UC Davis
Dermatology Online Journal

Title
Methotrexate-induced hypersensitivity pneumonitis in a patient with bullous pemphigoid

Permalink
https://escholarship.org/uc/item/6nc6x9xr

Journal
Dermatology Online Journal, 29(4)

Authors
Agarwal, Ashima
Falcone, Lauryn M
James, Alaina J

Publication Date
2023

DOI
10.5070/D329461916

Copyright Information
Copyright 2023 by the author(s).This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at https://creativecommons.org/licenses/by-nc-nd/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Methotrexate-induced hypersensitivity pneumonitis in a patient with bullous pemphigoid

Ashima Agarwal[1] BS, Lauryn M Falcone[2] MD PhD, Alaina J James[2] MD PhD

Affiliations: [1]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA, [2]Department of Dermatology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Corresponding Author: Alaina J James MD PhD, Department of Dermatology, University of Pittsburgh Medical Center, 3601 Fifth Avenue, Suite 5A, Pittsburgh, PA 15213, Email: jamesaj@upmc.edu

Keywords: bullous pemphigoid, hypersensitivity, methotrexate, pneumonitis

To the Editor:

Methotrexate (MTX) is a commonly prescribed medication for treating many dermatologic and rheumatologic conditions. It inhibits dihydrofolate reductase, an enzyme necessary for DNA synthesis, repair, and cellular replication. Common adverse reactions of MTX are gastrointestinal upset and elevated hepatic enzymes which affect 30-40% of patients [1]. Serious side effects such as hypersensitivity pneumonitis (HP), though rare, may also occur. Hypersensitivity pneumonitis is associated with pulmonary inflammation, swelling, and sensitivity of the lung tissue. Although HP typically results from breathing in specific environmental allergens, it can also occur from taking certain drugs like MTX [2]. This rare side effect of MTX presents with progressive respiratory symptoms such as cough, dyspnea on exertion, and fever [4]. Recognizing this complication early is important in order to prevent the development of irreversible and potentially fatal pulmonary fibrosis. In this report, we present a patient with recalcitrant biopsy-proven bullous pemphigoid who developed shortness of breath and dyspnea on exertion and was diagnosed with MTX-induced HP.

A 69-year-old woman with a history of hypertension and diabetes presented with a six-week history of a widespread, pruritic rash. On physical exam, the patient had blisters and erosions on the dorsal hands, forearms, chest, abdomen, lower legs, and feet. Two punch biopsies were performed. On hematoxylin and eosin-stained tissue sections, a subepidermal blister with neutrophils and eosinophils was noted. On direct immunofluorescence, linear deposits of IgG and C3 were present at the basement membrane. The clinic-pathologic diagnosis was consistent with bullous pemphigoid. A baseline comprehensive metabolic panel and complete blood count were within an acceptable range.

The patient was prescribed mycophenolate mofetil 500mg twice a day while continuing a slow prednisone taper for six weeks. The bullous lesions would flare when the prednisone dose was decreased to 20mg daily. The patient also developed severe back pain shortly after beginning mycophenolate mofetil. This is a known side effect of mycophenolate mofetil and prompted its discontinuation. Methotrexate was then initiated at a dose of 15mg once weekly with folic acid 1mg daily except on the day of taking MTX. Approximately six weeks after starting MTX, the patient developed a non-productive cough, fatigue, and severe dyspnea at rest and exertion. On admission to the hospital, the patient was afebrile and saturating at 96% on room air. Complete blood count was notable only for leukocytosis of 18,000 cells/mm^3 whereas comprehensive metabolic panel was within an acceptable range. An infectious work-up of viral panel and blood cultures were negative. The slight leukocytosis was considered secondary to prednisone use given no findings consistent with infection. A chest CT showed bilateral ground glass opacities. Based on the recent initiation of MTX, negative infectious work-up and ground glass opacities on CT, the patient was diagnosed with MTX-induced HP.

Methotrexate was discontinued and the patient continued prednisone treatment at 20mg daily. The patient was also given one dose of sulfamethoxazole/trimethoprim as prophylaxis for opportunistic infections. Within three weeks of discontinuing MTX, the patient's breathing returned to baseline and her chest CT improved, showing regression of pulmonary infiltrates. To treat the bullous pemphigoid, the patient received two rituximab 1000mg infusions two weeks apart. One month after the infusion her skin was clear with no new blister formation. Prednisone was tapered over five months with no recurrence of bullous lesions.

This letter reviews a treatment course for severe, recalcitrant bullous pemphigoid and serves as a reminder that MTX-induced HP is a rare but possible, serious side effect of MTX. Methotrexate-induced HP has been reported more often in patients with rheumatologic diseases. One review looking at 123 cases of MTX-pneumonitis showed that 77% of cases occurred in patients receiving treatment for rheumatoid arthritis or cancer [5]. Among rheumatoid arthritis patients, this reaction occurs with an overall frequency of 0.3 and 11.6% [4]. Although there are case reports published of this reaction occurring in psoriatic arthritis patients, one literature review showed that MTX does not increase the risk of pneumonitis in psoriasis and psoriatic arthritis patients [6]. Reports of MTX-pneumonitis occurring in patients treated for other dermatologic conditions are rare.

