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# METHOTREXATE: FRIEND OR FOE?

***[1]Pradeep Marur Venkategowda, [2]Anusha Raj, [3]Himaal Dev G. J. and [4]Chaitra C. Rao**

[1]M.D, FNB (Consultant), Department of Critical Care Medicine, Apollo Multi-Speciality Hospital, Sheshadripuram, Bangalore, India.
[2]M.D (Dr. NB Resident), Department of Critical Care Medicine, Apollo Multi-Speciality Hospital, Sheshadripuram, Bangalore, India.
[3]M.D, FNB (Consultant), Department of Critical Care Medicine, Apollo Multi-Speciality Hospital, Sheshadripuram, Bangalore, India.
[4]M.D, IDCCM, IFCCM (Consultant), Department of Critical Care Medicine, Apollo Multi-Speciality Hospital, Sheshadripuram, Bangalore, India.

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***Corresponding Author: Pradeep Marur Venkategowda**
M.D, FNB (Consultant), Department of Critical Care Medicine, Apollo Multi-Speciality Hospital, Sheshadripuram, Bangalore, India.

**ABSTRACT**
Methotrexate (MTX) is a life-saving drug used to treat various clinical conditions. Complications due to low-dose MTX are extremely rare. A 55-year-old woman with multiple health conditions was prescribed low-dose methotrexate (7.5 mg twice weekly) for arthritis. However, she developed various complications, including fever, cough, breathlessness, oral and perianal ulcers, and pancytopenia, indicating methotrexate toxicity. Imaging revealed lung abnormalities. The patient was received in intensive care and treated with antibiotics, ventilation support, hemodialysis, and blood components. Fortunately, her condition improved, and she was discharged (on request) early due to financial constraints. This case highlights serious risks associated with low-dose methotrexate and the importance of early recognition and treatment to minimize harm.

**KEYWORDS**: Methotrexate, Pancytopenia, Chronic kidney disease, Skin ulcers.

## INTRODUCTION

The low-dose MTX has been safely used for over 50 years to treat psoriasis.[1] Low-dose MTX toxicity, though rare, can occur after long-term usage.[2] Severe life-threatening complications of MTX due to just 2 doses are extremely rare. This is a case report of a patient who developed MTX toxicity after receiving only 2 doses of MTX.

## CASE REPORT

A 55-year-old female was admitted to our hospital with a history of fever, cough, and breathlessness for 3 days. She also has a history of oral and perianal ulcers. She was a known case of diabetes mellitus, systemic hypertension, and chronic kidney disease stage 5, and has been on maintenance hemodialysis for 6 years (thrice weekly). The patient was experiencing knee pain one week before admission to our hospital for which she was prescribed a low dose of 7.5mg methotrexate tablets twice weekly at an outside hospital.

The patient was initially evaluated in the emergency room (ER), she was conscious, afebrile, and hemodynamically stable. Initial blood investigations revealed a hemoglobin level of 6.9gm/dl, a total leucocyte count of 800 cells/cubic mm, and platelets numbering 30000 cells/cubic mm. Additionally, the serum creatinine was 5.3mg/dl, blood urea was 35mg/dl, and potassium level was 3.5meq/L. The blood culture and sensitivity tests came back negative. A high-resolution computed tomography of the chest showed nodular opacity in the apical and posterior segments of the right upper lobe. After seeking the opinion of a dermatologist, it was observed that there were erosions in the palate and buccal mucosa, along with multiple erythematous papular ulcerations. This was indicative of methotrexate toxicity, leading to pancytopenia with an oro-cutaneous rash and probable pneumonitis. Patient was shifted to intensive care unit (ICU), the patient received treatment with broad-spectrum antibiotics, non-invasive ventilation (NIV) support, intermittent hemodialysis (HD), nebulization, mucaine gel, zytee gel, folic acid, Granulocyte colony-stimulating factor (G-CSF) analog, 2 units of packed red blood cells (PRBCs), 4 units of random donor platelets (RDP), and one unit of single donor platelet (SDP). On the fourth day, the

patient's clinical condition improved gradually with improvement of hemoglobin level (9.7 g/dl), white blood cell count (8.9 cells/cu mm), and platelet count (1.87lakh cells/cu mm). The patient was discharged (on request) early due to financial constraints. We lost the follow-up of the patient as we could not trace her further admission and treatment.

