Case Report: Unilateral Methotrexate Pneumonitis

Dr Moya Young, Specialist Trainee 1 Doctor, Dr Lim Ven Gee, Foundation Year 1 Doctor & Dr Ghanim Hamza, Consultant Physician, Queen Elizabeth Queen Mother Hospital, Margate, Kent

ABSTRACT

Pneumonitis is a well-recognised complication of methotrexate and more so as it is increasingly prescribed for a variety of inflammatory conditions. In this case report, we aim to describe the second reported case of unilateral methotrexate-induced pneumonitis in a patient with a background of rheumatoid arthritis and chronic obstructive pulmonary disease (COPD). All other reported cases of methotrexate pneumonitis with the exception of one have had bilateral clinical and radiological features.

INTRODUCTION

Methotrexate has long been identified as a cause of pulmonary disease and it is prescribed more frequently than other drug [1]. Methotrexate-induced pneumonitis is a well-recognised adverse drug reaction and has clearly defined clinical and radiological features [2].

In this case report we aim to describe the second reported case of unilateral methotrexate-induced pneumonitis in a patient with a background of rheumatoid arthritis and chronic obstructive pulmonary disease (COPD). All other cases of methotrexate pneumonitis, with the exception of one [3], have had bilateral clinical and radiological features.

CASE REPORT

An 82 year old independent gentleman presented with a history of dyspnoea at rest for one day and dry cough for six weeks. He had previously received two courses of antibiotics for his cough but they did not ease his symptoms. He had a past history of COPD and rheumatoid arthritis for which he had been under the care of the rheumatologists for over ten years. His arthritis was well controlled on methotrexate 10mg, which had been administered for one year. He was also on folic acid and required only inhalers for his COPD.

On examination he was pyrexial (38.2°C), tachycardic, tachypnoeic (respiratory rate (RR) of 30) and had an oxygen saturation of 86% on air. Examination of the respiratory system revealed decreased air entry at the right lung and bibasal crepitations which were significantly greater on the right. Examination of the cardiovascular and gastrointestinal system was unremarkable.

An arterial blood gas on air revealed a pO2 of 6.44kPa, pCO2 of 4.09kPa and pH of 7.435. The ECG showed sinus tachycardia. His blood results revealed raised inflammatory markers (white cell count 22.7 x 10⁹/L, neutrophils 19.00 x 10⁹/L, C-Reactive protein 84 mmol/L) and acute renal failure (Creatinine 188 µmol/L).

The chest x-ray (CXR) demonstrated an extensive diffuse shadowing throughout the right lung field (Figure 1). The left lung was spared of any changes. He was diagnosed with type 1 respiratory failure secondary to a presumed right bronchopneumonia complicated by sepsis. He was managed with nebulisers, clarithromycin, amoxicillin and IV fluids. His methotrexate was withheld due to underlying sepsis.

After 24 hours, the patient’s condition stabilised (oxygen saturation of 93% on air, RR 20 and temperature of 36.6°C). The CXR was discussed with the radiologist who advised a computed tomography (CT) scan of the chest, abdomen and pelvis given the extensive right lung involvement and to rule out underlying malignancy. This revealed a normal looking left lung but extensive opacification of the right lung with appearances consistent with unilateral interstitial lung disease (Figure 2). Lung fibrosis and lymphangitis carcinomatosa were added to the differential diagnoses although the unilateral nature of the fibrosis was thought to be unusual.
The patient's dyspnoea and dry cough did not improve despite being on antibiotics for three days. His blood culture did not demonstrate any growth and no legionella antigens were detected in the urine. In view of the possibility of unilateral interstitial lung disease, corticosteroid therapy (prednisolone 40mg) was initiated at this point and his symptoms improved dramatically the following day. A repeat CXR showed that the florid interstitial shadowing of the right lung that was present seven days earlier had almost resolved (Figure 3).

On the eighth day, the patient was no longer dyspnoeic and his dry cough had markedly improved. Chest auscultation revealed good air entry bilaterally with scattered crackles at the right base. The patient was discharged on a tapered dose of prednisolone. He was diagnosed with presumed unilateral methotrexate-induced pneumonitis.

The patient was reviewed in clinic two weeks later and remained well on a maintenance dose of 15mg prednisolone. A high resolution CT scan (HRCT) was performed two months after the admission date and showed that the severe interstitial changes on the previous scan were now virtually absent (Figure 4). There was only minimal residual interlobar interstitial thickening in the right lung base with subtle ground glass appearance at the right apico-basal segment. There was a background of centrilobular emphysema consistent with his history of COPD.

**DISCUSSION**

Methotrexate was identified as the most likely causative agent of this patient's unilateral interstitial fibrosis. This was made on the basis of several points. Firstly, the patient's respiratory symptoms and signs and radiological findings rapidly improved following the withdrawal of methotrexate and initiation of corticosteroids. Secondly, the patient's condition did not improve with antibiotics and the blood culture and urine sample were normal. Thirdly, the HRCT findings of ground-glass opacities with interlobular interstitial thickening are characteristic of those reported for anti-neoplastic agent induced pneumonitis (4).
Fourthly, the patient’s history did not reveal any other possible causative agent to fully explain his interstitial pneumonitis. Furthermore, the patient’s presenting syndrome of respiratory illness comprising fever, non-productive cough, dyspnoea and alveolar infiltrate on CXR is similar to previously described syndromes of methotrexate-induced pneumonitis.

