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Case Report Dermatology

Pulmonary fibrosis developed secondary to methotrexate use in a patient with psoriasis vulgaris

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ABSTRACT

Methotrexate is the folic acid analogue drug that used in various dermatological disorders, especially in psoriasis. Cutaneous and systemic side effects can be seen during methotrexate treatment. A 58-year-old female patient presented with persistent cough last one month. The patients past medical history was remarkable for psoriasis, for which she was on follow up for the last 14 years and received systemic methotrexate (12.5 mg/week) within the last eight months. The patient was referred to pulmonology for persistent cough. Computed tomography (CT) of the chest revealed pleural thickenning on the left lung, interlobular septal thickenning on the right lung and frosted glass areas in both lungs. Methotrexate induced pulmonary toxicity was considered and lung biopsy and bronchoscopy was performed to patient. The patient was diagnosed with methotrexate induced pulmonary toxicity based on the clinical, radiological and histopathological findings. Methotrexate treatment was stopped and a therapy with systemic corticosteroid 32 mg/day was initiated. Significant improvement was observed clinically and radiologically after one month of therapy. Methotrexate is a toxic drug to the lungs, but this condition is not common. All patients prescribed MTX should be advised for lung toxicity and to report the development of respiratory symptoms to their physician.

Keywords: Methotrexate; psoriasis; pulmonary fibrosis.

Methotrexate (MTX) is a folic acid analogue used in the treatment of many dermatological disease mainly psoriasis. In patients receiving MTX treatment many cutaneous, and systemic adverse effects, and toxicities can be seen. Its most frequently known side effects are hepatotoxicity, bone marrow suppression, nausea, fatigue, alopecia, oral ulcers, and very rarely pulmonary fibrosis can be

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seen [1]. Herein, we are reporting a patient followed by us with the diagnosis of psoriasis vulgaris who developed pulmonary fibrosis secondary to MTX use continued for 8 months.

CASE REPORT

A 58-year-old female patient presented with complaints of coughing persisting for the previous one month. The patient had been followed up with the diagnosis of psoriasis vulgaris for 14 years. Previously she used topical corticosteroids, calcipotriol, narrow band UVB therapy for a total of 60 sessions, and acitretin therapy for nearly 2 years. Since she hadn't benefited from acitretin therapy, initiation of methotrexate treatment was planned. The patient's psoriatic area severity index (PASI) was 16.8 at her admission. The patient was started on systemic MTX (12.5 mg/wk/PO) and once weekly folbiol (5 mg/PO) therapy. During her treatment she demonstrated marked clinical improvement. At the end of 7 months a PASI score of 3.2 points were achieved. At the 7. month of the treatment (after administration of a total dose of 400 mg) her complaints of coughing, and exertional dyspnea became apparent which increased in severity with time. She was consulted to the outpatient clinics of the chest diseases with these complaints.

Findings of physical examination performed in the department of chest diseases were as follows: body temperature: 37.4 C, pulse rate: 66/min, arterial blood pressure (ABP): 120/70 mmHg, and respiratory rate (RR), 12/min. Sibilant rales were heard over both lungs. Oxygen saturation was 97%, as revealed by pulse oximetric measurement of blood sample taken from her fingertip. Her history of methotrexate use, and absence of signs of infection suggested presence of pulmonary toxicity. Then respiratory function tests (RFTs), and high-resolution chest tomographic (HRPT) examinations were planned for the patient.

On RFTs, forced expiratory volume in one second (FEV1), and forced vital capacity (FVC) were 93, and 90%, respectively. On HRCT, pleural areas of consolidation on both lungs, especially more prominent on the basal segment of the right lung, peripheral interlobular septal areas of thickening in the midlobe of the right lung, and pathcy areas of ground glass appearance, and consolidations in both lungs were detected (Figure 1). Since these findings reinforced the suspect diagnosis of methotrexate toxicity, tissue samples from both lungs were obtained. Bronchoscopy was performed to discard the possibility of malignancy.

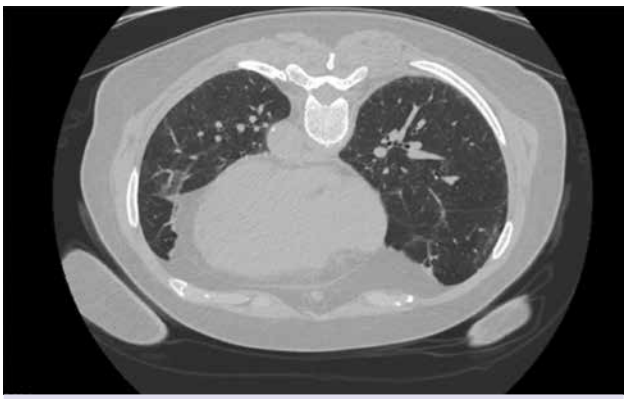

Figure 1. Marked reticular shadows, and patchy areas of ground glass appearance more prominent in the lower lobes of both lungs are observed.

