

Methotrexate pneumonitis in a patient with gestational trophoblastic neoplasia

M Agarwal,¹ DNB; K K Sharma,¹ MD; K Deokar,² MD, DM; N Bharti,³ DNB

¹ Department of Pulmonary Medicine, Eternal Hospital Care Center, Jaipur, Rajasthan, India

² Department of Pulmonary Medicine, Sapphire Hospitals, Thane, Maharashtra, India

³ Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Corresponding author: K Deokar (dkunal@live.in)

Methotrexate, an immunomodulatory agent used for a wide variety of indications, can cause pulmonary toxicity in the form of pneumonitis, organising pneumonia, pulmonary fibrosis, pleural effusion, pulmonary infections or lymphoproliferative disease. We report a case of methotrexate pneumonitis in a patient with gestational trophoblastic neoplasia. The diagnosis of methotrexate pneumonitis is challenging, as the signs and symptoms can be caused by intercurrent infection, concomitant medications or an underlying disease condition. A high index of suspicion is required for diagnosis. Management consists of drug discontinuation and steroids in patients with respiratory failure.

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Methotrexate (Mtx) is one of the most widely used immunomodulatory drugs, with a broad spectrum of indications. However, it comes at a cost of a wide range of side-effects ranging from gastrointestinal to haematological to less commonly recognised pulmonary toxicity. Pneumonitis is a serious adverse event and occurs in ~1 - 7% of patients treated with Mtx.^[1] A high index of suspicion is required, as these patients are immunosuppressed and are on multiple drugs. We describe the case of a 29-year-old woman with an invasive mole who was treated with Mtx and developed Mtx pneumonitis.

Case report

A 29-year-old woman was hospitalised with shortness of breath and cough, which she had experienced for the past 6 days. She had been diagnosed with gestational trophoblastic neoplasia (invasive mole) with a baseline serum human chorionic gonadotrophin (HCG) level >1 300 mIU/mL, and was on weekly doses of 50 mg Mtx. She reported breathlessness on exertion and fever, 2 - 3 days after the 9th Mtx dose. She was treated with oral antibiotics and oseltamivir. A throat swab for H1N1 influenza was negative. Her condition worsened after 3 days, with increasing shortness of breath and cough, and she was admitted to our hospital.

At the time of presentation, the patient's blood pressure was 105/65 mmHg, her pulse rate 122 bpm, her respiratory rate 32 breaths per minute, and her peripheral oxygen saturation 70% on ambient air. She was febrile with an axillary temperature of 38°C. Chest auscultation revealed crepitations in the basal areas. Arterial blood gas analysis revealed respiratory alkalosis with hypoxaemia. The white blood cell count was $8.08 \times 10^9/L$. A chest radiograph showed bilateral mid- and lower zone infiltrates (Fig. 1A). A high-resolution computed tomography scan of the thorax showed consolidation involving bilateral lower lobes and ground-glass opacities involving the middle and lingular lobes and both the upper lobes (Fig. 2). The patient received oxygen via a high-flow nasal cannula, and broad-spectrum

antibiotics were initiated. Blood and sputum for aerobic culture did not grow any micro-organisms. As the patient had developed new symptoms on Mtx, Mtx pneumonitis was suspected. The procalcitonin value was 0.035 ng/mL (normal <0.1 ng/mL). Two-dimensional echocardiography revealed normal chamber dimensions with an ejection fraction of 60%. Blood, urine and sputum cultures were negative.

The patient was given a single intravenous dose of methylprednisolone 125 mg on the 2nd day of admission. With a single dose, she experienced significant clinical improvement overnight and her oxygen requirement and work of breathing decreased. Pulmonary infiltrates on the chest radiograph also improved. Methylprednisolone was repeated for the next 2 days, after which oral steroids were started. The patient improved clinically and radiologically (Fig. 1B) and was weaned off oxygen. She was discharged on the 5th day on low-dose oral steroids. Serum HCG levels were monitored and were consistently <2 mIU/L.

Discussion

Mtx, a folic acid antagonist initially developed as an antineoplastic drug, is commonly used in various neoplastic as well as non-neoplastic inflammatory conditions, the most common being psoriasis and rheumatoid arthritis. Involvement of the lungs may become difficult to manage if not recognised early. Symptoms are nonspecific in the form of non-productive cough, shortness of breath, chest pain and fever. Mtx-induced lung injury is considered an idiosyncratic reaction, as the time of onset of symptoms after administration and the dose at which symptoms occur is highly variable.^[2] Risk factors associated with Mtx pneumonitis include age >60 years, hypoalbuminaemia, diabetes mellitus, daily dosing of Mtx as opposed to weekly, pre-existing lung disease, renal insufficiency, and previous use of disease-modifying antirheumatic drugs.^[3] A chest radiograph may show interstitial/alveolar infiltrates, nodular opacities, pleural effusion,

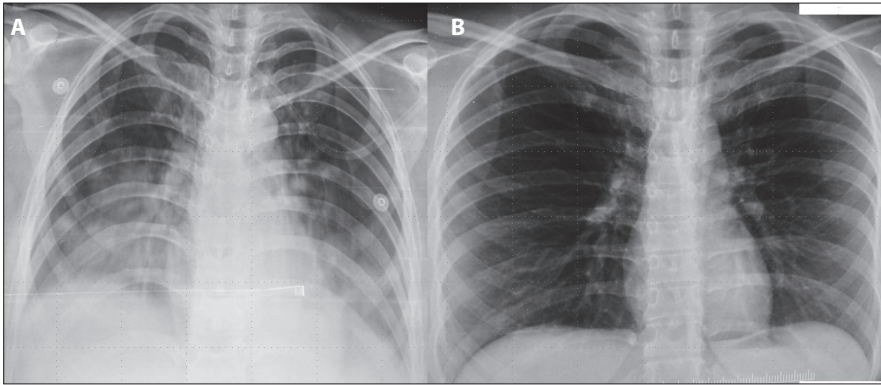


Fig. 1. (A) Chest radiograph of the patient on admission. (B) Chest radiograph at discharge.

