Indian Journal of Pharmacy Practice., 2025; 18(3):325-328.
https://www.ijopp.org

Case Report

Toxicity of Methotrexate in RA: Case of Oral Ulcers and Pancytopenia

Deeksha M[1,*], Chethan Kumar JK[1], Akshay Louis Dias[2], Mangala S[3]

[1]Department of Pharmacy Practice, Karavali College of Pharmacy, Vamanjoor, Mangalore, Karnataka, INDIA.
[2]Department of General Medicine, Father Muller Medical College, Kankanady, Mangalore, Karnataka, INDIA.
[3]Department of Pharmacology, Father Muller Medical College, Kankanady, Mangalore, Karnataka, INDIA.

ABSTRACT

Rheumatoid arthritis is a chronic autoimmune disease affecting approximately 1% of the population, primarily causing joint inflammation and leading to joint destruction, physical disability and cardiovascular disease. Methotrexate, a commonly used antimetabolite in rheumatoid arthritis treatment, is associated with toxicity, including mucositis and pancytopenia, particularly when used at high doses or without adequate folic acid supplementation. This report presents the case of a 69-year-old female with rheumatoid arthritis who developed bleeding oral ulcers, mucositis and difficulty swallowing while on methotrexate therapy. Laboratory investigations revealed pancytopenia, acute kidney injury on chronic kidney disease and atypical cells, resulting in a diagnosis of methotrexate-induced toxicity. The patient was treated with folinic acid, intravenous fluids and supportive care, including antibiotics for a lower respiratory tract infection and antifungal medication for oral candidiasis. Her condition improved, with healing of the ulcers and normalization of her blood cell counts. This case underscores the importance of regular monitoring of blood counts, renal function and methotrexate serum levels to prevent methotrexate toxicity. Clinicians should remain vigilant for methotrexate-related complications, especially in elderly patients with renal impairment and irregular follow-up care. Early detection and prompt treatment are essential to prevent life-threatening consequences.

Keywords: Dihydrofolate Reductase, Dihydrofolate, Methotrexate, Mucositis, Rheumatoid Arthritis, Tetrahydrofolate.

Correspondence:
Dr. Deeksha M
6th Pharm D Student, Department of Pharmacy Practice, Karavali College of Pharmacy, Vamanjoor, Mangalore-575028, Karnataka, INDIA.
Email: deeksham968@gmail.com
ORCID: 0009-0005-5581-5746

Received: 02-10-2024;
Revised: 12-11-2024;
Accepted: 22-12-2024.

INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic autoimmune disease that primarily causes inflammation of the joints. The prevalence of RA is 1% among the population and more common in women. Chronic inflammation in RA can result in joint destruction, physical disability, as well as cardiovascular disease.[1]

Oral ulcerations are a frequent mucocutaneous side effect of Methotrexate (MTX), often related to dosage and more common in patients who receive high doses without adequate folic acid supplementation.[2]

Methotrexate is a commonly used drug for the treatment of psoriasis, arthritis and many forms of cancer. Methotrexate is a chemotherapeutic agent used for treatment of acute lymphocytic leukaemia, lymphomas and some solid tumours. It is used in low dose regimens for a variety of non-neoplastic conditions.[3]

DOI: 10.5530/ijopp.20250161

An established antimetabolic medication MTX has been used to treat psoriasis since 1960s and was approved by Food and drug Administration for the indication in 1971. Its use for rheumatoid arthritis began in the 1980s, with Food and Drug Administration granting approval in 1988. The folate antagonist MTX was initially created by Farber *et al.* (1956) to treat malignancies, but it was later utilised to treat non-neoplastic conditions as well. MTX reduces the generation of inflammatory mediators by preventing the immune-stimulatory cells from proliferating, which is advantageous for the treatment of psoriasis and RA.[1,5,6]

While MTX regimens used in cancer frequently represent the maximum tolerated dose, oral treatment for rheumatoid arthritis can benefit from a lower dose of 5-35 mg per week. The frequency and severity of MTX toxicity is generally dose-dependent, the individual tolerances of MTX vary. Clinicians frequently encounter methotrexate in their practice due to its widespread use in treating RA. RA affects approximately 1% of the population and around 50% of RA patients undergo MTX treatment for at least five years.[4]

However, while MTX is generally effective, its main drawback is toxicity rather than inefficacy, leading to discontinuation in about

30% of rheumatoid arthritis patients. Several efforts are currently being made to develop strategies to decrease or prevent its toxicity which leads to discontinuation of MTX.[5]

In the context of autoimmune diseases and allografts, (MTX) is typically administered in doses of 7.5-15 mg per week, either as a single dose or split into two or three doses taken 12 hr apart, delivered orally or via intramuscular injection.

