antinuclear antibodies positive 1/80, DNA antibody 6.6 U/ml (normal <10 U/ml). Joint x rays showed periarticular osteoporosis; chest x ray was normal. Treatment with successive courses of hydroxychloroquine, gold, and penicillamine over the next two years was ineffective, and she continued with active synovitis and an ESR of 70-100 mm/h. In mid-1984, during a flare of her polyarthritis, she was noted to have an ESR of 140 mm/h, latex screen positive, Rose-Waaler test positive 1/8, antinuclear antibodies positive 1/40, DNA antibody 3 U/ml. An x ray examination showed early erosions in metacarpophalangeal joints, wrists, and shoulders; chest x ray normal. She

remained housebound by her synovitis, and treatment with oral prednisolone was started with some benefit. Later, in 1985, azathioprine 150 mg a day was added because of inability to control the disease with less than 10 mg prednisolone a day.

In July 1986 she was again housebound because of active disease. Fortnightly intramuscular steroid injections (80 mg triamcinolone hexacetonide) were ineffective. In October 1986 it was decided to give methotrexate 7.5 mg weekly. The only additional drug was prednisolone 10 mg. Investigation at this time showed Hb 113 g/l, white cell count $5.6 \times 10^9/l$ (normal $4-11 \times 10^9/l$) with a mild lymphopenia $0.9 \times 10^9/l$ (normal $1.5-3.5 \times 10^9/l$), platelets $296 \times 10^9/l$ (normal $150-400 \times 10^9/l$), ESR 56 mm/h, liver function tests normal. During the second week of treatment, having received a total of 12.5 mg MTX, she was brought to the clinic acutely unwell with a four day history of fever, non-productive cough, and increasing dyspnoea. On examination she was tachypnoeic and tachycardic, temperature 37.8°C with bilateral basal inspiratory crackles. Chest x ray showed widespread bilateral alveolar infiltrates disproportionate to the auscultatory signs. Additional investigation at this time showed Hb 140 g/l, total white cell count $7.0 \times 10^9/l$, lymphocytes $1.3 \times 10^9/l$, eosinophils $0.6 \times 10^9/l$ (normal $0.4-4.0 \times 10^9/l$), ESR 57 mm/h, platelets $261 \times 10^9/l$, blood cultures negative. A provisional diagnosis of atypical pneumonia was made, and she was treated with intravenous corticosteroids and

erythromycin. Over the next 48 hours her condition deteriorated and a further chest x ray showed bilateral confluent shadowing (Fig. 1). She became markedly hypoxaemic with a Po_2 of 40 mmHg while breathing 40% inspired oxygen and was transferred to the intensive care unit for elective ventilation and transbronchial lung biopsy.

Histology from the biopsy showed a distorted pulmonary parenchyma with a dense inflammatory cell infiltrate with abundant histiocytes and fibrin (Fig. 2). There was only slight interstitial fibrosis. No cytomegalovirus, pneumocystis, or granulomata were seen. Bronchial washings proved negative for pneumocystis and tuberculosis. Serology for cytomegalovirus, legionella, and mycoplasma was negative.

The absence of any positive evidence for an infective cause and the histological appearance were felt to be consistent with an acute pneumonitis secondary to MTX. Treatment with assisted ventilation and steroids was continued, and over the next five days the gas exchange improved sufficiently for her to be weaned from the ventilator, though the chest x ray showed a less rapid improvement than that seen clinically. After transfer back to the ward she continued to require supplementary oxygen to maintain normal blood gases for a further two weeks. At this stage blood gas analysis showed a Po_2 of 77.1 mmHg while breathing air and the chest x ray had cleared considerably (Fig. 3).

Fig. 1 An x ray after 48 hours of clinical deterioration with confluent shadowing.

A repeat transbronchial lung biopsy was performed before discharge and showed mild inflammatory changes with a moderately severe interstitial fibrosis (Fig. 4). Her clinical course in hospital was otherwise complicated by steroid induced diabetes mellitus,

which required insulin. She was discharged on prednisolone 20 mg a day. When reviewed in January 1987 she complained of some exertional dyspnoea, but her joints were asymptomatic with prednisolone 10 mg daily. At follow up in September

Fig. 2 Transbronchial lung biopsy specimen showing a dense inflammatory cell infiltration with abundant histiocytes and fibrin.

Fig. 3 A further x ray concurrent with the clinical recovery.

Fig. 4 Repeat lung biopsy performed before discharge showing mild inflammatory changes and moderately severe interstitial fibrosis.

1987 she was still free of joint symptoms and had no limiting dyspnoea.

Subsequent tissue typing showed her to have HLA-DRw3 but not DRw4 or DRw2.

