



Methotrexate Pneumonitis: Clinical suspension, approach to diagnosis and treatment

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INTRODUCTION

Methotrexate (MTX) induced lung toxicity most often occurs after weeks to months of low-dose methotrexate therapy [10,12-14]. In a literature review about 50% arose in patients receiving therapy for rheumatoid Arthritis (RA), 20% during treatment for leukemia, and 8% were in patients treated for other malignancies. The precise frequency is difficult to assess as some reports have included patients who were receiving other cytotoxic medications [1]. In a systematic literature review of 3463 patients with RA only 15 of which were felt to be attributable to methotrexate [26].

Hypersensitivity pneumonitis is most common type of pulmonary toxicity associated with MTX. There are other types of lung injury have been associated with MTX use including: Organizing pneumonia (bronchiolitis obliterans with organizing pneumonia or BOOP) Acute interstitial pneumonia with edema, Pulmonary fibrosis (rapidly progressive) [9,28] Pleural effusion and symptomatic pleuritis occur infrequently.

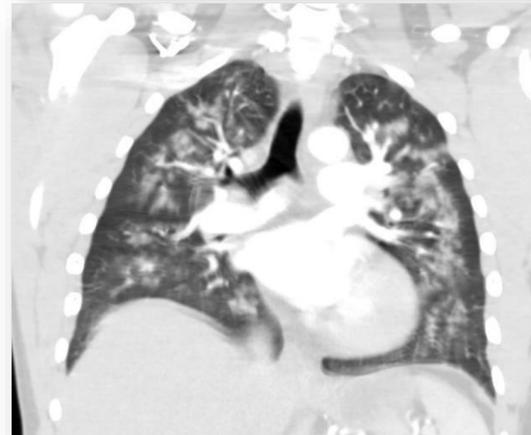
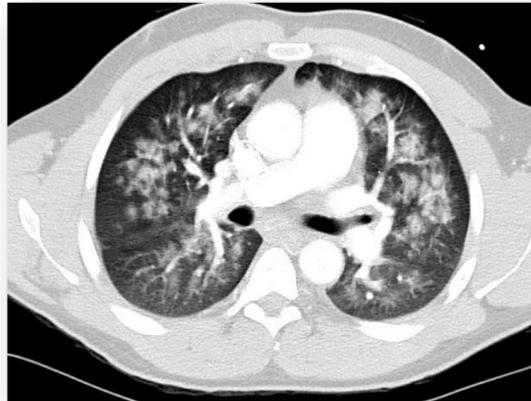
MTX pneumonitis present as insidious onset of dyspnea (82 percent), nonproductive cough (81 percent), fever (76 percent), crackles (50 percent), and cyanosis over a few weeks [10,30,52].

CASE DESCRIPTION

HISTORY:

- 34-year-old gentleman with history of RA diagnosed one year ago who presents with worsening shortness of breath for 3 weeks.
- He is usually in an excellent state of health. His RA is well controlled with methotrexate and prednisone.
- About 3 weeks ago, he started noticing more dyspnea, when working out, slowly progressed to the point where he was short of breath on mild exertion.
- He has a cough with intermittent hemoptysis, mixed with pink or frothy sputum. He is worse when he is supine, but he denies any paroxysmal nocturnal dyspnea. He reports no sick contacts or environmental or industrial exposure, prior to the onset.
- He states that he did travel to Lake Havasu, and spent a lot of time outdoors, but he claims that symptoms had already begun before this exposure. There is no contact with birds. He does not have a hot tub. He denies fever or chills.

Initial CT of chest with IV contrast in ER:



- Ground-glass nodules in centrilobular distribution most consistent with hypersensitivity pneumonitis.

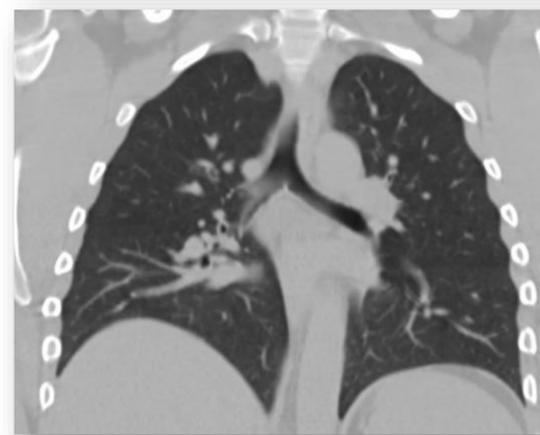
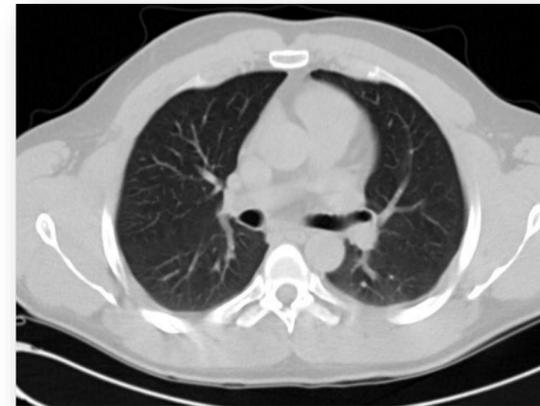
PHYSICAL EXAM:

