

Case report

Pneumocystis carinii pneumonia complicating low dose methotrexate treatment for psoriatic arthropathy

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SUMMARY A case of *Pneumocystis carinii* pneumonia complicating low dose methotrexate treatment for psoriasis and psoriatic arthropathy is described. This potentially fatal event was probably precipitated by an interaction between methotrexate and concurrent non-steroidal anti-inflammatory drugs, resulting in serious potentiation of the effects of methotrexate.

Low dose methotrexate treatment is often used to control psoriasis or psoriatic arthropathy, or both, in patients who have failed to respond to conventional treatment. It is also increasingly used for severe rheumatoid arthritis. When the treatment is carefully monitored the incidence of serious side effects is low.¹ We report a case of *Pneumocystis carinii* pneumonia in a patient with psoriasis and psoriatic arthropathy who was receiving weekly low dose oral methotrexate in conventional dosage. This complication of methotrexate treatment for psoriasis alone has not been reported previously and might have been precipitated by concurrent non-steroidal anti-inflammatory drug (NSAID) treatment.

Case report

A 16 year old girl developed psoriasis at the age of 5 years and psoriatic arthropathy one year later. At the age of 13 years treatment with disease modifying drugs became necessary to control her severe deforming erosive arthritis. During the ensuing two years treatment with sulphasalazine, gold, chloroquine, and D-penicillamine failed, owing to lack of effect or toxic cutaneous reactions. Treatment with prednisolone 30 mg daily was started at the age of 15 years to control uveitis, the dose being reduced over

three months to 7.5 mg daily with the addition of local steroid eye drops. Nevertheless, active arthritis and extensive psoriasis persisted (erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) persistently above 60 mm/h and 60 mg/l respectively); thus aged 16 years treatment with low dose oral methotrexate 5 mg weekly was started after full discussion between doctors, patient, and parents. Her condition rapidly improved and with further dose increases (rising to 7.5 mg at two months and 10 mg at three months) her psoriasis resolved completely, the arthritis improved (ESR 24 mm/h, CRP 25 mg/l), and she was able to start work. She continued to take slow release ibuprofen 1200 mg daily, and prednisolone was reduced to 3 mg daily. Monthly full blood counts and tests of liver and renal function remained normal.

Ten months after starting methotrexate treatment mouth ulceration, epistaxis, and pancytopenia were noted, and methotrexate was discontinued. One week later breathlessness and cough developed and within 48 hours she became extremely ill. Examination showed a thin girl, weight 38 kg, height 1.6 m, with a tachypnoea of 44/min, heart rate 165/min, and blood pressure 95/60 mmHg. There were no abnormal breath sounds, no signs of heart failure, and no lymphadenopathy or hepatosplenomegaly. Investigations disclosed: haemoglobin 71 g/l, leucocytes $15.1 \times 10^9/l$ (69% neutrophils, 20% lymphocytes, 6% eosinophils, 5% monocytes), platelets $113 \times 10^9/l$, normal liver and renal function tests, and

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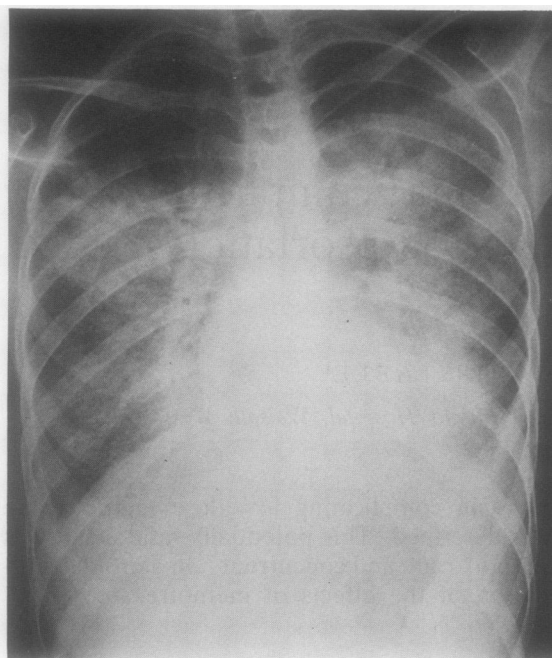


Fig. 1a

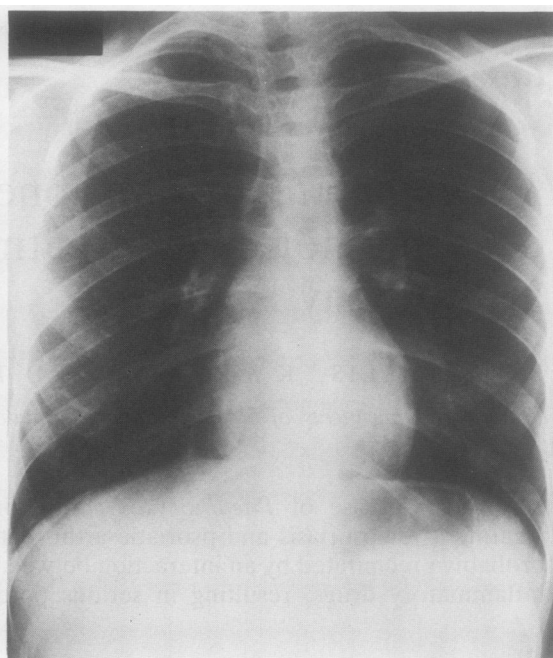


Fig. 1b

Fig. 1 (a) Chest x ray showing widespread pulmonary infiltration due to *Pneumocystis carinii* with (b) complete resolution six weeks later.