CASE PRESENTATION

A 69-year-old female patient came with complaints of bleeding ulcers in the mouth for six days and difficulty in swallowing liquids and solids. She had pain on the right side of her neck associated with swallowing. On observation, ulcers which spontaneously bleed were present over her lower lip which was suggestive of mucositis (Figure 1). Her vital signs included a blood pressure of 100/70 mm Hg and a pulse rate of 80 beats/min. Examination of the cardiovascular system revealed normal S1 and S2 heart sounds without murmurs and examination of the respiratory system revealed bilateral normal vesicular breath sounds with no added sounds.

She was known hypertensive for 30 years on amlodipine 5 mg, arthritis for 10 years and was on methotrexate (unknown dose) and folic acid for rheumatoid arthritis. She had not attended regular follow-ups although she continued the same dose of methotrexate.

Lab investigations showed: haemoglobin-9 g/dL (11-16.5 g/dL), platelets-55,000 cells/cumm (1-4 lac), total count-1310 cells per microliter (4,500-11000 cells per microliter), total bilirubin-1.26 mg/dL (0.1 to 1.2 mg/dL), AST-22IU/L (8-48IU/L), ALT-17IU/L (7-55I U/L), uric acid-3.2 mg/dL(3.5 and 7.2 mg/dL), serum creatinine of 2 (0.7 to 1.3 mg/dL), serum methotrexate levels were 0.019 umol/L. Peripheral smear showed WBCs are reduced in number with absolute decrease in neutrophils (ANC=292 cells/cumm) and shows atypical cells (16%) the trend of the complete blood count (Table 1). These cells have high N:C ratio, irregular nuclear membrane, occasional nucleoli, fine chromatin and scant amount of cytoplasm. Malaria and dengue serology were negative. The USG showed bilateral small-sized kidneys. Urine routine showed no sediments, protein or red blood cells. The patient was diagnosed with methotrexate induced pancytopenia and mucositis, acute kidney injury on chronic kidney disease, hypertension.

She received intravenous fluids (0.9% saline), choline salicylate gel for local application for the mucositis. In addition, methotrexate toxicity was treated with folinic acid 15 mg Intravenously (IV) every 6 hr, multivitamin injection IV once daily, folic acid 5 mg once daily and xylocaine mouth rinse.

Since she complained of cough with expectoration persisting for 15 days in the background of methotrexate induced pancytopenia with low absolute neutrophil count (292 cells/cumm) and patient having a lower respiratory tract infection patient was initiated in meropenem. Chest X-ray which was done showed no infliltrates.

Candid oral paint thrice daily and Fluconazole 100 mg once daily was added. G-Granulocyte colony-stimulating factor-filgrastim 300 mg S/C daily was added and hydration of 2 L per day was continued.

Due to the peripheral smear showing atypical cells, haematological malignancy due to unmonitored chronic methotrexate use was suspected and a flow cytometry showed no evidence of a lymphocytic process and a bone marrow aspiration and biopsy showed mild erythroid hyperplasia.

Patient showed improvement with the ulcers healed (Figure 2), also improvement in all the three marrow cell lines, disappearance

Figure 1: Methotrexate induced ulcers on the lips.

Table 1: Complete blood count over the course of 2 days.[9]

	Day 1	Day2	References
Haemoglobin	9.0 g/dL	8.6 g/dL	11-16.5 g/dL
Red blood cells	3.00 million/cumm	2.80 million/cumm	3.80-5.80 m/cu
Packed cell volume	25.1%	23.4%	35-50%
MCV	83.7fl	83.6 fl	80-100 fl
MCHC	35.9g/dL	36.8g/dL	32-36g/dL
RDW	12.3%	12.7%	12-15%
Platelet count	55000 cells/cumm	Platelets are severely reduced in number. (Pancytopenia atypical cells seen, suggested further evaluation).	1-4 lac cells/cum
Leukocyte count total	1310 cells per microliter		4,500-11000 cells per microliter
Differential count	-	34%	40-60%
Neutrophils	56%	44%	20-40%
Lymphocytes	43%	06%	1-4%
Eosinophils	00		

of fever and better general condition. She was discharged with folic acid 5 mg orally, sodium bicarbonate 500 mg thrice daily, furosemide 40 mg once daily and amlodipine 5 mg oral once daily. She was counselled about attending regular out-patient clinic visits and to watch out for any pain in the joints due to RA. Further plan of management for RA was to be decided on follow-up.

