Case Report

Low-dose methotrexate-induced acute interstitial pneumonitis: Report of two cases from South India and review of literature

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Abstract

Methotrexate (MTX) is an antimetabolite used as a disease-modifying agent for various rheumatological conditions. We report two patients who were treated with daily low-dose MTX and developed acute interstitial pneumonitis requiring hospital admission. MTX-induced pneumonitis is a rare life-threatening side effect, high index of clinical suspicion is required, treatment is mainly withdrawal of MTX, supportive therapy, and adjunctive steroids, outcome is good if condition is recognized early, and appropriate treatment is given.

Keywords: Interstitial pneumonitis, methotrexate, toxicity

Introduction

Methotrexate (MTX) is an antimetabolite and antifolate drug developed in 1948. It acts by interrupting the synthesis of both DNA and RNA by inducing a deficiency of folate-dependent coenzymes. In high doses, it is used in the treatment of malignancies; in low doses, it is used as an anti-inflammatory for rheumatological illnesses.[1]

MTX-induced adverse effects mainly affect the rapidly dividing cells of the bone marrow and gastrointestinal tract but it can also involve the liver, kidneys, and lung. MTX-induced acute lung injury is a rare and life-threatening complication. We report two cases of MTX-induced pneumonitis (MTXP) in two patients given low-dose MTX (LD-MTX).

Case Reports

Case 1

A 40-year-old woman from Tamil Nadu had presented with high-grade fever with chills, rigors, dry cough, and breathlessness which worsened over 3 days. Three months back, she was diagnosed to have Takayasu's arteritis by her family physician. She was initiated on MTX 2.5 mg twice daily and prednisolone 60 mg/day.

On examination, she was tachypneic, tachycardic, and hypoxic. Left upper limb pulses were weak. Blood pressure was 100/70 mmHg on her right upper limb. Significant finding on systemic examination revealed bilateral basal crepitations only. The possibility of community-acquired pneumonia (including atypical pneumonia), *Pneumocystis jirovecii* pneumonia, pulmonary alveolar hemorrhage, and MTX-induced acute pneumonitis was considered.

Chest radiograph [Figure 1] revealed fluffy, alveolar opacities in the mid and lower zones. She was initiated on noninvasive ventilation, empirical cotrimoxazole, antibiotics, and intravenous hydrocortisone. Initial biochemical and hematological admission were normal [Table 1].[2] Fluorescent-antibody testing for *P. jirovecii* was negative. Since cultures remained sterile, she was diagnosed to have MTX-induced acute pneumonitis. Antibiotics

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were withdrawn, and steroids were continued. Her respiratory distress improved over 1 week, and chest radiograph showed complete resolution [Figure 2]. She was switched to oral prednisolone and oral anticoagulants at discharge.

Case 2

A 55-year-old Indian sales executive employed South Korea was treated with oral MTX 2.5 mg once daily for psoriasis. One month later, he developed fever, dry cough, and dyspnea during his travel to India. He was admitted; MTX was withdrawn and was started on noninvasive ventilation, antibiotics, antifungals, and steroids. Chest radiograph [Figure 3] and High-resolution computerized tomography (HRCT) of the thorax showed extensive multilobar alveolar consolidation. His antibiotics and antifungals were stopped after the blood and sputum cultures remained sterile. He showed gradual improvement clinically and weaned off the noninvasive ventilation. His repeat chest radiograph [Figure 4] and HRCT of the thorax showed resolution of the lung opacities.

In view of above clinical background, we considered the diagnosis of MTXP and psoriatic erythroderma. His hematological and biochemical investigations were normal. Pulmonary function test revealed a restrictive pattern of ventilatory defect. Skin biopsy confirmed psoriasiform erythroderma with chronic dermatitis. HRCT done 4 weeks later showed complete resolution of the previous findings. He was advised not to use MTX again and was discharged with advice to follow up with the dermatologists.