On bronchoscopy, both main bronchi were observedly patent up to their subsegments. Bronchial lavage fluid, and transbronchial needle biopsy material were obtained from the distal segment of the left lower lobe. Histopathological examination of the bronchial lavage fluid retrieved during bronchoscopy did not contain atypical cells, however in cell blocks cut from tissue biopsy material revealed vascular endothelial structures, rarely dispersed acute inflammatory cells and fibrinous areas. On lung biopsies, denudation of the surface epithelium, consolidation of basal membrane, subepithelial edema, a slight increase in fibrotic tissue, and lymphoid cells were observed.

Based on the HRCT, and histological examination results, MTX-related interstitial pulmonary disease was detected in the patient, and hence methylprednisolone treatment at daily doses of 32 mg was initiated by the department of chest diseases. The patient was discharged one month later with recommendations of postoperative control in the outpatient clinic, one month later. Her MTX therapy was terminated. In control visit performed one month later, she expressed decrease in her exertional dyspnea. Besides, based on RFTs, levels of FEV1, and FVC increased up to 100, and 93%, respectively. Besides, on chest X-rays, decrease in the number of reticular

areas was observed. Regression of pulmonary manifestations was suspected, and so methylprednisolone dose was tapered, and stopped within 4 months. Her pulmonary symptoms regressed nearly completely. Her skin lesions did not activate, and her PASI value was 2.1 points. Topical corticosteroid ointment was recommended for her skin lesions.

DISCUSSION

MTX is a folate antagonist used in severe chronic inflammatory diseases. Its most frequent adverse effects have been observed in the liver, and hematological system. Rarely pulmonary toxicity has been reported. However MTX is one of the drugs which demonstrate extremely important toxic effects on the pulmonary system [1].

The pathogenesis of MTX-associated pulmonary disease has not been elucidated fully. Various theories as hyperactivity reaction, folate insufficiency, and idiosyncratic reaction have been proposed [2]. Nowadays, in the treatment of psoriasis MTX has been used very prevalently, scarce number of cases with pulmonary involvement further reinforce the theory of idiosyncratic reaction [3].

In patients who developed MTX-related pulmonary toxicity, clinical symptoms of shortness of breath, coughing, fever, and dyspnea can be seen. Symptoms are usually seen in the subacute phase, some cases after MTX use have been also reported. In the majority of the patients rales are heard over basal zones. Typical findings detected on chest X-rays include interstitial or alveolar infiltrations in the basal zones [3, 4].

Radiologically, bilateral interstitial and/or alveolar infiltrations, areas of ground glass appearance, septal thickening, areas of consolidation, pleural fluid and/or pleural consolidations can be observed [5].

When pulmonary symptoms are observed in patients undergoing MTX therapy, posteroanterior (PA) chest radiograms should be obtained. However PA chest X-ray may not be adequate in establishing diagnosis. During the early period, chest radiograms are unremarkable, while RFTs can reveal restrictive type respiratory disorder [3].

On pulmonary biopsy material, alveolar damage, and pulmonary fibrosis associated with cellular interstitial infiltrations, granulomas, and peribronchial inflammation can be seen. These findings are not specific to MTX-related pulmonary fibrosis, and they can be seen in cases with pulmonary toxicities associated with other drugs [4].

In conditions where MTX-related pulmonary involvement is contemplated, the drug should be promptly discontinued. In symptomatic cases with severe respiratory failure, steroid therapy should be initiated. The prognosis of symptomatic cases is mostly benign, however some cases resulting in fulminant respiratory failure, and death have been reported [6]. In our case, the drug was promptly discontinued as soon as the toxicity was discerned, and systemic steroid therapy was initiated. Consequently, marked symptomatic improvement was observed.

Although pulmonary toxicity is rarely seen, MTX ranks on the upper rows among drugs with pulmonary damage. Besides, respiratory system symptoms in patients who are using MTX should be taken into consideration, and these patients should be carefully monitored regarding pulmonary toxicity.

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REFERENCES

1. Pınarbaşı A, Akman A, Yılmaz E, Başaran E. Is Folic Acid Supplementation Necessary for Patients Treated with Methotrexate?. Türk Dermatoloji Dergisi 2008;2:39–42.
2. van Ede AE, Laan RF, Blom HJ, De Abreu RA, van de Putte LB. Methotrexate in rheumatoid arthritis: an update with focus on mechanisms involved in toxicity. Semin Arthritis Rheum 1998;27:277–92.
3. McKenna KE, Burrows D. Pulmonary toxicity in a patient with psoriasis receiving methotrexate therapy. Clin Exp Dermatol 2000;25:24–7.
4. Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000;15:373–81.
5. Yalnız E, Kömürcüoğlu B, Gürbüz S, Çelikten EP. Pulmonary Involvement in a Patient With Psoriasis Due to Methotrexate Therapy. Toraks Dergisi 2003;4:179–82.
6. Zisman DA, McCune WJ, Tino G, Lynch JP 3rd. Drug-induced pneumonitis: the role of methotrexate. Sarcoidosis Vasc Diffuse Lung Dis 2001;18:243–52.