DISCUSSION

Methotrexate is a folate analogue originally designed to inhibit the enzyme dihydrofolate reductase. Reduced folate serves as the proximal single carbon donor in several reactions involved in the de novo synthesis of purines and pyrimidines, formation of polyamines and treatment processes. Methotrexate is an antifolic drug used in the treatment of immune-mediated and neoplastic diseases. Initiation or dosage changes in methotrexate therapy can cause mucositis and bone marrow suppression.[1,2] Skin lesions due to acute methotrexate toxicity are rare. Methotrexate reduces cell proliferation and, at lower doses, inhibits the proliferation of lymphocytes and cytokine synthesis. Methotrexate (MTX) is a folate antagonist used to treat various malignancies, autoimmune disorders. It enters cells through active transport and is removed by an active efflux transporter. Inside the cell, MTX inhibits Dihydrofolate Reductase (DHFR), it is an enzyme that converts Dihydrofolate (DHF) to Tetrahydrofolate (THF). This inhibition reduces thymidylate and purine biosynthesis, decreasing DNA synthesis and preventing cell replication.[4-6] MTX undergoes polyglutamation, which prolongs its presence inside the cell. Consequently, cells capable of effective polyglutamation, such as leukemic myeloblasts, synovial macrophages, lymphoblasts and epithelial cells are more susceptible to MTX. Methotrexate is a widely used as chemotherapeutic and immunosuppressive agent. Also, effective in treating various other conditions, it can cause adverse effects, such as cutaneous ulcerations. These ulcerations often serve as indicators of systemic toxicity, such as pancytopenia, which finally arise in various dermatologic condition. Since MTX-induced cutaneous ulcerations were first noted in patients with psoriasis. These ulcerations often appeared as pre-exist psoriasis plaques and were seen with severe, potentially life-threatening conditions like pancytopenia (a reduction in the number of red and white blood cells and platelets).[7-8]

However, increase in polyglutamation raises the risk of toxicity due to prolonged intracellular exposure. This can lead to ulcers and bleeding, as seen in this case, due to the increased concentration of MTX in myeloid lineage, megakaryocytes and epithelial cells. Similarly, WBC (White Blood Cells) and RBC (Red Blood Cells) involvement can result in infections and macrocytic anaemia, which were also present in this patient. MTX should not been given more frequently, which can lead to toxicity.

Treatment of methotrexate toxicity includes withdrawal of the drug, measuring the level of drug, hydration and folinic acid rescue. Hydration since MTX is excreted by the kidneys to achieve a urine output of 2 L/m^2. Leucovorin rescue for methotrexate overdose typically involves administering 10 mg/m^2 orally, IM, or IV every 6 hr, starting as soon as possible or within 24 hr if methotrexate elimination is delayed till MTX levels drop <0.2 µmol/L. Urine alkalinization also facilitates MTX elimination. Prompt treatment initiation can prevent the complications and fatalities associated with MTX toxicity.[5]