## DISCUSSION

Methotrexate (MTX) is an anti-metabolite, used in the treatment of various conditions such as leukemia, lymphoma, osteosarcoma, gestational trophoblastic disease, leptomeningeal metastasis, breast cancer, autoimmune diseases like rheumatoid arthritis, psoriasis, Crohn's disease, and ectopic pregnancies. MTX can enter the cells through multiple mechanisms, such as energy-dependent saturable carrier proteins.[3,4] concentration-dependent passive diffusion[5,6] endocytosis[7] and upregulation of mitochondrial enzymes.[8] MTX disrupts folate metabolism by inhibiting dihydrofolate reductase, thymidylate synthetase, and glycinamide ribonucleotide transformylase. These enzymes are necessary for synthesizing purines and thymidine, which are essential for the production of DNA. The unavailability of these components leads to cell death. MTX has a half-life of 8-12 hours, and 90% of it is excreted unchanged in urine. In kidney diseases and with certain drug interactions (Sulfa drugs, non-steroidal anti-inflammatory drugs, Penicillin, Amiodarone, Ciprofloxacin, and Levetiracetam), there is a delay in the clearance of MTX from the body. Our patient had only chronic kidney disease, she did not take any drugs which prolong its half-life by drug interaction. The presence of acidic urine and dehydration can lead to increased urinary precipitation. When using methotrexate (MTX), it is important to take Leucovorin (folinic acid) to protect normal cells from toxicity.[9] Leucovorin should be administered within 24-36 hours of starting MTX.[5]

The adverse effects of this medication include nausea, vomiting, liver toxicity, inflammation of the mouth and throat, kidney damage, decreased production of blood cells, stomatitis, morbilliform drug rashes on the neck and trunk, desquamation, hypersensitive pneumonitis, interstitial lung opacities, and patchy acinar consolidation. MTX toxicity is commonly observed in patients with psoriasis and rheumatoid arthritis who take regular, low-dose, and oral medications. Our patient took only 2 doses (a low dosage of 7.5mg) of methotrexate. The toxicity in our patient is due to pre-existing kidney disease. The medication dosage should be adjusted based on the patient's creatinine clearance (CrCl). The dose should be halved in the case of CrCl 10-50 ml/min. If CrCl is less than 10 ml/min, the use of the medication should be avoided. For hemodialysis patients, 25-50% of the dose should be administered after hemodialysis. "Based on Kintzel's recommendation."[10] If the creatinine clearance (Cr Cl) is 46-60 ml/min, MTX should be given at 65% of the usual dose. If the Cr Cl is 31-45 ml/min, the dose should be reduced to 50%, and in the case of Cr Cl <30 ml/min, MTX should be avoided. Management involves drug discontinuation, adequate hydration, and urine alkalization. The prognosis is favourable if detected and treated early.

## CONCLUSION

This case report emphasizes a significant complication with a low dose of methotrexate. These complications have not been reported previously with low doses. Early recognition of these symptoms, discontinuation of the drug, and providing supportive treatment can help reduce morbidity and mortality.

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## REFERENCES

1. Roenigk HH, Maibach HI, Weinstein GD. Use of methotrexate in psoriasis. Archives of Dermatology, 1972; 105(3): 363–365.
2. Pankti Jariwala, Vinay Kumar, Khyati Kothari, Sejal Thakkar, Dipak Dayabhai Umrigar. Acute Methotrexate Toxicity: A Fatal Condition in Two Cases of Psoriasis. Case Reports in Dermatological Medicine, 2014; 11: 1-3.
3. Goldman ID, Matherly LH. The cellular pharmacology of methotrexate. Pharmacol Ther, 1985; 28: 77.
4. Kamen B. Folate and antifolate pharmacology. Semin Oncol., 1997; 24: S18.
5. Ackland SP, Schilsky RL. High-dose methotrexate: a critical reappraisal. J Clin Oncol., 1987; 5: 2017.
6. Jolivet J, Chabner BA. Intracellular pharmacokinetics of methotrexate polyglutamates in human breast cancer cells. Selective retention and less dissociable binding of 4-NH2-10- CH3-pteroylglutamate4 and 4-NH2-10-CH3-pteroylglutamate5 to dihydrofolate reductase. J Clin Invest, 1983; 72: 773.
7. Walling J. From methotrexate to pemetrexed and beyond. A review of the pharmacodynamic and clinical properties of antifolates. Invest New Drugs, 2006; 24: 37.
8. Vazquez A, Tedeschi PM, Bertino JR. Overexpression of the mitochondrial folate and glycine-serine pathway: a new determinant of methotrexate selectivity in tumors. Cancer Res., 2013; 73: 478.
9. Goldin A, Venditti JM, Kline I, Mantel N. Eradication of leukaemic cells (L1210) by methotrexate and methotrexate plus citrovorum factor. Nature, 1966; 212: 1548.
10. Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. Cancer Treat Rev., 1995; 21: 33.