Methotrexate induced Hypersensitivity pneumonitis: Review of Literature with Case report

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Citation

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Abstract

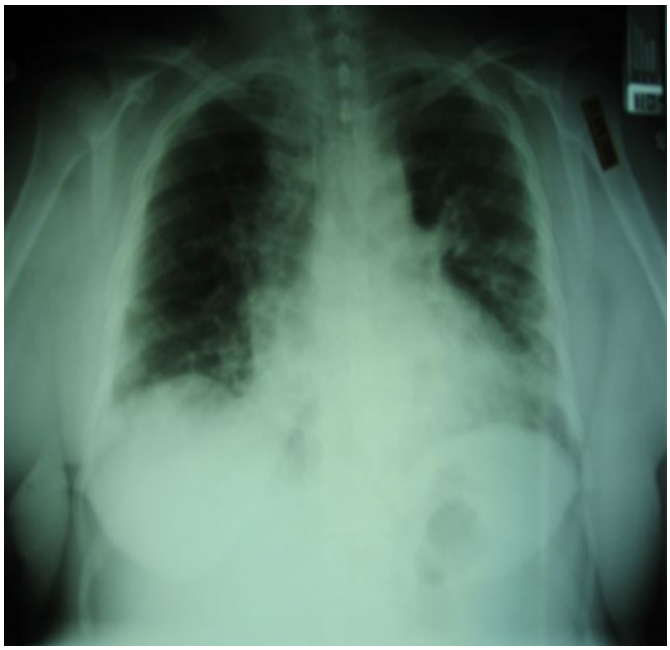
Methotrexate induced interstitial pneumonitis can easily be misdiagnosed as it usually presents as community acquired pneumonia. Also, when a patient presents with symptoms of pneumonia, esoteric causes stands at the bottom of our differential diagnosis. Unrecognized Methotrexate induced interstitial pneumonitis can lead to serious complications like ARDS or death. We report a case of Methotrexate induced interstitial pneumonitis to familiarize primary care physicians about the presentation, risk factors, treatment and literature updates of this rare adverse effect of Methotrexate.

CASE REPORT

A 45 year old Hispanic woman came to the emergency room with a complaint of worsening shortness of breath for four weeks, fever with chills, nausea, vomiting and a productive cough with blood-tinged sputum. She denied any night sweats or sick contacts. She also had occasional chest pain after taking a few steps. But she denied paroxysmal nocturnal dyspnoea or orthopnea. She did not have any history of smoking, drinking or substance abuse. Her past medical history included diabetes mellitus for 3 years, rheumatoid arthritis for one month, for which symptoms started seven years ago. She was on Rosiglitazone, prednisone, folic acid, methotrexate, hydrocodone/APAP

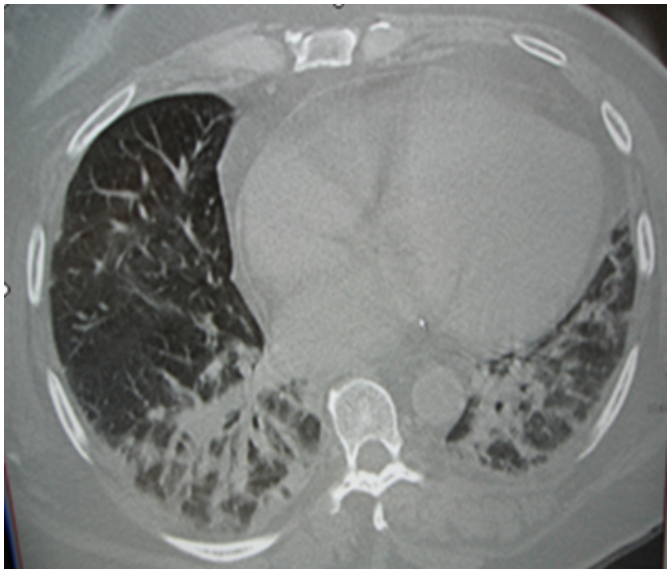
Physical examination revealed mild respiratory distress. Lung examination was significant for mild bibasilar lower lobe crackles. Cardiac and abdomen examinations were normal. Admission laboratory data showed low Hgb and Hct, but other wise within normal limits. Renal panel showed Na 131, K 3.3, but other wise within normal limits. Chest X ray showed diffuse ill-defined bilateral pulmonary infiltrates.

