

Fatal pneumocystis carinii pneumonia as a complication of methotrexate in rheumatoid arthritis

M Suleman, MB Chaudri, C Deighton & RB Hubbard

Abstract

Low dose methotrexate has been used successfully to treat patients with refractory rheumatoid arthritis.¹ Methotrexate-induced pneumonitis occurs in about 1 to 5% of patients, although opportunistic infections have also been reported.¹ We report a case of fatal pneumocystis carinii pneumonia (PCP) in an otherwise healthy female patient treated with methotrexate for rheumatoid arthritis and review the literature.

Keywords

Pneumocystis carinii pneumonia, methotrexate

Teaching Point

Always consider Pneumocystis pneumonia when a patient taking methotrexate presents with respiratory symptoms and interstitial shadowing on chest x-ray. Failure to diagnose and treat this condition promptly may have fatal consequences.

Case report

A 73 year old Caucasian woman, with a 5 year history of rheumatoid arthritis, was admitted with a six week history of general weakness, poor mobility, and exertional dyspnoea. Her exercise tolerance was less than 5 yards on the flat. For the preceding three weeks she had complained of a dry cough. She also reported nausea and weight loss of approximately 1.5 stones over the course of one year.

Her drug treatment consisted of methotrexate 15mg a week, prednisolone 5 mg daily, *Didronel PMO* (Procter and Gamble pharm.) one tablet daily, and metolazone 5mg twice weekly. Methotrexate treatment had commenced 4 years previously.

On examination she was apyrexial, with a dry tongue, reduced skin turgor, and bilateral ankle oedema. Auscultation of her chest revealed fine crackles bibasally, and Chest x-ray showed bilateral basal fibrotic shadowing with consolidation in both midzones (see Figure 1). Electrocardiogram showed partial right bundle branch block. Full blood count was normal apart from a raised mean cell volume of 103. Electrolytes revealed mild dehydration with a low albumin of 17 g/l. Cardiac enzymes were normal. C-reactive protein (CRP) and erythrocyte sedimentation rate were elevated at 230 and 85 respectively. Blood cultures were negative. Urine examination for legionella antigen was negative, but urine culture revealed $>10^8$ coliform bacilli, sensitive to trimethoprim.

A provisional diagnosis of urinary tract infection



Figure 1. CXR showing bilateral basal fibrotic shadowing with consolidation in both midzones.

and drug-induced pneumonitis secondary to methotrexate was made. The methotrexate was stopped, the prednisolone increased to 20 mg a day, and she was started on trimethoprim 200mg twice daily.

Her condition failed to improve, and a number of further investigations were therefore undertaken. Echocardiogram showed normal left ventricular function and dimensions. Ventilation/perfusion scan showed matched ventilation/perfusion defects bilaterally. CT thorax (Figure 2) revealed widespread

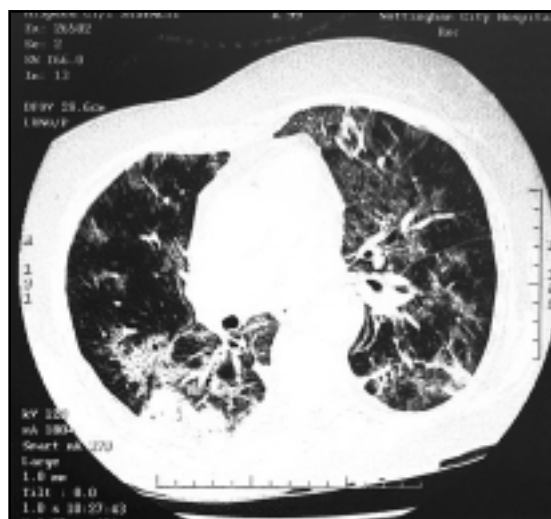


Figure 2. CT chest showing areas of ground glass opacification and areas of more confluent shadowing. These features are consistent with but not diagnostic of methotrexate pneumonitis.

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linear shadowing in both lung fields especially the lower zones, with areas of diffuse as well as confluent shadowing. Although non-diagnostic, these findings were felt to be consistent with methotrexate exposure.