The mean duration and dosage of MTX use in patients who develop MTX-pneumonitis is variable. In a review of 3463 patients who were treated with MTX for rheumatoid arthritis, 15 patients (0.43%) developed MTX-pneumonitis. These patients had a mean duration of MTX use of 36.4 months and an average dose of 8.8mg per week [7]. Our patient was on 15mg of MTX per week for six weeks before displaying symptoms. Existing literature indicates that MTX dose may not directly increase the risk of developing toxicity. However, some established risk factors include age >60 years, hypoalbuminemia, diabetes, initiation of a second immunomodulatory medication, and daily dosing instead of weekly [8]. Our patient had some of these risk factors as she was 69 years old and had diabetes.

To our knowledge, this is just the second report of MTX-induced HP developing in a patient with bullous pemphigoid. The first published case occurred in a patient receiving 5mg of MTX per week for three weeks. Similar to our patient, this patient's symptoms and CT imaging improved after discontinuation of the medication [9].

Diagnosing MTX-induced pneumonitis is often considered a diagnosis of exclusion [10]. Although there is no definitive diagnostic test, a set of criteria have been proposed to establish a diagnosis. The outlined major criteria for the diagnosis of HP is 1) histopathology without evidence of pathogenic organisms, 2) radiologic evidence of patchy/diffuse pulmonary ground glass opacities, and 3) negative blood cultures and/or sputum cultures if sputum is produced. The minor diagnostic criteria include shortness of breath for less than 8 weeks, nonproductive cough, oxygen saturation over 90% on room air, diffusion capacity of the lung for carbon monoxide less than or equal to 70% of that predicted for the patient's age, and a leukocyte count of less than 15,000 cells/mm^3. For *definite* diagnosis of MTX-induced HP, one or two of the major criteria must be met as well as three of the 5 minor criteria; two of the 5 minor criteria would degrade it to *probable* diagnosis [8]. Based on this paradigm, our patient would be considered to have a *probable* diagnosis. Notably, our patient had a leukocytosis of 18,000cells/mm^3 which was mostly likely related to her long-term prednisone use. Many patients with immunobullous disease have concomitant corticosteroid use which could affect the *definitive* diagnosis for MTX-induced HP.

Methotrexate-induced HP is a rare but serious adverse reaction which can occur in patients receiving treatment for bullous pemphigoid. Clinicians should be aware of this side effect as it is a reversible disease through cessation of MTX use if diagnosed early. Diagnosing MTX-induced lung toxicity is a multifaceted process that involves ruling out infectious etiology, imaging of the lungs, trialing MTX discontinuation, and reviewing confounding factors such as concomitant prednisone use. Due to

the non-specific signs and symptoms of patients who develop HP, clinicians should be vigilant in monitoring patients for the development of MTX-induced pneumonitis.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Ćalasan MB, van den Bosch OFC, Creemers MCW, et al. Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis. *Arthritis Res Ther*. 2013;15:R217-R. [PMID: 24345416].
2. Ohshimo S, Bonella F, Guzman J, Costabel U. Hypersensitivity pneumonitis. *Immunol Allergy Clin North Am*. 2012;32:537-56. [PMID: 23102065].
3. Saravanan V, Kelly CA. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. *Rheumatology*. 2003;43:143-7. [PMID: 12923285].
4. Fragoulis GE, Nikiphorou E, Larsen J, et al. Methotrexate-Associated Pneumonitis and Rheumatoid Arthritis-Interstitial Lung Disease: Current Concepts for the Diagnosis and Treatment. *Front Med (Lausanne)*. 2019;6:238-. [PMID: 31709258].
5. 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. [PMID: 10706507].
6. Conway R, Low C, Coughlan RJ, et al. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. *BMJ*. 2015;350:h1269. [PMID: 25770113].
7. Salliot C, Heijde DM. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: A systematic literature research. *Ann Rheum Dis*. 2009;68:1100-4. [PMID: 19060002].
8. Salehi M, Miller R, Khaing M. Methotrexate-induced Hypersensitivity Pneumonitis appearing after 30 years of use: a case report. *J Med Case Rep*. 2017;11:174-. [PMID: 28655345].
9. Kjellman P, Eriksson H, Berg P. A Retrospective Analysis of Patients With Bullous Pemphigoid Treated With Methotrexate. *Arch Dermatol*. 2008;144:612-6. [PMID: 18490587].
10. Jakubovic BD, Donovan A, Webster PM, Shear NH. Methotrexate-induced pulmonary toxicity. *Can Respir J*. 2013;20:153-5. [PMID: 23762881].