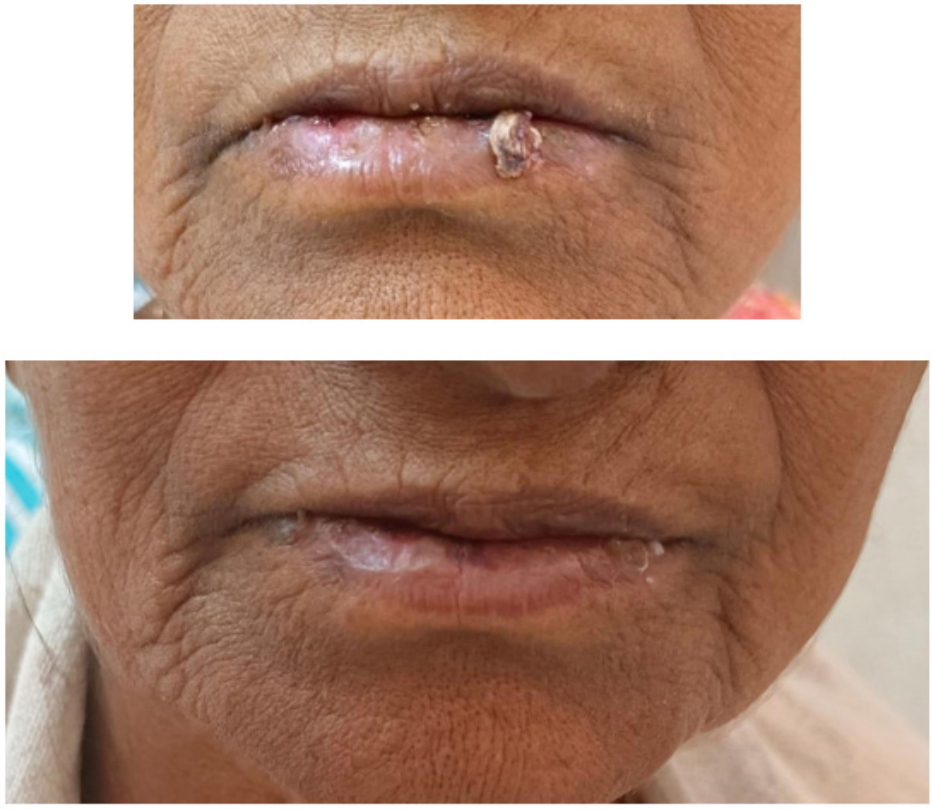

Figure 2: Resolved oral ulcers on the lower lip.

CONCLUSION

A complete blood count, serum creatinine and liver function test should be performed on patients receiving methotrexate therapy on a frequent basis to detect myelosuppression and prevent pancytopenia. Renal function testing is also necessary because the patient's kidney size is decreased and the medications primarily use the kidneys for excretion. The primary role of physicians is thus needed to be aware of these complications.

ACKNOWLEDGEMENT

I acknowledge Dr. Akshay Louis Dias, Department of General Medicine, Father Muller Medical College Hospital, Mangalore, for his support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MTX: Methotrexate; **RA:** Rheumatoid Arthritis; **CBC:** Complete Blood Count.

REFERENCES

1. Kapoor T, Bathon J. Renal Manifestations of Rheumatoid Arthritis. Rheumatic Disease Clinics of North America. 2018;44(4):571-84.
2. Berna R, Dasilva D, Xu GX, Baumrin E. Methotrexate-induced cutaneous ulceration without pancytopenia in a patient treated for inflammatory arthritis. JAAD Case Reports. 2021;13:130-3.
3. Kalantzis A, Marshman Z, Falconer DT, Morgan PR, Odell EW. Oral effects of low-dose methotrexate treatment. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 2005;100(1):52-62.
4. Troeltzsch M, von Blohn G, Kriegelstein S, Woodlock T, Gassling V, Berndt R, *et al.* Oral mucositis in patients receiving low-dose methotrexate therapy for rheumatoid arthritis: report of 2 cases and literature review. Oral surgery, oral medicine, oral pathology and oral radiology. 2013;115(5):e28-33.
5. 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. In Seminars in arthritis and rheumatism 1998; 27(5): 277-92. WB Saunders.
6. Genestier L, Paillot R, Quemeneur L, Izeradjene K, Revillard JP. Mechanisms of action of methotrexate. Immunopharmacology. 2000;47(2-3):247-57.
7. Berna R, Dasilva D, Xu GX, Baumrin E. Methotrexate-induced cutaneous ulceration without pancytopenia in a patient treated for inflammatory arthritis. JAAD Case Reports. 2021;13:130-3.
8. Gonzalez-Ibarra F, Eivaz-Mohammadi S, Surapaneni S, Alsaadi H, Syed AK, Badin S, *et al.* Methotrexate Induced Pancytopenia. Case Reports in Rheumatology. 2014; 2014:1-4.
9. https://fathermuller.edu.in/frmullerhospital/biochemistry-fmmchl.php

Cite this article: Deeksha M, Kumar JKC, Dias AL, Mangala S. Toxicity of Methotrexate in RA: Case of Oral Ulcers and Pancytopenia. Indian J Pharmacy Practice. 2025;18(3):325-8.