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RESEARCH ARTICLE

CASE REPORT: METHOTREXATE INDUCED PNEUMONIA

Dr. Nael Mustafa Quraishy[1], Dr. Manal Sayed Rezzek[1], Dr. Rami Khaled Abou El Foul[2] and Dr. Amer Abdulmola Albawab[2]

1. Rheumatology Internal Medicine Unit, Hatta Hospital, Dubai, United Arab Emirates.
2. Internal Medicine Unit, Hatta Hospital, Dubai, United Arab Emirates.

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Abstract

Introduction:-

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.It is a commonly used medicine for conditions such as psoriasis, polyarticular juvenile idiopathic arthritis, rheumatoid arthritis, and cancer[1].
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[2,3].

Case:
52-year-old female.PMH includes Seropositive Rheumatoid Arthritis in remission, Sjogren's syndrome, and Hypothyroidism, Shedenied any smoking history and denied to be negative smoker.
She presented with one-week history of fatigue, then started to have cough, chest heaviness and exertional dyspnea.She reported daily yellowish sputum in the morning only with mild dry cough during the past few days. She has no fever, no chest pain, no tender or swollen joints.
Vital signs: BP: 124/75 mmHg, T: 37 C, RR: 18 /min, HR: 74 /min, SPO2: 96-98% room air
Clinical Examination:Within normal limits, Chest is clear, no wheezes, no rales.
Firs X-Ray Chest: figure 1: Unremarkable Chest X – Ray.

She was seen by cardiologist and cleared from cardio point of view.She was considered as a case of Upper respiratory tract infection, and Treated symptomatically and sent home.
Three days later She presented again to AE with Breathing difficulty, Hypoxia, and Tachypnea. She has no fever, no chest pain, no tender or swollen joints.
Vital signs: BP: 135/78 mmHg, T: 37.3 C, RR: 20-22 /min, HR: 70-84 /min, SPO2: 86-90 % in room air.
She was distressed and her Chest examination revealed Bilateral Mid and basal rales.
2nd X-Ray Chest: figure 2: Interstitial disease process probably pneumonitis or related to collagen disorder.

CT Chest Pulmonary Angiogram:was done and reported as:
- NO CT angiographic evidence of major pulmonary embolism.
- Wide spread bilateral pulmonary air space shadowing, based on the clinical history methotrexate lung induced pneumonia is 1st to be considered.

Corresponding Author:- Dr. Nael Mustafa Quraishy
Address:- Rheumatology Internal Medicine Unit, Hatta Hospital, Dubai, United Arab Emirates.

- Mild mediastinal lymphadenopathy.

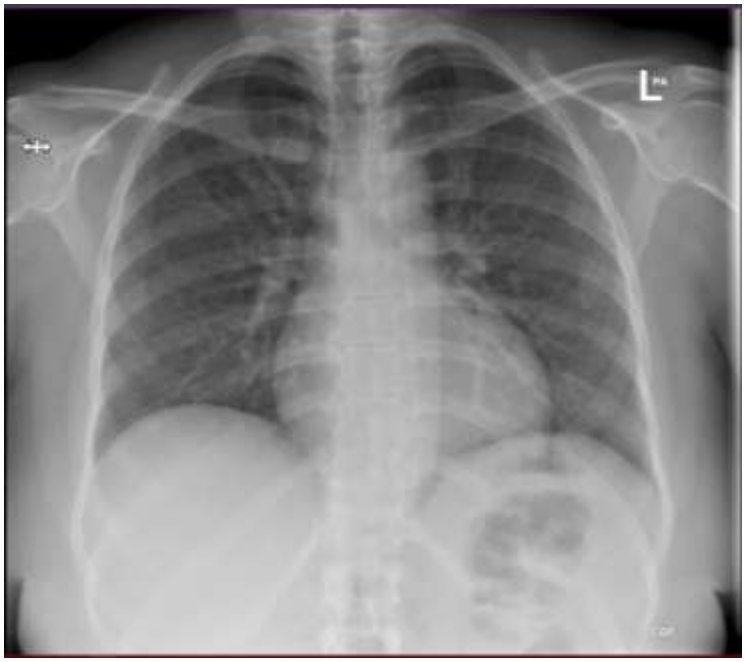

Figure 1:- Chest X Ray:

- Central trachea. - Average cardio-thoracic ratio.
- Clear lungs fields. - No enlarged hilar lymph nodes seen.
- Free C/P angles. - Bones are unremarkable.

