Methotrexate induced pneumonitis – A case report and review of literature

Vinay V, Sushil K. Munjal, Paras Verma, Sandeep Jain, Ompradeep Yadav B, Amit Sharma

Department of TB and Respiratory Diseases, National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi, India

ABSTRACT

Methotrexate (MTX) is the commonly preferred drug in the treatment of various chronic inflammatory conditions. An uncommon, life-threatening, and fatal event associated with methotrexate use is methotrexate-induced pneumonitis (M-pneu). M-pneu does not correlate with the dosage, duration, or method of administration. We present a case of M-pneu in a diagnosed rheumatoid arthritis patient after six years of initiation of MTX. Prompt recognition, withdrawal, and supportive therapy have a positive outcome. If untreated, M-pneu has a proven fatality of 17-30% in published cases.

Keywords: Idiosyncratic hypersensitivity reaction, interstitial pneumonitis, methotrexate-induced pneumonitis, rheumatoid arthritis, toxicity

Background

Methotrexate (MTX), developed in 1948, is an antifolate and antimetabolite drug that disrupts deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis by inducing a deficiency of folate-dependent coenzymes. It is used to treat rheumatological diseases in low doses and malignancies in high doses.[1] It is a commonly used medicine for conditions such as psoriasis, polyarticular juvenile idiopathic arthritis, rheumatoid arthritis, and cancer. Though MTX has many benefits, however, in a few instances, the risks outweigh the benefits. This case demonstrates that the risk might stay even after years of tolerance.

Case

A 61-year-old male smoker presented to the emergency department with worsening shortness of breath and non-productive cough for one month and fever for five days with no history of chest pain, hemoptysis, palpitation, or pedal edema. He had been on methotrexate (MTX) 15 mg weekly for the last six years for rheumatoid arthritis (RA), and metformin 500 mg and glimepiride 1 mg for diabetes mellitus for the past two years. He did not have any exposure to dust or toxic fumes priorly. On examination, his temperature was 38.4°C, blood pressure was 124/86 mmHg, the heart rate was 98 beats/min, and the respiratory rate was 26 breaths/min. Initial oxygen saturation on room air was 84% but improved to 94% on FiO₂ 0.6 via facemask at 10 L/min. On systemic examination, there were bilateral vesicular breath sounds with fine bibasilar crackles, and other systems were unremarkable. Blood investigations, including hemogram, procalcitonin, and brain natriuretic peptide (BNP), were unremarkable, and the electrocardiogram was normal. The possible differentials that were considered: coronavirus disease (Covid-19) pneumonitis,
rheumatoid associated-interstitial lung disease (RA-ILD), extrinsic allergic alveolitis, community-acquired pneumonia, Pneumocystis jiroveci pneumonia, and MTX induced pneumonitis (M-pneu).

Chest radiograph [Figure 1a] showed bilateral poorly-defined infiltrates, predominantly involving the middle and lower zones. High-resolution computed tomography (HRCT) of the chest revealed diffuse ground-glass haze (GGO) and reticular opacities [Figure 1b]. A course of empirical antibiotics and intravenous hydrocortisone were initiated. Reverse transcription-polymerase chain reaction (RT-PCR) for Covid-19 was negative, blood cultures were sterile, and sputum cultures were negative for bacterial pathogens, including mycobacterium tuberculosis. Bronchoscopy was done, and bronchoalveolar lavage (BAL) samples were negative for acid-fast bacilli (AFB), gram stain, GenXpert, bacterial and fungal culture, and pneumocystic jiroveci pneumonia. A diagnosis of MTX induced acute pneumonitis was made, and methotrexate was discontinued forever. Antibiotics were stopped, and intravenous hydrocortisone was changed to oral prednisone, and it was continued for two weeks with tapering doses. A follow-up chest X-ray showed resolution of opacities [Figure 2]. The patient was counseled not to use MTX and discharged on room air to follow up with a rheumatologist.

**Discussion**

Methotrexate is the preferred initial disease-modifying agent (DMARD) in patients with rheumatoid arthritis as it is an anti-inflammatory and immunomodulating agent. In one in 100 patient-years, methotrexate is discontinued because of M-pneu associated pulmonary toxicity. Manifestations of pulmonary toxicity of MTX include acute interstitial pneumonitis, interstitial pulmonary fibrosis, non-cardiogenic pulmonary edema, pleuritis/pleural effusion, pulmonary nodules, and cough.[3] According to western literature, MTX-induced interstitial pneumonitis (M-pneu) is uncommon, with a frequency ranging between 0.3 and 11.6%.[4]

The onset of M-pneu can occur at any time after initiating MTX (days to a year) and can be either acute or subacute. M-pneu is a T-cell-mediated (CD4 and CD8) idiosyncratic hypersensitivity reaction characterized by type 2 alveolar cells proliferation, and release of cytokines causing alveolitis. Although there are several risk factors that contribute to the disease, the extent to which they do so is still unclear. Following factors can contribute: diabetes, hypoalbuminemia, rheumatoid lung involvement, H/O use of DMARDS, renal dysfunction, male gender, a higher Health Assessment Questionnaire (HAQ) score, decreased pain Visual Analog Scale (VAS) score, age >60 years, and pre-existing lung disease.[5] They have also found other risk factors that might contribute to the development of M-pneu, including genetic factors (HLA-A31:01 haplotype),[6] and environmental factors (increased latitude).[7]

