ORIGINAL RESEARCH PAPER

Pulmonary Medicine

METHOTREXATE INDUCED PULMONARY TOXICITY

KEY WORDS: Methotrexate, pneumonitis and pulmonary toxicities

Dr. Arjunsinh A. Gohil* Third Year Resident , B J M C and Civil Hospital, Ahmedabad. *Corresponding Author

Dr. Nitin Third Year Resident , B J M C and Civil Hospital, Ahmedabad.

Dr. Keyur Patel Assistant Professor , B J M C and Civil Hospital, Ahmedabad.

Dr. Nalin T. Shah Head of the Department, B J M C and Civil Hospital, Ahmedabad.

ABSTRACT

Methotrexate is widely used medication with an array of recognized side effects. The present report describes a case of Methotrexate induced pneumonitis in a patient with HLA positive Ankylosing Spondylitis and demonstrates the hallmark clinical and investigational finding that support this infrequently encountered diagnosis. The ensuing discussion reviews the pathogenesis, management and prevention of this adverse drug reaction.

CASE PRESENTATION

A 22 year old Indian borned female student presented to civil hospital Ahmedabad on 03/02/2021 with complain of fever and nonproductive cough since 7 days and breathlessness since 3 days. She denied other constitutional symptoms. Patient was nonsmoker. The patient lived at home with her husband who denied similar symptoms. The patient did not have pets, birds, history of water damage at home or mold exposure, did not use hot tub or Jacuzzi or did not have contact with farm animals. She was a known case of Ankylosing Spondylitis since 4.5 months and she was on following medication as illustrated below.

Table 1history Medications Taken By Patient

Methotrexate		Other Medications	
Duration	Dosage	Duration	Dosage
02/10/2020 TO 18/10/2020	10 mg tablet OD on Saturday and Sunday	30/09/2020 TO 01/10/2020	Tab Prednisolone 10 mg BD
19/10/2020 TO 09/12/2020	15 mg injection s.c. once a week	02/10/2020 TO 12/10/2020	Tab Prednisolone 10 mg BD then tapered off Tab HCQ 200 mg OD Tab Folic acid 5 mg OD Monday to Saturday
10/12/2020 TO 07/01/2021	7.5 mg tablet OD on Saturday and Sunday	13/10/2020 TO 02/02/2021	Tab Methylprednisolone 8 mg TDS then tapered off Tab Leflunomide 10 mg OD Tab Folic acid 5 mg OD Monday to Saturday
08/01/2021 TO 02/02/2021	10 mg tablet OD on Saturday and Sunday		

On examination she was febrile. Her heart rate was 90 beats per minute, blood pressure was 94/70 mm of Hg and a respiratory rate of 30 per minute. Initial saturation 80 percent on room air but was increased to 98 % on 50% oxygen by nonrebreathing mask at 8 litre per min. Bilateral air entry present with bilateral basal crackles on auscultation. Remaining physical finding were unremarkable. Blood test within normal limits and electrocardiogram and 2D ECHO was unremarkable. Chest xray revealed diffuse interstitial pattern. HRCT thorax dated 04/02/2021(Fig.1) revealed diffuse ground glass opacities.

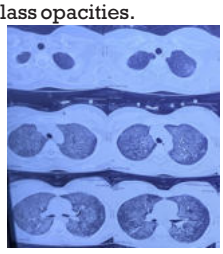

Fig.1 At the time of presentation (04/02/2021)