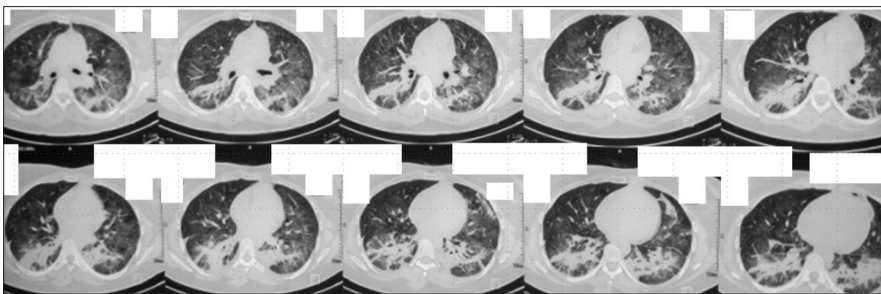


Fig. 2. High-resolution computed tomography scan of the thorax showing consolidation involving bilateral lower lobes and ground-glass opacities involving the middle, lingular and upper lobes.

Table 1. Characteristics of cases of methotrexate pneumonitis in patients with gestational trophoblastic neoplasia reported in the literature to date

| Reference | Age (years) | Symptoms | Total dose of methotrexate after which symptoms appeared |
|---|-------------|---|--|
| Gillespie <i>et al.</i> , ^[7] 1997 | 23 | Shortness of breath, pleuritic chest pain | 200 mg |
| | 28 | Shortness of breath, pleuritic chest pain | 600 mg |
| | 18 | Shortness of breath, pleuritic chest pain | 600 mg |
| Zhang <i>et al.</i> , ^[8] 2008 | 47 | Shortness of breath, chest pain, cough, fever | 500 mg |
| Present case, 2022 | 29 | Shortness of breath, cough, fever | 450 mg |

non-cardiogenic pulmonary oedema or hilar/mediastinal lymphadenopathy, or may be normal.^[4] Various diagnostic criteria have been proposed, but the most commonly used is that of Searles and McKendry.^[5]

Our patient had acute onset of shortness of breath, her oxygen saturation was 70% on room air at the time of admission, she had radiographic evidence of diffuse pulmonary ground-glass opacities and consolidation, and blood and sputum culture did not grow any pathogenic organism. She was therefore a 'definite' case of Mtx pneumonitis. On

reviewing the literature, we could find only four reported cases of Mtx pneumonitis in patients with gestational trophoblastic neoplasia. These cases are summarised in Table 1.

Management of Mtx pneumonitis is not yet established and includes discontinuation of the drug. Corticosteroids are indicated in patients who deteriorate despite drug discontinuation and in those with respiratory failure, at a dose of 1 mg/kg of prednisolone or equivalent. Methylprednisolone is given in cases of impending respiratory failure.

The dose and duration of steroids are not validated and depend on the individual patient's response to therapy. Reinstitution of Mtx may result in relapse, but successful reinstitution has been reported.^[6]

Conclusion

Mtx-induced pneumonitis is a serious adverse event. Diagnosis is based on a combination of clinical and radiological features, and response to drug discontinuation. Steroids are indicated if there is no response to drug discontinuation, and in cases of respiratory failure.

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Conflicts of interest. None.

- Jakubovic BD, Donovan A, Webster PM, Shear NH. Methotrexate-induced pulmonary toxicity. *Can Respir J* 2013;20(3):153-155. <https://doi.org/10.1155/2013/527912>
- Chhabra P, Law AD, Suri V, Malhotra P, Varma S. Methotrexate induced lung injury in a patient with primary CNS lymphoma: A case report. *Mediterr J Hematol Infect Dis* 2012;4(1):e2012020. <https://doi.org/10.4084/MJHID.2012.020>
- Salehi M, Miller R, Khaing M. Methotrexate-induced hypersensitivity pneumonitis appearing after 30 years of use: A case report. *J Med Case Rep* 2017;11(1):174. <https://doi.org/10.1186/s13256-017-1333-0>
- Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: Review of the literature and histopathological findings in nine patients. *Eur Respir J* 2000;15(2):373-381. <https://doi.org/10.1034/j.1399-3003.2000.15b25.x>
- Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: Potential risk factors. Four case reports and a review of the literature. *J Rheumatol* 1987;14(6):1164-1171.
- Barrera P, Laan RFJM, van Reil PLCM, Dekhuijzen PNR, Boerbooms AMTh, van de Putte LBA. Methotrexate related pulmonary complications in rheumatoid arthritis. *Ann Rheum Dis* 1994;53(7):434-439. <https://doi.org/10.1136/ard.53.7.434>
- Gillespie AM, Lorigan PC, Radstone CR, Waterhouse JC, Coleman RE, Hancock BW. Pulmonary function in patients with trophoblastic disease treated with low-dose methotrexate. *Br J Cancer* 1997;76(10):1382-1386. <https://doi.org/10.1038/bjc.1997.564>
- Zhang D, Ding Z, Qian J, Xie X, Wang Y. Two rare cases of methotrexate-induced pneumonitis and pleurisy in patients with gestational trophoblastic neoplasms. *Eur J Gynaecol Oncol* 2008;29(4):390-392.

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