Five days later she became acutely dyspnoeic. On examination she was afebrile, but clammy with a respiratory rate of 40 breaths per minute. On auscultation there were widespread fine and coarse inspiratory crackles bilaterally. Arterial blood gas measurement revealed pH 7.54, PaCO₂ 3.6kPa and PaO₂ 7.39kPa, while breathing 40% oxygen. It was assumed that she had developed a hospital-acquired pneumonia, despite a drop in her CRP to 35. She was started on intravenous vancomycin 1g/bd IV, ciprofloxacin 400mg bd IV and gentamicin 3 mg/kg IV. The FIO₂ was increased, and her condition appeared to stabilise, with repeat blood gases showing pH 7.51, PaCO₂ 3.41 and PaO₂ 10.61 on 3li / min via nasal cannulae.

The following day her condition deteriorated again. She became pyrexial at 38.2°C, with persistent tachypnoea and tachycardia. PaO₂ had fallen to 6.45 kPa, despite high-flow oxygen. Her condition failed to improve with continuous positive airways pressure (CPAP) at 5cmH₂O and she was transferred to the intensive care unit, where she was intubated and mechanically ventilated.

Blood cultures were again negative. Bronchoscopy was normal and bronchial washings were negative for acid-fast bacilli, fungi and legionella, but positive for *pneumocystis carinii*. She had been started empirically on intravenous cotrimoxazole 120 mg/kg daily the previous day, which was continued, while the other antibiotics were stopped. Despite active treatment she failed to recover and died six days later.

Discussion

Pneumocystis carinii pneumonia (PCP) is a recognised complication of treatment with low-dose methotrexate. Our review of the literature revealed thirteen cases, eight of whom were women, with ages ranging from 16 to 74 years. Ten patients were being treated for rheumatoid arthritis, two for asthma and one for psoriatic arthritis. The duration of methotrexate treatment prior to presentation varied between 11 weeks^{2,3} and four years.^{4,5} The maximum dose varied

between 5 and 22.5 mg a week. Five patients died as a result of PCP.^{2,6,4,7,5} Eight of the 13 cases had a reduced white cell count, at presentation, due to either leucopenia or lymphopenia. However, two of the five fatalities had a normal white cell count, as did our patient.

Concomitant anti-inflammatory drug treatment may increase a patient's susceptibility to PCP. In addition to methotrexate, some patients were taking both steroids and non-steroidal anti-inflammatory drugs (NSAIDs).^{2,8,9,5} Others, as in our case, were taking either steroids^{3,7} or NSAIDs^{10,11,4,5} alone. Only one patient was taking methotrexate alone.⁶ It has been suggested that methotrexate interacts with NSAIDs.¹² NSAIDs are known to increase the plasma concentration of methotrexate, possibly by competing for protein binding sites and by reducing renal tubular excretion. It has also been suggested that significant weight loss (as occurred in our patient) may further impair host immunity and predispose to PCP.⁴

It may be very difficult to distinguish clinically between drug-induced pneumonitis and PCP in a patient taking methotrexate. Methotrexate pneumonitis typically presents with progressive shortness of breath and cough, often associated with fever. Hypoxaemia and tachypnoea are always present and crackles are frequently audible. Chest radiography reveals a diffuse interstitial or mixed alveolar and interstitial infiltrate with a predilection for the lower lung fields. These clinical and radiological features are not specific to methotrexate pneumonitis and therefore the careful exclusion of infection is important.¹³ Although methotrexate pneumonitis is more common than PCP infection in a patient taking methotrexate, failure to identify and treat the latter may have fatal consequences. Furthermore, treatment with corticosteroids may ameliorate the cellular response to *P. carinii*, and therefore mask the diagnosis of PCP.

Conclusion

It is essential to consider PCP in any patient on methotrexate, presenting with respiratory symptoms and evidence of interstitial shadowing on chest x-ray. This diagnosis should be sought actively in such cases, so that treatment may be started early.

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