CRP 219 mg/l. Chest x ray showed diffuse bilateral interstitial pulmonary infiltration (Fig. 1), and arterial oxygen pressure, breathing air, was 4.3 kPa. Bronchoalveolar lavage showed *Pneumocystis carinii*, while bacterial, viral, and fungal cultures proved negative. Serum IgG was reduced at 3.3 g/l (normal range 6–16 g/l), but other immunoglobulins were normal.

High dose intravenous co-trimoxazole was given for 14 days, and the patient made a full recovery, though ventilation via tracheostomy was necessary for seven days. Haematological values and immunoglobulin concentrations returned to normal. Twelve months later she remained well without serious relapse of psoriasis or arthritis, and with normal liver function and haematology. Lung function tests showed a mild restrictive defect with a normal gas transfer coefficient, consistent with a mechanical restriction of ventilation secondary to arthritis. Her chest x ray remained normal.

Discussion

After treatment with low dose methotrexate this

patient developed bone marrow suppression and hypogammaglobulinaemia complicated by *Pneumocystis carinii* pneumonia. Surprisingly, methotrexate 10 mg weekly had been tolerated for six months previously without ill effect. Why toxicity should become apparent in this way at this stage is of interest. The patient's low body weight was probably a contributory factor. Alternatively, inadvertent overdosage might have occurred, but the patient denied this. Another possibility is drug interaction.

The patient had been receiving high dose ibuprofen treatment and this, together with her small size, could have predisposed to toxicity as NSAIDs can potentiate the effects of methotrexate by several mechanisms. Firstly, NSAIDs compete for protein binding sites with methotrexate. Because 50–70% of methotrexate is bound to albumin appreciable increase in the pharmacologically active unbound drug can occur with concurrent NSAID treatment,² resulting in toxicity.³ Secondly, NSAIDs may competitively inhibit renal tubular excretion of methotrexate.⁴ Finally, by suppressing renal prostaglandin synthesis, NSAIDs may cause a reduction

in renal blood flow and glomerular filtration rate, thus further decreasing renal elimination of the drug.⁵

Pneumocystis carinii pneumonia is a well recognised complication of high dose methotrexate treatment⁶ but to our knowledge has not been reported to follow weekly low dose oral treatment for psoriasis. This case, together with a report describing *Pneumocystis carinii* pneumonia complicating methotrexate treatment for rheumatoid arthritis,⁷ emphasises the need to remain alert to the possibility of opportunistic infection even when methotrexate is used in low dosage at weekly intervals.

It is possible that low dose corticosteroid treatment also contributed to the development of *Pneumocystis carinii* infection in this case. The potential interaction between methotrexate and concurrent NSAID treatment cannot be ignored, however. Consequently, extra caution is needed when low dose methotrexate is used to control psoriasis in patients who also have an associated arthropathy. Such patients may be receiving NSAID

treatment by prescription or indeed as 'over the counter' self medication, and this may seriously potentiate the effects of methotrexate treatment.

References

- 1 Nyfors A. Methotrexate therapy of psoriasis. *Dan Med Bull* 1980; **27**: 74-96.
- 2 Taylor J R, Halprin K M. Effect of sodium salicylate and indomethacin on methotrexate-serum albumin binding. *Arch Dermatol* 1977; **113**: 588-91.
- 3 Daly H M, Boyle J, Roberts C J C, Scott G L. Interaction between methotrexate and non-steroidal anti-inflammatory drugs. *Lancet* 1986; **i**: 557.
- 4 Liegler D G, Henderson E S, Hahn M A, Oliverio V T. The effect of organic acids on renal clearance of methotrexate in man. *Clin Pharmacol Ther* 1969; **10**: 849-57.
- 5 Thyss A, Kubar J, Milano G, Namer M, Schneider M. Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. *Lancet* 1986; **i**: 256-8.
- 6 Hughes W T, Feldman S, Aur R J A, Verzosa M S, Hustu H O, Simone J V. Intensity of immunosuppressive therapy and the incidence of *Pneumocystis carinii* pneumonitis. *Cancer* 1975; **36**: 2004-9.
- 7 Perrouquet J L, Harrington T M, Davis D E. *Pneumocystis carinii* pneumonia following methotrexate therapy for rheumatoid arthritis. *Arthritis Rheum* 1983; **26**: 1291-2.