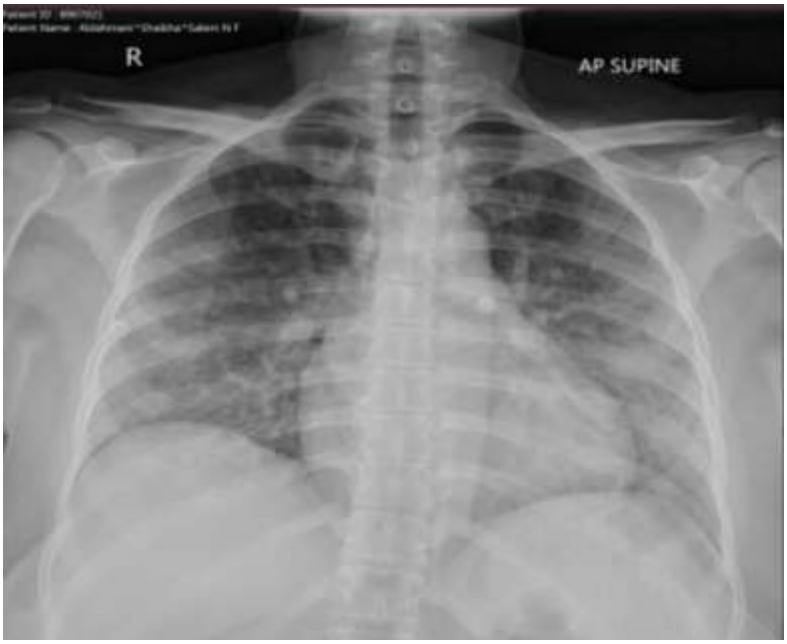

Figure 2:- Chest X Ray:

Diffuse bilateral pulmonary veiling by significantly increased interstitial marking yielding fine tabular pattern in addition to increased vascular markings denoting underlying interstitial process.
Clear both costophrenic recesses.
Impression: Interstitial disease process probably pneumonitis or related to collagen disorder.

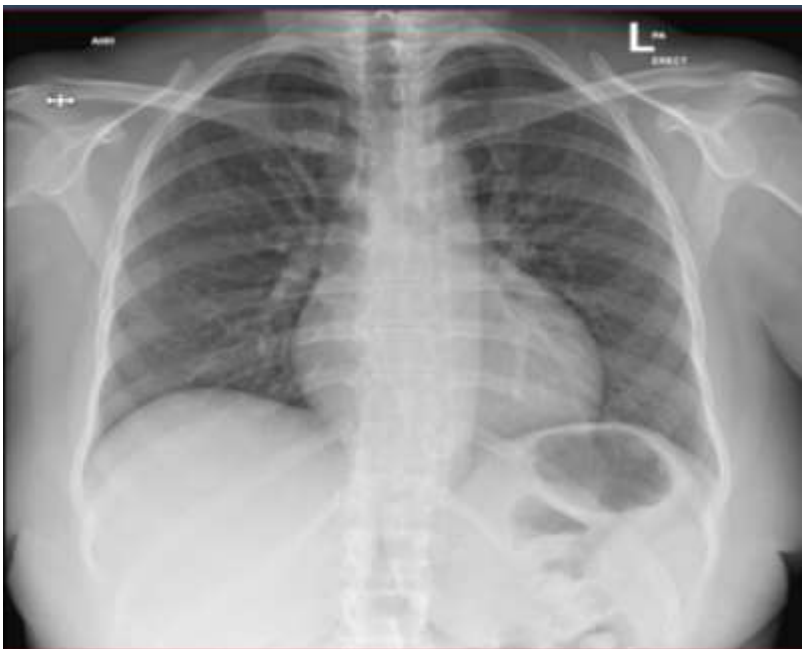

Figure 3:- Chest X Ray:
Interval resolution of diffuse bilateral pulmonary veiling.
Clear both costophrenic recesses.
Normal cardiac size and configuration.
No mediastinal or hilar abnormal soft tissue shadows.
Impression: Regressive coarse of the disease.