Figure 1



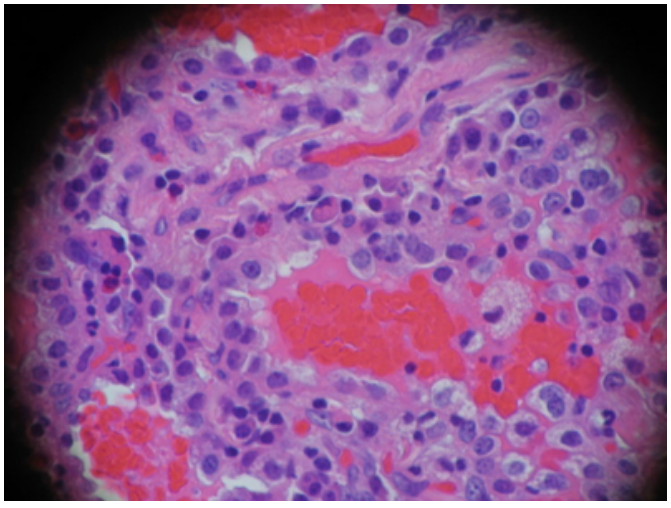
She was diagnosed with community acquired pneumonia. Sputum, blood and urine cultures were sent and patient was started on empiric antibiotics. All her home medications including methotrexate were continued. Patient became progressively hypoxemic with PaO2 as low as 64 on FiO2 of 36 %. SpO2 readings were in high 80's and patient was transferred to ICU. Sputum AFB X 3 were negative and repeat chest X ray one week later showed decreasing infiltrate on left side but right side infiltrates were unchanged. CT scan of the chest was done which also confirmed bilateral lower lobe infiltrates and atelectasis.

Figure 2



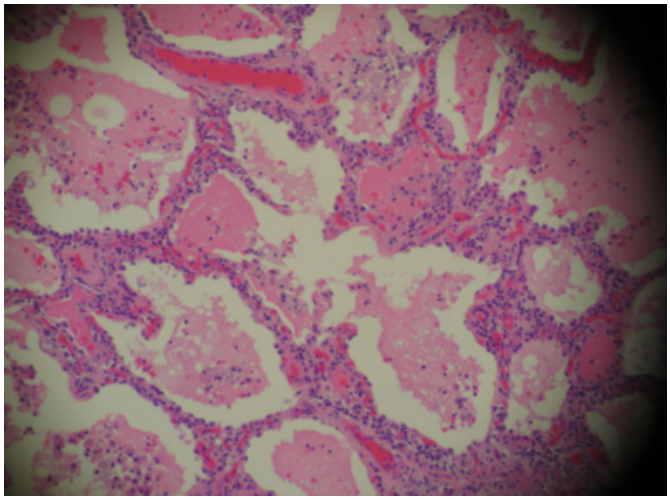
A chest x ray taken by her primary care doctor 6 months prior to initiation of methotrexate treatment showed interstitial changes consistent with pulmonary involvement due to rheumatoid arthritis. Methotrexate was stopped on 10th day of hospital admission. At that point, a bronchoscopy was done and samples were sent for gram stain, bacterial and fungal culture, pneumocystic jiroveci pneumonia, coccidiodomycosis and HIV which all came back negative. But patient continued to have hypoxemia. A video assisted thoracoscopic surgery with biopsy of the right lung was done which showed hypersensitivity pneumonitis with cellular alveolitis suggesting methotrexate-induced hypersensitivity reaction with eosinophilic infiltrates.

Figure 3



And early honeycombing

Figure 4



Antibiotics were stopped and prednisone was increased to 100 mg per day. Patient's respiratory status gradually improved and she was discharged without oxygen on the 29th day of hospital stay. She was discharged on 100 mg of prednisone per day and tapered to 5 mg per day by rheumatologist. Her respiratory status in follow up outpatient visits has been stable.