Discussion

The clinical features of this case are entirely consistent with previous descriptions of acute pneumonitis associated with MTX.¹² In particular, the disproportionate absence of crackles on auscultation compared with the gross radiological changes has been described.¹²⁻¹⁵ Our patient did not have the peripheral blood eosinophilia which is present in about half the cases,³ therefore its absence does not preclude the diagnosis of MP. Chest x ray changes can vary from linear reticular shadowing to florid alveolar shadowing as in our patient. Severe hypoxaemia is characteristic.^{3,4} Lung histology in our case is consistent with a drug induced pneumonitis, though granulomata are sometimes seen in MP^{4,16} but not in pneumonitis due to other cytotoxic drugs. Fibrosis following acute MP has only rarely been described,¹⁶ and most patients surviving the initial insult recover without permanent sequelae.

The first two reports of acute pneumonitis associated with low dose intermittent MTX for RA appeared in 1983.^{8,9} Both described cases similar to our own but occurring after at least 14 weekly doses of 7.5 mg. Only in one instance has MP been recorded as occurring with a lower weekly dosage,

but this was in a patient whose renal failure would have raised the circulating concentration of the drug.¹³ St Clair *et al* then reported acute pneumonitis in three of 95 patients treated with MTX at a dose of 5–15 mg a week.¹⁰ All were severely hypoxaemic as was our patient, and of these three, two recovered without apparent sequelae but one died from secondary infection—the only one who required assisted ventilation. Cannon *et al* have reported their wider experience with five patients with MP out of 127 treated with MTX, all with a similar clinical picture.⁸ Four of these recovered quickly after withdrawal of the drugs and the administration of high dose steroids, and one recovered with residual dyspnoea, which continued to improve. They thus suggested that MP in RA had a favourable prognosis. A recent report of 168 patients receiving low dose pulse MTX for RA showed seven probable and two possible cases of MP. All nine patients fully recovered from their pulmonary disease.¹⁷

The occurrence of acute MP at lower doses than previously associated with this complication raises the possibility of a particular susceptibility in patients with RA. Possible reasons include a susceptibility specific to RA lungs or a general susceptibility within an RA population to a drug side effect, for example an immunogenetic reason, as in the case of gold treatment.¹⁸ Indeed both factors could operate together. It is interesting to find that our patient had HLA-DRw3, which is associated with an increased risk of toxicity from gold and penicilla-

mine,¹⁸ but she did not have DRw2, which may have a similar association. Bell *et al* provided some evidence for pre-existing lung disease predisposing to MP in RA.¹¹ They reported the development of MP in four of only 22 patients treated with low dose MTX. All had longstanding disease and all had evidence of pulmonary dysfunction before treatment with MTX: three an abnormal chest x ray and one a markedly reduced K_{co} (50%). In addition, the patient described earlier by Engelbrecht *et al*, who developed MP while receiving only 10 mg MTX a week, had shown clinical evidence of rheumatoid lung earlier in the course of his RA.⁹ This could be of clinical importance in that rheumatoid lung involvement may have a very insidious onset with a long asymptomatic phase but significant impairment of alveolar gas transfer.¹⁹ There remains therefore the distinct possibility that other patients already reported with MP could have had subclinical rheumatoid lung before the development of MP. It is noteworthy that MTX is concentrated in lung tissue,²⁰ and possible that pre-existing lung damage may accentuate this accumulation and predispose to toxicity. These aspects of subclinical RA lung may be worthy of prospective study in any future assessments of MTX in RA.

With such a fulminant reaction to such a low dose of MTX the possibility of a drug interaction was carefully looked for, but we should emphasise that our patient was receiving only prednisolone as well as the MTX and there was no history of current or recent non-steroidal anti-inflammatory drug (NSAID) usage. A further report of fatal bone marrow and renal toxicity after a single dose of MTX in a patient with RA receiving two NSAIDs²¹ highlights the potential risks from interaction between MTX and several NSAIDs.²²

The foregoing discussion centres around the concept that MP in RA is a reaction due to cumulative toxicity. Several authors, however, have suggested that MP represents a drug hypersensitivity reaction in view of the wide range of prior dosage of MTX and the frequent accompaniment of eosinophilia in the peripheral blood and sometimes in the lung biopsy specimens. There are, however, features of the condition which suggest that it may be more than an idiosyncratic allergic reaction. Firstly, the fact that some of the patients reviewed by Sostman *et al* improved while continuing to take the drug.³ Secondly, and more importantly, other patients have generally not developed recurrent MP on rechallenge with the drug.¹² These facts, the reports reviewed here, and our own case suggest that MTX may eventually be added to the list of drugs which appear unusually prone to produce certain adverse effects in patients with RA.

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