- Examination revealed a tachypnic distressed patient setting at the edge of bed on 50% vent mask.
- Vitals: HR 110, tachypnea RR 24 and hypoxia O2% at 88%.
- The patient had decreased air entry bilaterally in the lower lobes with gross bilateral crackles and some faint expiratory.
- Laboratory and cultures: WBC 22.50, Eos% 1.7%,
- All Blood and sputum cultures are negative, AFB negative, Auto-imm panel Negative. Cocci negative.

HOSPITAL COURSE:

- Patient was started on broad spectrum antibiotics initially with no clinical significant improvement.
- Continued to be hypoxic at rest and required high flow oxygen to keep sats% >90%.
- Pulmonary service was consulted for further recommendations and possible Bronchoscopy.

6 weeks follow up CT chest after discontinuation of Methotrexate :



- CT chest showed: Almost complete resolution of interstitial infiltrates seen on presentation.

BRONCHOSCOPY/ BAL:

- Normal vocal cords with blood streak posterior to the laryngeal. Normal airway anatomy.
- Examination of the left and right bronchial trees showed generous amount of frothy secretions bilaterally with mild mucosal inflammation.
- Cutters from BAL came back all negative including fungal cultures. AFB negative.

PATHOLOGY:

- The prepared slides contained numerous lymphocytes in a background of fresh blood. The lymphocytes are mature and reactive appearing.
- No atypical lymphocytes are seen. No acute inflammation or granuloma are seen. No other atypical features are identified.

Available Treatment:

- Optimal therapy for methotrexate-induced lung toxicity has not been established and no prospective trials of therapy have been performed.
- Treatment for MTX pneumonitis relies on early diagnosis, discontinuation of the offending drug, supportive care and trial of corticosteroids treatment.
- Treatment with high dose corticosteroids. The patient was started on high dose of prednisone daily, stopped MTX treatment and
- Our patient: See Images!

DISCUSSION:

➤ While no test is absolutely diagnostic of methotrexate-induced pneumonitis, some tests can help in the inclusion or exclusion of other processes. Radiographic evaluation, a trial of drug cessation, bronchoalveolar lavage, and lung biopsy are the primary ways to narrow the differential diagnosis when methotrexate-induced lung disease is suspected.

➤ Risk factor for developing lung injury from MTX:

- Age greater than 60 years
- Rheumatoid pleuro-pulmonary involvement
- Previous use of disease-modifying antirheumatic drugs
- Higher dose of Methotrexate use.
- Diabetes mellitus

➤ Pneumonitis associated with MTX toxicity characterized by a lymphocytic infiltration of the interstitium with epithelial cell hyperplasia, small, poorly formed granulomas, and sometimes eosinophilic infiltration [1-3,9,19].

➤ 50% of patients demonstrate peripheral blood eosinophilia, our patient didn't.

➤ Clinical course varies from patient to other, depending on base line lung function, presence of other comorbidities and using of other immune modulating drugs as well.

➤ Pulmonary function tests (PFTs) are helpful for characterizing the pattern and severity of respiratory impairment in patients with respiratory symptoms. It's usually Restrictive in pattern. The use of PFT's as screening modality for MTX Pneumonitis is not well studied.

A CLINICIAN'S PERSPECTIVE:

➤ Mortality is around 13% (6). Early detection and treatment is crucial in these patients as they symptoms can progress quickly with unfavorable outcome.

➤ Awareness of the other differentials of hypoxia in patients on Immunosuppressive treatment who present with pneumonia like picture.

➤ It's imperative to exclude the possibility of pulmonary infection early in the course of diagnosis and prior to initiating treatment with glucocorticoids.

References: 8523359, 10706507, 3511808, 15611303