Discussion

MTXP is a rare complication with only 123 case reports in literature. Considering the wide use of LD-MTX for various rheumatological disorders in India and the estimated prevalence of 0.3%–18% in Western literature,[3] there has been paucity of data on MTXP from the Indian subcontinent.[4]

LD-MTXP is mainly a diagnosis of exclusion because the clinical presentation is similar to infectious or inflammatory pneumonias, which are common in the patients with autoimmune diseases and on immunomodulator therapy, especially in developing countries like India. The current criteria to diagnose MTXP are given in Table 2. In these two cases, LD-MTXP was diagnosed after fulfillment of five of the eight criteria.

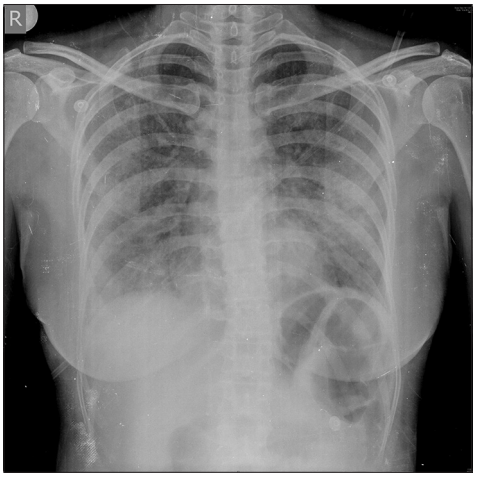

Figure 1: Chest radiograph of the patient one at admission

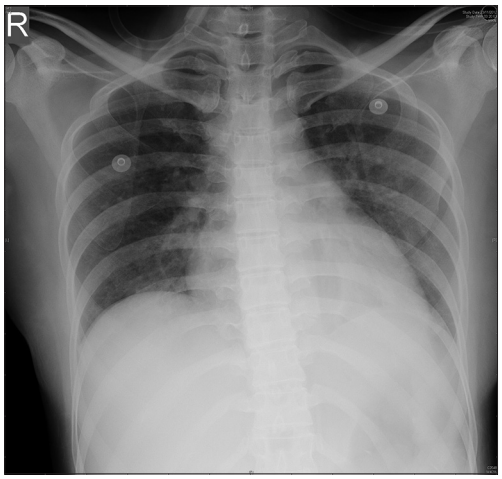

Figure 2: Chest radiograph of patient one at discharge

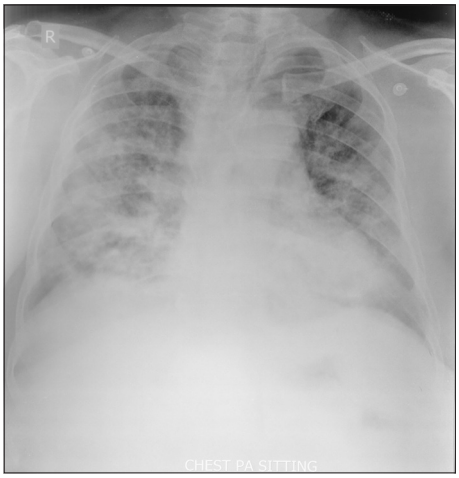

Figure 3: Chest radiograph of the patient two at admission

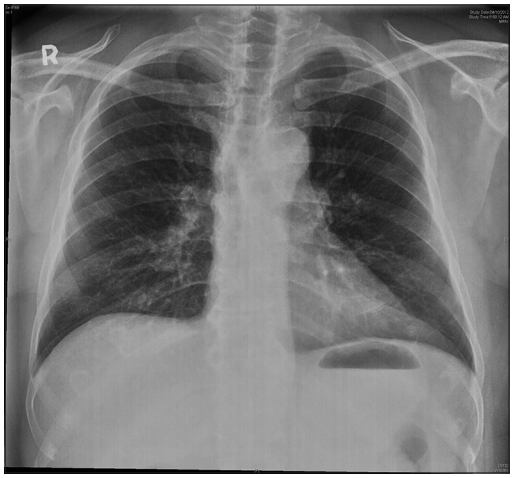

Figure 4: Chest radiograph of patient two at discharge

Table 1: Methorexate induced pneumonitis diagnostic criteria

Clinical
Acute subacute dyspnoea
Dry cough
Laboratory
Oxygen saturation of <90% when breathing on room air
Infection
Negative sputum and blood cultures (mandatory)
Radiological
High resolution Computed Tomogram of chest – diffuse interstitial changes, diffuse and bilateral patchy ground glass shadowing and nodules
Histopathology
Lymphocytic infiltrate, microgranulomata, diffuse alveolar damage,perivascular infiltrate and proliferation of type 2 alveolar cells
Bronchoalveolar lavage
Bronchoalveolar lavage >30% +/- increased CD4/CD8 ratio
Treatment
Rapid resolution of symptoms when MTX is withdrawn +/- treatment with corticosteroids
5 out of 8 criiteria = definite MTXP
4 out of 8 criteria = likely MTXP
3 out of 8 criteria = possible MTXP
<3 out of 8 criteria MTXP unlikely

Table 2: Laboratory investigations

	Case 1	Case 2
Hemoglobin (gm%)	14.4	13.2
Total WBC Count (cells/dL)	14,400	9,000
Differential WBC Count (%)		
Neutrophils	79	58
Lymphocytes	6	37
Platelet Count (cells/dL)	3,36,000	1,41,000
Creatinine (mg%)	0.7	0.98
Procalcitonin	?	
Liver Function test		
Total bilirubin	0.6	0.4
Indirect bilirubin	0.2	0.2
Total Protein	6.6	6.5
Albumin	3.7	4.1
SGOT	11	22
SGPT	19	34
Alkaline phosphatase	55	67
C- reactive protein	110	10
Microbiological report		
Sputum bacterial culture	Negative	Negative
Acid fast bacilli culture	Negative	Negative
