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CASE REPORT

Concurrent Methotrexate Induced Bone Marrow Suppression and Diclofenac Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome) in a Patient with Rheumatoid Arthritis: A Case Report

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ABSTRACT

Methotrexate and diclofenac are commonly used drugs for the treatment of rheumatoid arthritis. Methotrexate is a disease modifying antirheumatic drug utilized for managing rheumatoid arthritis for long term disease control, while diclofenac is frequently used for symptomatic relief of pain and inflammation. Low dose weekly treatments are generally regarded as safe and effective; however, significant side effects may arise due to dosing mistakes, older age, folate deficiency or accompanying health issues. On the other hand, diclofenac can cause rare but serious adverse hypersensitivity reactions like DRESS syndrome. We describe a 68- year- old man with rheumatoid arthritis who experienced severe leukopenia, thrombocytopenia, mucocutaneous ulcerations, and a secondary bacterial infection after unintentionally taking an extra dose of methotrexate while having discontinued folic acid supplementation for an extended period. Furthermore, the patient had a recent history of diclofenac usage for aggravated joint pain and then presented with a widespread skin rash, eosinophilia, liver involvement and other systemic inflammatory response aligning with DRESS syndrome. The patient was treated with intravenous leucovorin rescue, granulocyte colony- stimulating factor, and broad spectrum antibiotics when methotrexate was stopped right away. With supportive care, a gradual hematologic recovery was accomplished. This instance highlights how crucial it is for patients using methotrexate to receive regular laboratory testing, folic acid therapy and patient education and not to self- medicate.

Keywords: Leucovorin rescue, Rheumatoid arthritis, Bone marrow suppression, Pancytopenia, Methotrexate toxicity, Medication mistake, DRESS syndrome, Diclofenac

INTRODUCTION

The first-line treatment of rheumatoid arthritis and other inflammatory diseases is methotrexate, a folate antagonist that blocks dihydrofolate reductase. It has a well-known safety profile and is usually well tolerated at low weekly dosages^{1, 2}. On the other hand, severe toxicities include opportunistic infections, mucositis, hepatotoxicity and bone marrow suppression could occur. Advanced age, hypoalbuminemia, renal impairment, medication interactions, incorrect dosages, and insufficient folic acid

supplements are risk factors. Timely intervention depends on early detection of warning signals, including mucositis and unexplained cytopenias.

DRESS syndrome is an uncommon but potentially fatal hypersensitivity reaction marked by widespread skin rash, fever, blood disorders such as eosinophilia, lymph node swelling and involvement of internal organs especially the liver. While typically linked to antiepileptics and antibiotics, nonsteroidal anti-inflammatory drugs like diclofenac have been noted as rare triggers³.

The coexistence of methotrexate induced bone marrow suppression and diclofenac induced DRESS syndrome is uncommon and presents a clinical challenge. A detailed drug history and appropriate adverse drug reaction causality assessment are important when more than one drug-related toxicity is suspected.

CASE REPORT

A 68-year-old man with a history of rheumatoid arthritis appeared with severe crusted lesions over his face and anterior chest for four days along with oral ulcerations. After first developing on the face, the lesions later spread to the upper trunk while lesions over the scrotum were noted five days prior to hospital entry. His oral intake was severely hampered by pain due to oral mucosal lesions.

For rheumatoid arthritis, the patient had been taking 7.5 mg of methotrexate once a week (every Tuesday) in addition to 10 mg of prednisolone twice a day and hydroxychloroquine. He had been prescribed folic acid, but he stopped taking it about two months before his presentation. He accidentally took an extra 7.5 mg dose of methotrexate on a Saturday, one week prior to admission in addition to his usual weekly dosage. During the fortnight prior to hospital entry, he had taken oral diclofenac, deriphyllin, chlorampheniramine maleate and pantoprazole in addition to his usual medication for upper respiratory tract infection and arthritis. He experienced the progression of mucocutaneous lesions alongside fever and malaise.

Evaluation on 02-02-2026 revealed marked leukopenia (TC- 760/microlitre with deranged AST -167 U/L, ALT- 354 U/L, blood urea- 63mg/dL CRP- 142mg/L.

Upon cutaneous examination, the face and anterior chest showed several crusted, hyperpigmented papules. The oral examinations revealed friable mucosal erosions. Examination of the scrotum revealed redness and superficial ulcerations. No vesiculobullous eruptions were detected. Laboratory tests on admission showed significant leukopenia, with the total leukocyte count dropping to around 500-550/microL. On account of improvement in leucocyte counts but worsening thrombocytopenia, besides peripheral eosinophilia & atypical lymphocytes possibility of another drug induced allergic complication was considered. Peripheral smear on 05-02-2026 showed lymphocytes 47%, neutrophils 3% on DC counted for 50 cells and on 07-02-2026 showed lymphocytes 28%, neutrophils 1%, eosinophilia 20% and monocyte 1% on DC counted for 50 cells.

The presence of fever, morbilliform rash, peripheral eosinophilia, atypical lymphocytes, liver dysfunction and recent exposure to diclofenac increased concern for DRESS syndrome. A dual diagnosis was made:

1. Methotrexate induced bone marrow suppression evidenced by profound leukopenia and thrombocytopenia

and mucositis.

2. Diclofenac induced DRESS syndrome characterized by acute cutaneous eruption, eosinophilia, atypical lymphocytes, hepatic involvement and fever (Fig. 1).