Over the past 30 years pulmonary toxicity secondary to the use of methotrexate and related agents has been increasingly recognised (1,3,5). Methotrexate has been linked as a causative agent in both interstitial pneumonitis and fibrosis, although the exact mechanism is still not known with theories ranging from a hypersensitivity-type drug reaction to that of a direct toxic reaction (6,7).

Methotrexate-induced pneumonitis has, in all but one previous case, been reported as a bilateral pulmonary parenchymal disease process (3). In that case, the patient had carcinoma of the tonsil which metastasized to the lung and developed right sided methotrexate-induced pneumonitis. The authors suggested that the pneumonitis was confined to the right lung because of altered circulation to the left lung which received its blood supply only from the systemic bronchial circulation. Autopsy confirmed that the left pulmonary artery had been invaded and obstructed by the tumour.

They speculated that the reduced circulation to the left lung protected the parenchyma from the toxic effects of methotrexate and the effector cells that led to the interstitial changes seen within the right lung of that patient (3). In our case, no formal imaging of the patient’s vascular system was undertaken although the original CT scan did reveal a 4.1cm saccular aneurysm of the arch of the aorta. We did consider if the patient’s emphysema was more severe in one lung it may have affected the pattern of expression of the pneumonitis. However, the HRCT demonstrated little asymmetry between both lungs. We are therefore unable to comment on this hypothesis.

Methotrexate is now more frequently recognised as a cause of pneumonitis as its use continues to increase. Several reports have suggested that the incidence of methotrexate pneumonitis in rheumatoid arthritis patients varies widely from 0.86-6.9%. The risk is at its greatest during the first year of therapy with the agent and the overall frequency is one in every 100 patient years (8). Patients identified as being at greatest risk include smokers and those with underlying lung disease (9,10,11). Mortality from methotrexate pneumonitis is estimated at around 20% in most series published (9,12).

The single most predictive test for the development of pneumonitis is a markedly reduced gas transfer on pulmonary function tests (13). The offering of pulmonary function tests prior to the administration of methotrexate may be advisable to identify those at higher risk of developing pneumonitis so that an alternative therapy may be offered. However, pneumonitis has been reported in patients with normal baseline pulmonary function although they were associated with a more favourable outcome. If the patient becomes symptomatic whilst on methotrexate there is a role for repeat pulmonary function tests to compare to the documented baseline levels. If there is a reduction of 20% or more in gas transfer then methotrexate should be stopped (5,13,14).

Pneumonitis is often heralded with the onset of acute/subacute dyspnoea often associated with cough and fever. Examination reveals fixed basal lung crackles and hypoxia. Eosinophilia is reported together with evidence radiologically of pulmonary infiltrates. Although our patient did not undergo lung function tests, bronchoalveolar lavage (BAL) or lung biopsy he had a definite diagnosis of methotrexate-induced pulmonary toxicity based on his clinical and radiological findings (Table 1).

---

**Table 1: Criteria of Searles and McKendry for diagnosis of methotrexate pneumonitis.**

- **Definite:** ≥ 6 criteria
- **Probable:** 5 of 9 criteria
- **Possible:** 4 of 9 criteria

1. Acute onset dyspnoea
2. Fever > 38°C
3. Tachypnoea ≥ 28/min, and dry cough
4. Radiological evidence of pulmonary interstitial or alveolar infiltrates
5. WBC < 15,000/cu mm with or without eosinophilia
6. Negative blood and sputum cultures (mandatory)
7. Restrictive defect and decreased DLCO on lung function tests
8. pO2 < 60 mm Hg on room air
9. Histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection.
More recently, Chikura et al. demonstrated an association between the degree of methotrexate exposure and the immunological responses in methotrexate-induced pneumonitis (MTX-P) \(^{(15)}\). Their findings suggested that MTX-P can be divided into two categories: type 1 or early onset MTX-P (<6months) that is predominated by neutrophilia, lung fibrosis and high mortality and type 2 or late onset MTX-P (>6months) that is predominated by lymphocytosis and low mortality. Although our patient had late onset MTX-P according to their classification, the findings could not be applied to him as all the subjects in their study (n=56) had bilateral pulmonary involvement.

HRCT is a key investigation in the diagnosis of drug-induced pneumonitis. A retrospective study of 60 patients with drug-induced pneumonitis including anti-neoplastic agents and non-neoplastic agents has highlighted the different CT findings seen with each group of agents. In patients with neoplastic agent-induced pneumonitis, the predominant CT findings were those of diffuse or multi-focal ground-glass opacities with interlobar interstitial thickening. In contrast, the non-neoplastic agent-induced pneumonitis demonstrated predominant changes of patchy ground-glass opacities with centrilobular and interlobular septal lines \(^{(4)}\).

The treatment of methotrexate pneumonitis consists of immediate cessation of methotrexate and commencement of steroids, usually orally although severe cases may warrant IV methylprednisolone \(^{(2,5)}\).

As in this case, it may not always be easy to differentiate between methotrexate pneumonitis from an acute respiratory infection. It is therefore advisable to treat both conditions if there is a delay in confirming the diagnosis with investigations such as HRCT or BAL. In atypical presentations, such as unilateral disease, infections are more likely and should be treated promptly with antibiotics \(^{(5)}\).

**CONCLUSION**

Although pneumonia and malignancy are more common causes of unilateral lung pathology, our case highlights the importance of considering the diagnosis of methotrexate-induced pneumonitis in patients on methotrexate who do not respond to antibiotics or conventional treatment. To aid the diagnosis, it is worth performing a HRCT to demonstrate the characteristic radiological changes.

**REFERENCES**