Fungal culture	Negative	Negative
Pneumocyctis	Negative	Not done

In a systematic review, 15 of 3463 patients (0.43%) with rheumatoid arthritis who were receiving MTX developed MTXP. Unlike other organ involvements, it is less predictable[1] and can develop within the 1st year of treatment.[5] In a small case–control study of 29 cases,(6). estimated the risk factors associated with developing MTXP were older age (odds ratio [OR]: 5.1 [1.2–21.1]), diabetes (OR 35.6 [confidence interval [CI]: 1.3 to infinity]), rheumatoid pleuropulmonary involvement (OR 7.1 [1.1–45.4]), previous use of disease-modifying antirheumatic drugs (OR 5.6 [1.2–27.0]), and hypoalbuminemia (OR 19.5 [3.5–109.7]).

MTXP is idiosyncratic hypersensitivity reaction due to activated T-cell-mediated (CD_4 and CD_8) stimulation of type 2 alveolar cells to release cytokines which lead to recruitment inflammatory cells leading to alveolitis.

The most common presentation of MTXP is subacute onset of cough, dyspnea, chest pain, and crackles. Chest radiograph findings include combined alveolar and interstitial infiltrates. Diagnosis is based on clinical features, radiological findings, and ruling out alternative diagnosis. HRCT is more sensitive than chest radiograph and shows patchy ground-glass opacities and centrilobular nodule formation. Pulmonary function test is typically that of a restrictive pattern. Bronchoalveolar lavage cytology findings of neutrophils in the absence of infection are associated with high risk of pulmonary fibrosis. Lung biopsy (sensitivity = 90%–95%) may be done for prognostication, but it is associated with complications such as hemorrhage and infection. For our first patient, HRCT or bronchoscopy could not be done as she was on noninvasive ventilation.

Treatment of MTXP is withdrawal of MTX, supportive therapy, and corticosteroid therapy (prednisolone at 1 mg/kg reducing at 5 mg/week) if oxygen saturation <90%. Severe cases should be treated with parenteral steroids. Both the patients were treated with noninvasive ventilation and corticosteroid. At 6-month follow-up, both the patients were doing well.

This case highlights three main learning points. The patients on LD-MTX are at high risk of developing acute pneumonitis, and clinicians should have high index of suspicion. It is a diagnosis of exclusion. Prompt withdrawal of MTX and supportive therapy has good outcome.

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Conflicts of interest

There are no conflicts of interest.

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