DISCUSSION

Methotrexate is a folic acid analogue that inhibits dihydrofolate reductase, which in turn blocks the conversion of dihydrofolate to tetrahydrofolate. This impairs the thymidine synthesis in DNA and RNA production. For its anti-inflammatory and immunomodulating properties, Methotrexate is used as the initial disease-modifying agent in patients with early aggressive rheumatoid arthritis who are at high risk for the development of joint destruction

Methotrexate can cause many adverse reactions most commonly skin, gastrointestinal tract, hematopoietic, central nervous system, pulmonary and hepatotoxicity. Fortunately, many of those adverse reactions, such as stomatitis, gastrointestinal upset and hematologic abnormalities, can be prevented by supplemental folic or folinic acid, without changing the efficacy of methotrexate. However, it does not reduce the risk for methotrexate pulmonary or hepatic toxicity. [1-6]

Methotrexate can cause hypersensitivity pneumonitis (extrinsic allergic aleveolitis), bronchiolitis obliterans with organizing pneumonia (BOOP), acute lung injury with noncardiogenic pulmonary edema, pulmonary fibrosis and bronchitis with airways hyperreactivity. Among them, hypersensitivity pneumonitis is most common. [6-8]. But it

is relatively rare and only 51 cases have been reported world wide. (17,21)

RISK FACTORS

Since pulmonary toxicity can lead to respiratory failure and death, a strong suspicion should be entertained in patients being treated who develop dyspnea. Multicenter case-control studies have been performed which may predict the possibility of methotrexate lung injury and the following risk factors have been identified. (9, 1)

1. Diabetes { OR 35.6 (CI 1.3 - ∞)}
2. Hypoalbuminemia {OR 19.5 (CI 3.5-109/7)}
3. Rheumatoid pulmonary involvement { OR 7.1 (CI 1.1-45.4)}
4. Previous use of disease modifying antirheumatic drugs {OR 5.6 (CI 1.2- 27)}
5. Older age - > 60 yrs { OR 5.1 (CI 1.2-21.1)}
6. Preexisting lung disease (5.2 % Vs 17.2 % p value = 0.0610)

SIGNS AND SYMPTOMS

Patients may present acutely as early as 12 days after treatment initiation or in a chronic form after 18 years. Most commonly present as sub acute. [1,8, 14,15,17].

Two to five percent of the rheumatoid patients treated with methotrexate may develop acute pneumonitis. [8, 14,15,17]. Most common symptoms are fever, chills, malaise, cough, dyspnea, and chest pain [1,13-15,17]. In severe cases, it may rapidly progress to respiratory failure [7].

DIAGNOSIS

There is no specific diagnosis for methotrexate induced lung injury. A combination of clinical signs and symptoms, radiology, bronchoalveolar lavage, and pulmonary cytology are used today. Improvement of patient's signs and symptoms with discontinuation of drug and response to steroid therapy (1mg per kg per day) is used in diagnosis as well as the treatment .In routine chest X ray, widespread interstitial opacities in early stage which later may progress rapidly to patchy acinar consolidation [12, 13]. High resolution CT scan may show patchy areas of ground glass attenuation with small areas of consolidation. They are usually bilateral, symmetric, and predominantly in lower lung zones [19]. Bronchoalveolar lavage studies may reveal lymphocytic predominance with an increase in the number of CD4+ lymphocytes and the CD4/CD8 ratio [18,20]. Lung biopsy may show alveolitis with epithelial cell hyperplasia and cytologic dysplasia. Small, poorly formed granulomas and eosinophilic infiltration is a common presentation of hypersensitivity pneumonitis [7].

SEARLES AND MCKENDRY DIAGNOSTIC CRITERIA (9)

MAJOR

1. Hypersensitivity pneumonitis by histopathology without evidence of pathogenic organism
2. Radiologic evidence of pulmonary interstitial or alveolar infiltrates
3. Negative blood and initial sputum cultures

MINOR

1. Shortness of breath for less than eight weeks
2. Nonproductive cough
3. Oxygen saturation ≤ 90 % on room air on initial evaluation
4. DLCO ≤ 70 % of predicted for age
5. Leukocyte count ≤ 15,000 Cells/mm3

Definite - Major criterion 1 with 3 minor criteria (or) Major 2 and 3 with 3 minor criteria

Probable – Major 2 and 3 criteria with 2 minor criteria

Awareness of methotrexate pulmonary toxicity has become better appreciated since its introduction for the treatment of rheumatoid arthritis. Our case is noteworthy because of the short time interval between initiation of therapy and development of symptoms. Our patient's 3 year history of diabetes and preexisting pulmonary involvement of rheumatoid interstitial lung disease with high odds ratios of 36 and 7 respectively may have contributed to her almost immediate hypersensitivity response to the drug.

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