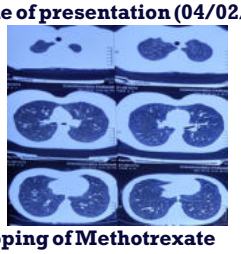

Fig.2 After stopping of Methotrexate

No effusion or lymphadenopathy was observed. RT PCR for COVID 19 was negative. In sputum culture no microorganism seen. The patient clinical presentation in addition to subsequent investigational findings, supported a diagnosis of interstitial pneumonitis resulting from an idiosyncratic reaction to Methotrexate. She was given Coamoxiclav, Cefotaxime and Azithromycin, Methylpredinosolone ,Leflunomide during hospital stay and oxygen support by oxygen face mask. Methotrexate was discontinued which was coinciding with improvement of her pulmonary disease. By the time of discharge after 5 days of hospital stay, her condition improved symptomatically (oxygen saturation 98% on room air). The patient was discharged back to her house. Under the same environment, the patient had no recurrence of similar symptoms which made a diagnosis of hypersensitivity pneumonitis from environmental allergens more remote. After 4 month of discharge patient respiratory symptoms improved significantly and HRCT (Fig.2) finding are nonsignificant and her PFT suggestive of mild restrictive change (FVC 71 % of predicted).

DISCUSSION

As a folic acid analogue that antagonizes cellular proliferation, Methotrexate can be used to manage a spectrum of inflammatory and neoplastic disorder. Approximately 1 to 7% of patient receiving MTX treatment

will develop pulmonary side effect(2,3). Prompt recognition of interstitial pneumonitis is essential before it progresses to irremediable pulmonary fibrosis.

Table 2 Diagnostic criteria matching in our patient

Diagnostic criteria(1):	Our Patient
Acute onset of shortness of breath	Yes
Fever (>38.0°C)	Yes
Tachypnea (≥28 breaths/min) with nonproductive cough	Yes
Radiographic evidence of interstitial or alveoliar infiltrates	Yes
WBC ≤15,000	Yes
Negative blood or sputum cultures for pathogenic organisms (required)	Yes
Pulmonary function tests demonstrating restrictive disease with low diffusion capacity	NA
PaO2 <55 mm Hg on room air (at presentation)	Yes
Biopsy histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of pathogenic microorganisms	NA
Presence of Methotrexate pneumonitis: Definite: at least 6 of 9 criteria Definite(7 criteria) Probable: 5 of 9 criteria Possible: 4 of 9 criteria	

proliferation, Methotrexate can be used to manage a spectrum of inflammatory and neoplastic disorder. Approximately 1 to 7% of patient receiving MTX treatment will develop pulmonary side effect(2,3). Prompt recognition of interstitial pneumonitis is essential before it progresses to irremediable pulmonary fibrosis.

CLINICAL FEATURE

Patient characteristically present with a history of progressive respiratory complaints within one year of initiating MTX therapy (4).In Rheumatoid arthritis patient, MTX induced pulmonary toxicity commonly present within 32 weeks(5).Part of the difficulty in recognizing MTX lung toxicity also relates to the nonspecific symptoms voiced by patients, including progressive dry or productive cough and dyspnea, with or without fever(2,6).Because no single test can confirm a diagnosis of MTX-induced pneumonitis, investigations serve to rule out other possible etiologies. CXRs will reveal a diffuse interstitial pattern not consistent with typical bacterial pneumonias – although *Pneumocystis jirovecii* and other atypical pneunomias may produce a similar radiographic pattern (2).

CT Thorax will show characteristic ground-glass opacities with or without foci of consolidation (4). Evidence of restrictive lung disease will be apparent in pulmonary function tests. Bronchoalveolar lavage findings are nonspecific and include increases in both CD4+ cell number and CD4/CD8 ratio (4,7). Finally, lung biopsy (transbronchial and/or surgical) may also be performed and is generally indicated in instances of more severe or evolving respiratory disease in which cessation of MTX does not rapidly result in clinical improvement. Biopsy findings are also nonspecific, and may demonstrate evidence of acute pneumonitis with type II cell hyperplasia/dysplasia and interstitial infiltration.

