Methotrexate-induced Pulmonary Toxicity

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Abstract

A fifty-one-year-old lady being treated with methotrexate for leucocytoclastic vasculitis, developed respiratory symptoms and signs. These improved on drug withdrawal and with four weeks of steroid treatment.

Introduction

Methotrexate is one of the most widely used broad-spectrum immunomodulatory drugs. It can be used upfront as a primary option or as a combination drug in various immunological conditions. Methotrexate is generally safe in the dosages used. However, a clinician has to be alert regarding some of its less common side-effects. We discuss here a patient who developed methotrexate-induced pulmonary toxicity.

Case report

A fifty-one-year-old lady initially presented with purpuric spots over her lower limbs. Skin biopsy was suggestive of leucocytoclastic vasculitis. She was started on 40 mg of prednisolone and four weeks later, due to inadequate response, 7.5 mg once a week of methotrexate was added. This was stepped up to 15 mg every week in the next 4 weeks, and prednisolone was tapered-off and continued at 5 mg doses. Six months later, while still on methotrexate, she presented with gradually progressive exertional breathlessness and dry cough of two months duration. She had high grade, intermittent fever with chills along with anorexia and worsening breathlessness since nine days.

On examination, she was tachypnoeic with a respiratory rate of 28/minute and had a temperature of 38°C. Chest auscultation revealed bilateral, fine inspiratory crepitations in the infra-axillary and infra-scapular areas. The rest of the systemic examination was normal. Her WBC count was 13,800/cu mm with P-68, L-30, M-1, and E-1. Chest x-ray (CXR) showed haziness in both lower zones (Fig. 1). Sputum could not be examined, as she did not produce any. Contrast-enhanced computed tomograph (CECT) of the thorax showed patchy areas of ground glass haziness in both middle and lower lobes, suggestive of alveolitis (Fig. 2).

A diagnosis of methotrexate-induced pulmonary toxicity was made. The drug was stopped, and she was started on antibiotics and steroids, with other supportive treatment.

Her fever started settling down and she symptomatically started to improve with lesser cough and breathlessness. Her repeat WBC was 9,300/cu mm and chest X-ray after two weeks was normal.

Fig. 1: CXR showing basal haziness.

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Discussion

Methotrexate is a folate antagonist used as a chemotherapeutic agent as well as for the treatment of non-neoplastic inflammatory diseases, rheumatoid arthritis (RA) being the commonest prototype. Methotrexate-induced pulmonary toxicity occurs in 1 - 5% patients with RA and is most commonly seen in the first year of treatment. The patient typically presents with fever, cough, dyspnoea, and inspiratory crepitations occur one to five months into therapy. Investigations reveal hypoxaemia with peripheral leukocytosis and eosinophilia in some patients. Patients on low-dose methotrexate are at increased risk for opportunistic infections. These include *Pneumocystis carinii* pneumonia, disseminated histoplasmosis, and herpes zoster. Therefore, exclusion of opportunistic pathogens is important in the differential diagnosis of methotrexate pneumonitis. It is a diagnosis of exclusion (Table I). Radiologically, bilateral mixed interstitial-alveolar pulmonary shadows, pleural effusion, hilar lymphadenopathy may be present. Pulmonary function tests show a restrictive ventilatory defect with decreased diffusing capacity. The pathogenesis of this entity is not known. It probably has a hypersensitivity mechanism suggested by the frequent finding of peripheral eosinophilia and lymphocytosis on bronchoalveolar lavage. BAL lymphocyte CD4: CD8 may be increased, decreased, or normal. It may be an idiosyncratic immune reaction. Thus, different mechanisms may be operative in different subjects.

On histology, mononuclear cell infiltrates with type II pneumocyte hyperplasia in acute cases, and interstitial fibrosis in chronic cases, may be present. Isolated areas of bronchiolitis obliterans and non-caseating granulomas may be present.

Factors that increase risk for methotrexate lung toxicity are: higher daily and cumulative doses, renal insufficiency, concomitant high-dose aspirin or non-steroidal anti-inflammatory drug therapy, and pre-existing lung disease.

The treatment of methotrexate pneumonitis includes withdrawal of the drug and supportive care. Oral or intravenous pulse corticosteroid therapy may be useful and is initiated after infection has been excluded. However, there are no clear guidelines for the optimal dose or duration of therapy. Patients with significant hypoxia will require oxygen therapy and intensive care with mechanical ventilation. Cyclophosphamide has been used successfully in significant pneumonitis. Although there are instances of successful reintroduction of methotrexate after pneumonitis, there is not enough evidence to support this.

The prognosis with methotrexate-associated lung injury is generally favourable. The overall mortality is approximately ten per cent.

Our patient had a probable diagnosis of methotrexate-induced pulmonary toxicity (Table II). Also, as per the causality assessment scale provided by Naranjo CA et al., she had a probable adverse drug reaction to methotrexate (score - 6). She responded well to drug withdrawal and steroids, the latter having been tapered off in four weeks time. A re-challenge of methotrexate was not attempted.

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Fig. 2: CXR two weeks post-treatment: clearance of basal haziness.

Fig. 3: CECT scan of thorax showing areas of ground glass haziness, suggestive of alveolitis (arrow).
Table I: Pulmonary involvement with methotrexate use².

<table>
<thead>
<tr>
<th>Pulmonary syndrome</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pneumonitis/pulmonary fibrosis</td>
<td>Discontinue drug; give corticosteroids</td>
<td>Most common type</td>
</tr>
<tr>
<td>Hypersensitivity-type lung disease</td>
<td>Discontinue drug; give corticosteroids</td>
<td>May resolve even if drug is continued; may progress to fibrosis</td>
</tr>
<tr>
<td>Acute chest pain syndrome</td>
<td>Discontinue drug</td>
<td>Often associated with pleural effusion</td>
</tr>
<tr>
<td>Non-cardiogenic pulmonary oedema</td>
<td>Discontinue drug; provide supportive care</td>
<td>Associated with intrathecal administration</td>
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</tbody>
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Table II: Criteria of Searles and McKendry for diagnosis of methotrexate pneumonitis⁴.

1. Acute onset dyspnoea
2. Fever > 38°C
3. Tachypnoea >/= 28/min, and dry cough
4. Radiological evidence of pulmonary interstitial or alveolar infiltrates
5. WBC < 15,000/cu mm with or without eosinophilia
6. Negative blood and sputum cultures (mandatory)
7. Restrictive defect and decreased DLCO on PFT
8. PO2 < 60 mm Hg on room air
9. Histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of infection.

Definite: >/= 6 criteria; Probable: 5 of 9 criteria; Possible: 4 of 9 criteria

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References