LABORATORY PARAMETERS

Parameters	3-2-26	5-2-26	7-2-26	10-2-26	13-2-26
HB	13	13.1	12.5	12.4	12.7
TC	550	890	1430	13740	9640
ALT	255	83	-	25	34
AST	59	11	-	22	25
PLATELETS	1.52	0.64	0.15	1.53	3.51
CRP	142.9	233.4	233.4	130.7	63.8
CREATININE	0.86	-	-	0.83	0.81
BLOOD UREA	54.4	-	-	-	30.1

TREATMENT

Methotrexate was promptly stopped on admission. The patient was placed in isolation and treated with intravenous leucovorin rescue therapy at a dosage of 30 mg every six hours. Filgrastim 300 mcg was given subcutaneously for severe neutropenia.

Therapy with broad spectrum antibiotics began using piperacillin- tazobactam and was later intensified to meropenem because of ongoing neutropenia and increased inflammatory markers.

In view of DRESS syndrome, systemic corticosteroids were continued and optimised. Supportive care was provided along with intravenous fluids, mucosal care and monitoring was done.

DIAGNOSTIC ASSESSMENT OF DRESS SYNDROME

DRESS is an adverse drug reaction; the clinical findings were assessed using the RegiSCAR diagnostic framework. The findings included fever, skin eruptions, eosinophilia, atypical lymphocytes and hepatic involvement. Recent exposure to diclofenac was considered in assessing the suspected drug-related reaction. The RegiSCAR framework considers fever, lymphadenopathy, eosinophilia, atypical lymphocytes, skin eruption and its extent, internal organ involvement and exclusion of alternative causes. In this patient, hepatic involvement was documented by elevated AST and ALT, while eosinophilia and atypical lymphocytes were identified on serial peripheral smear examinations.

A numerical RegiSCAR score is not assigned in this revised manuscript because the original case details do not provide the exact maximum temperature, percentage of body-surface area involved by rash, lymph node findings, or complete exclusion of alternative causes investigations. Assigning numerical points for undocumented findings would introduce information not presented in the original case. This assessment supports the clinical suspicion of DRESS while preserving the original patient information and avoiding unsupported additions.

Following treatment, the patient showed progressive clinical and laboratory improvement, including improvement in leukocyte and platelet counts, liver enzyme levels and inflammatory markers. The mucocutaneous manifestations also improved. The patient was discharged in a stable condition.



Fig. 1: Facial involvement of the face demonstrating resolving DRESS syndrome by crusted hyperpigmented papules

DISCUSSION

Methotrexate produces its therapeutic and harmful effects by blocking folate dependent DNA synthesis, which impacts rapidly growing tissues like bone marrow and mucosal epithelium. While low dose methotrexate treatment is typically safer, toxicity may arise even within the therapeutic dose limits especially when additional risk factors are involved¹⁻³. In this situation the unintentional additional dosing with methotrexate and extended cessation of folic acid supplementation probably played a major role in the onset of severe cytopenias. Older age and low albumin levels might have further heightened drug bioavailability and risk of toxicity. Mucositis frequently serves as an initial clinical sign of systemic methotrexate toxicity and should trigger prompt assessments of blood counts³. Severe neutropenia heightened the risk of opportunistic infections and can quickly worsen if not managed promptly. Leucovorin functions by circumventing the inhibition of dihydrofolate reductase, thus protecting normal cells from the cytotoxic effects of methotrexate. Concurrently the patient's exposure to diclofenac probably caused DRESS syndrome. In addition to isolated methotrexate toxicity the

presence of eosinophilia, hepatic dysfunction, systemic inflammatory response and distinctive morbilliform rash suggested an immune mediated hypersensitivity reactions.

DRESS syndrome was assessed using Regi SCAR criteria ($\geq 3/7$ characteristics, rating: certain/probable/likely): Rash, fever $>38^{\circ}\text{C}$, lymphadenopathy in ≥ 2 locations, involvement of ≥ 1 organs, eosinophilia, lymphocytosis or cytopenia, thrombocytopenia. In the present case, the documented findings of fever, skin eruption, eosinophilia, atypical lymphocyte and hepatic involvement supported the clinical suspicion of DRESS. Bocquet criteria include rash, eosinophilia or atypical lymphocytes, involvement of ≥ 1 organs. Japanese DIHS classic (all 7): Rash > 3 weeks after medication, lasts ≥ 2 weeks after stopping, fever $>38^{\circ}\text{C}$, ALT 100U/L or organ involvement, leucocytosis, atypical lymphocytes, lymphadenopathy, HHV-6 reactivation.

Granulocyte colony stimulating factor speeds up neutrophil recovery in instances of severe neutropenia⁴⁻⁷. Timely drug discontinuation and intensive supportive treatment are vital for enhancing results. Errors in medication related to weekly methotrexate dosing continue to be well recognised and avoidable source of toxicity globally. Concise verbal and written directions, educating patients and regular lab checks are crucial preventive measures. Early intervention helps to prevent life threatening complications in people.

CONCLUSION

This case demonstrated a rare coexistence of methotrexate-induced bone marrow suppression and diclofenac-induced DRESS syndrome resulting from low dose methotrexate treatment triggered by accidental extra dosing and lack of adherence to folic acid supplementation. Timely identification of mucocutaneous warning signs, swift cessation of methotrexate and timely initiation of leucovorin rescue along with G-CSF therapy led to a positive recovery. Ongoing patient education and consistent monitoring are essential for preventing severe complications related to methotrexate.

Repeated evaluation of peripheral smear to assess for drug induced reaction with systemic complication in addition to a good drug history is essential to rule out multiple drug toxicities and to treat them appropriately.

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