The common presentations are progressive shortness of breath, non-productive cough, pleuritic chest pain, crackles, and systemic features like fever, fatigue, and malaise.[8] Laboratory findings include mild peripheral blood eosinophilia and lymphopenia.[9] Chest X-ray findings are non-specific, may be normal early in the disease, and also might reveal bilateral acute interstitial or alveolar infiltrates and increased interstitial lung markings singly or in combination. HRCT reveals ground-glass opacities and/or centrilobular nodules that are more evident than the chest radiograph.[3]

A combination of clinical and radiological findings is used to diagnose M-pneu. Various other diagnostic procedures, including pulmonary function testing and BAL, could also be used. Pulmonary function testing might reveal a restrictive pattern and reduced diffusing capacity for carbon monoxide (DLCO). The cytology findings of BAL are non-specific and may reveal lymphocytic or neutrophilic patterns, and are primarily used to rule out the presence of infection and other conditions. Lung biopsy is 90%–95% sensitive and is used for prognostication but is associated with multiple complications.[8]

The diagnosis of M-pneu was made using Chikura et al.[9] criteria mentioned in Table 1. The diagnosis of M-pneu was made after seven of the eight criteria were met. The treatment of M-pneu involves MTX withdrawal, supportive therapy, and corticosteroid therapy. Severe cases at the time of admission may require parenteral steroids.[9] In steroid

![Figure 1: Chest X-ray PA view (a) shows bilateral ill-defined infiltrates in the mid and lower zone, and CT chest-coronal view (b) shows bilateral GGOs with reticular opacities.](Image)

![Figure 2: Chest X-ray PA view showing resolution of opacities one week after treatment (a) and three weeks after cessation of MTX (b).](Image)
failure cases, cyclophosphamide has been successfully used to treat M-pneu.\[9\] Our patient developed M-pneu five years after initiation of MTX and was successfully treated with corticosteroids and supportive therapy. At the six-months follow-up, the patient is doing well. **Take-home messages from this case are:** a) M-PNEU is an uncommon and life-threatening event b) Diabetes mellitus is a potential risk factor, c) It is a diagnosis of exclusion, d) Early diagnosis, withdrawal of MTX, and supportive therapy have a favorable outcome.

### Conclusion/Summary

A rare but potentially deadly adverse event of methotrexate is pneumonitis. M-pneu should not be confused with RA-ILD as they both have overlapping features. The long-term prognosis of M-pneu is usually favorable and recovers fully on prompt recognition and treatment and does not progress to pulmonary fibrosis.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

1. Saravanan V, Kelly CA. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. Rheumatology (Oxford) 2004;43:143-7.
2. Nagaraj S, Joshi P, Joshi VR. Methotrexate induced pneumonitis. Indian J Rheumatol 2022;7:83. doi: 10.1016/J.INJR.2012.04.001.
3. Fragoulis GE, Nikiphorou E, Larsen J, Korsten P, Conway R. Methotrexate-associated pneumonitis and rheumatoid arthritis-interstitial lung disease: Current concepts for the diagnosis and treatment. Front Med 2019;6:238. doi: 10.3389/FMED.2019.00238/BIBTEX.
4. Garcha G, Dominguez B, Otegbeye O, Nasser W. Methotrexate-induced pneumonitis. Chest 2021;160:A1652. doi: 10.1016/J.CHEST.2021.07.1503.
5. Furukawa H, Oka S, Shimada K, Tsuchiya N, Tohma S. HLA-A*31:01 and methotrexate-induced interstitial lung disease in Japanese rheumatoid arthritis patients: A multidrug hypersensitivity marker? Ann Rheum Dis 2013;72:153-5.
6. Jordan SR, Stevanovic VR, Herbison P, Dockerty J, Highton J. Methotrexate pneumonitis in rheumatoid arthritis: Increased prevalence with increasing latitude: An epidemiological study of trends in New Zealand. J Clin Rheumatol 2011;17:356-7.
7. Iiyadurai R, Carey RAB, Satyendra S. Low-dose methotrexate-induced acute interstitial pneumonitis: Report of two cases from South India and review of literature. J Fam Med Prim Care 2016;5:875. doi: 10.4103/2249-4863.201163.
8. Chikura B, Sathi N, Dawson JK. Methotrexate induced pneumonitis: A review article. Curr Respir Med Rev 2009;5:12-20.
9. Suwa A, Hirakata M, Satoh S, Mimori T, Utsumi K, Inada S. Rheumatoid arthritis associated with methotrexate-induced pneumonitis: Improvement with i.v. cyclophosphamide therapy. Clin Exp Rheumatol 1999;17:335-8.