A course of empirical antibiotics and intravenous hydrocortisone were initiated. PCR for Covid-19 was negative, blood cultures were sterile, and sputum cultures were negative.

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 after discharge with tapering doses. A follow-up chest X-ray (figure 3) showed Regressive course of the disease.

The patient was counseled not to use MTX and discharged on room air to follow up with a rheumatologist

Multislice CT chest high resolutionwas done forfollow up 4 weeks after discharge, showed:
- Interval regression with near complete resolution of bilateral ground glass opacities as described suggestive of resolving infectious/inflammatory process.

On follow up visits the patient was very well, prednisolone tapered successfully with no remaining need for Oxygen therapy.

Discussion:-

The diagnosis of MTX-pneumonitis is difficult since there are no pathognomonic findings, and this condition may mimic other pulmonary diseases. When a patient treated with MTX develops new respiratory symptoms, the differential diagnosis includes MTXpneumonitis, rheumatoid lung disease, and pulmonary infection or emboli. Exclusion of other pathology, particularly of infectious origin, is time consuming and therefore MTXpneumonitis is often diagnosed retrospectively. [8,9]

In our case the diagnosis was made using Chikura et al criteria mentioned in Table 1. [4].

Methotrexate can cause any of those pulmonary disease's acute interstitial pneumonitis, interstitial pulmonary fibrosis, non-cardiogenic pulmonary edema, pleuritis or pleural effusion, pulmonary nodules, and cough.[11,12,13,14].

The onset of MTX pneumonitis can occur at any time after initiating MTX (days to a year) and can be either acute or subacute.The common presentations are progressive shortness of breath, non-productive cough, pleuritic chest pain, crackles, and systemic features like fever, fatigue, and malaise.[5] Laboratory findings include mild peripheral blood eosinophilia and lymphopenia. [2] 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.[6]

MTX pneumonitis is most frequent within the first year of treatment and the reported incidence of this adverse reaction varies from 0.86 to 6.9%. The variable incidence and usual occurrence within a year of starting MTX suggests that pneumonitis is an idiosyncratic immune reaction rather than a dose-related toxic insult to the lung. A review of the literature shows that there are some risk factors that increase the incidence of MTX-induced lung toxicity, including age >60 years, hypoalbuminemia, diabetes, initiation of a second rheumatoid arthritis medication, and daily dosing as opposed to weekly. However, the exact underlying mechanism involved in the disease pathogenesis, and the mechanism by which some of the above factors may increase the lung toxicity risk remains unclear. [1,7]

Conclusion:-

A rare but potentially deadly adverse event of methotrexate is pneumonitis. MTX pneumonitis 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.

Take-home messages from this case are: a) MTX pneumonitis 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.

Table 1:- The 2008 diagnostic criteria for methotrexate-induced pneumonitis.

Diagnostic criteria for methotrexate-induced pneumonitis (Chikura et al.diagnostic criteria)[8]
Clinical
A. Onset of dyspnea- Acute/subacute
B. Dry cough
Laboratory
C. SaO_2 <90% on room air
Infection
D. Negative blood and sputum cultures (Mandatory)
Radiological
E. Diffuse interstitial changes, diffuse bilateral and patchy ground glass opacities and nodules on HRCT.
Histopathology
F. Lymphocytic infiltrate, and diffuse alveolar damage.
Bronchoalveolar Lavage
G. Lymphocytosis >30% +/− increased CD4 +/CD8+ratio on BAL
Treatment
H. Prompt symptomatic improvement following MTX withdrawal +/− corticosteroid treatment.
Interpretation
5/8 criteria- Definite M-PNEU
4/8 criteria- Likely M-PNEU
3/8 criteria- Possible M-PNEU <3/8 criteria- Unlikely of M-PNEU

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