Pneumocystis carinii pneumonia as a complication of methotrexate treatment of asthma

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Abstract

A 32 year old man with chronic severe asthma, requiring maintenance oral corticosteroids, was started on a weekly dose of methotrexate. Eleven weeks later he developed Pneumocystis carinii pneumonia. In the two years following treatment there has been no recurrence while oral corticosteroid treatment has been continued. Pneumocystis pneumonia should be considered in asthmatic patients taking methotrexate who present with fever, pulmonary infiltrates, and hypoxia.

Methotrexate has been used in low dose as immunosuppressive and anti-inflammatory treatment in patients with rheumatoid arthritis for many years. Recent studies have shown that low dose methotrexate lowers the requirement for oral corticosteroids in patients with asthma.1-3 Opportunistic infections are uncommon.4 We report a patient with steroid dependent asthma in whom the development of Pneumocystis carinii pneumonia was directly related to low dose methotrexate.

Case report

A 32 year old white man who had suffered from asthma and eczema since infancy was troubled with increasingly severe asthma. He was a lifelong non-smoker. In 1985 he required short courses of prednisone every four to six weeks and by January 1986 he required maintenance prednisone. His other medications included inhaled fenoterol, inhaled beclomethasone 1500 μg/day, slow release theophylline, beclomethasone intranasally, and prazosin for hypertension. His asthma control was still suboptimal and he experienced side effects, including emotional lability (leading to a change to dexamethasone, which produced fewer problems), weight gain, catacra, a Cushingoid habitus, hypertension that was difficult to control, and osteoporosis, with wedge fractures of the thoracic spine in 1988. He had persistent rhinitis and snored (without evidence of the sleep apnoea syndrome).

In July 1988 low dose methotrexate treatment was started in an effort to reduce his symptoms, improve overall asthma control, and allow a reduction in steroid dosage (at that stage dexamethasone 6 mg/day). After a test dose of 7.5 mg, which he tolerated without problems, the dose was increased to 15 mg a week. After 11 doses (total dose 157.5 mg) he complained of dizziness, sweating, tiredness, and nausea, and stopped the methotrexate in September 1988. Liver enzyme tests gave normal results throughout.

Five days later he was admitted to hospital to improve his asthma control before a septoplasty. The dexamethasone was increased to 12 mg/day, fenoterol by nebuliser and theophylline were continued, and physiotherapy was started. Forty eight hours later he became unwell. He had a temperature of 38.2°C, his chest was wheezy with bilateral basal crackles, and a chest radiograph showed extensive alveolar shadowing. There was no clinical evidence of cardiac failure; a trial of frusemide was unhelpful, and normal results from impedance plethysmography of both lower limbs made deep venous thrombosis with pulmonary embolism unlikely. His dexamethasone was reduced to 6 mg daily and he was given intravenous amoxycillin/clavulinate. Sputum and blood cultures taken before antibiotic treatment showed no growth; sputum smears for acid fast bacilli were negative, as were subsequent cultures. Erythromycin was added when four days of antibiotics resulted in no improvement. He continued to be febrile, and became increasingly hypoxaemic, with an arterial oxygen saturation of only 90% with 60% inspired oxygen (arterial oxygen tension (Pao2) 8.5 kPa; breathing air he had a Pao2 of 4.7 kPa). The radiological changes worsened.

As he continued to deteriorate an open lung biopsy was performed three weeks after admission. At operation the right lung was woody with 1–5 mm firm nodules throughout. A biopsy specimen from the right middle lobe showed diffuse alveolar damage and interstitial pneumonitis, a toluidine blue stain imprint was positive for P carinii, and a Gram stain showed a moderate number of pus cells but no organisms. There was no growth from cultures for the usual bacterial pathogens, Legionella, acid fast bacilli, fungi, or cytomegalovirus. The results of an HIV antibody screen were negative and of cytomegalovirus and mycoplasma complement fixation tests only weakly positive.

A clinical diagnosis of pneumocystis pneumonia was made and treatment was changed to high dose oral co-trimoxazole (four 480 mg tablets four times a day). Within 48 hours his fever had abated and his oxygen requirement had fallen so that 3 litres/min oxygen by nasal prongs maintained an arterial Pao2 of 10.1 kPa. He completed three weeks of co-trimoxazole treatment and continued to improve, and the radiological changes resolved. Two years later he remains stable on maintenance oral steroids (dexamethasone 1 mg and 0.5 mg on alternate days) with no recurrence of pneumocystis pneumonia.


**Discussion**

We believe that this man had *P carinii* pneumonia as a consequence of his treatment with methotrexate. He had been having maintenance oral corticosteroids for over two years without problems but developed pneumocystis pneumonia within 11 doses of starting methotrexate, despite a concomitant reduction in steroid dose.

Methotrexate has anti-inflammatory and antineoplastic effects but is not thought to cause immunosuppression. Recent reports have highlighted the occurrence of pneumocystis pneumonia in patients with arthritis taking methotrexate. In some of these cases concomitant treatment with non-steroidal anti-inflammatory agents may have raised serum concentrations of methotrexate. Our patient was not taking such drugs.

We are concerned that the use of methotrexate in asthma is not without risk, even in the low weekly doses currently recommended. New infiltrates in a patient with asthma who is taking methotrexate should be investigated thoroughly to determine whether the cause is *P carinii* pneumonia and to differentiate it from drug induced pneumonitis.


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