DIAGNOSTIC CRITERIA

While different criteria for diagnosing MTX lung toxicity have been previously suggested (1,4,6), they have not been clinically validated. One such criteria is discussed above (1). MTX-induced pneumonitis is, thus, considered to be a diagnosis of exclusion (4). Several mechanisms for the pathogenesis of MTX-induced pneumonitis have been surmised including hypersensitivity, direct drug toxicity to the lung tissue or immunosuppression leading to repeated viral or other infections. Typical bronchoalveolar lavage and histological findings involving these patients support the concept that MTX-induced pneumonitis represents a hypersensitivity reaction (4). However, MTX also induces injury to alveolar epithelial walls, suggesting a direct drug toxicity route (8). While several risk factors for MTX lung toxicity have been identified, they are limited to patients with rheumatoid arthritis. These include older age, previous disease-modifying antirheumatic drug treatment, hypoalbuminemia and diabetes mellitus, in addition to pleuropulmonary rheumatoid involvement (2,9). Smoking has not been implicated in an increased incidence of MTX lung toxicity(4).

MANAGEMENT AND PREVENTION

Cessation of MTX may itself be sufficient for symptom resolution and condition reversal (3). However, corticosteroid treatments have anecdotally been shown to be effective in accelerating symptom improvement – not unlike their utility in hypersensitivity pneumonitis (4). Patients presenting with severe hypoxia may require close monitoring and supplemental oxygen and/or assisted ventilation (3). Unlike the gastrointestinal and hematological complications than can result from MTX, the risk of pulmonary toxicity is not mitigated by folic acid supplementation. Furthermore, MTX lung toxicity is not typically associated with the gastrointestinal and hematological adverse effects that may ensue during treatment. Outcomes for patients who experience MTX toxicity are usually good, with a low rate of progression to pulmonary fibrosis. However, a literature review involving 123 patients with suspected MTX lung toxicity reported a mortality rate of 13% (6). Nevertheless, despite the potential consequences of MTX lung toxicity, long-term monitoring with serial pulmonary function testing and CXR is not recommended (10). Thus, all patients prescribed MTX should be advised of the potential for lung toxicity and to report the development of respiratory symptoms to their physician (11). This will enable timely investigations to be initiated to search for the underlying etiology and, if no alternative can be identified, MTX treatment discontinued

ACKNOWLEDGEMENTS

The authors thank the patient who this report describes for consenting to have her case and medical imaging submitted for publication.

DICLOSURES

The authors have no financial disclosures or conflicts of interest to declare.

REFERENCES

1. Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: Potential risk factors. Four case reports and a review of the literature. J Rheumatol 1987;14:1164-71.
2. Kremer JM, Alarcon GS, Weinblatt ME, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: A multicenter study with literature review. Arthritis Rheum 1997;40:1829-37.
3. Saravanan V, Kelly CA. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. Rheumatology 2004;43:143-7.
4. Lateef O, Shakoor N, Balk RA. Methotrexate pulmonary toxicity. Expert Opin Drug Saf 2005;4:723-30.
5. McKenna KE, Burrows D. Pulmonary toxicity in a patient with psoriasis receiving methotrexate therapy. Clin Exp Dermatol 2000;25:24-7.
6. 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.
7. Schnabel A, Richter C, Bauerfeind S, Gross WL. Bronchoalveolar lavage cell profile in methotrexate induced pneumonitis. Thorax 1997;52:377-9.
8. Ohbayashi M, Suzuki M, Yashiro Y, et al. Induction of pulmonary fibrosis by methotrexate treatment in mice lung in vivo and in vitro. J Toxicol Sci

2010;35:653-61.
9. Alarcon GS, Kremer JM, Macaluso M, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. Ann Int Med 1997;127:356-64.
10. Cottin V, Tebib J, Massonnet B, Souquet PJ, Bernard JP. Pulmonary function in patients receiving long-term low-dose methotrexate. Chest 1996;109:933-8.
11. Ameen M, Taylor DA, Williams IP, Wells AU, Barkert JN. Pneumonitis complicating methotrexate therapy for pustular psoriasis. J Eur Acad Dermatol Venereol 2001;15:247-9.