



METHOTREXATE TOXICITY IN A RHEUMATOID ARTHRITIS PATIENT

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ABSTRACT

Background: Methotrexate is the most commonly prescribed disease-modifying antirheumatic drug for rheumatoid arthritis because of its effectiveness and affordability. Despite its therapeutic benefits, methotrexate toxicity may occur due to dosing errors, renal impairment, drug interactions, or inadequate monitoring. Low-dose methotrexate toxicity can result in severe complications including pancytopenia, mucositis, hepatotoxicity, nephrotoxicity, and life-threatening infections.

Case Presentation: A 58-year-old female with seropositive rheumatoid arthritis presented with fever, painful oral ulcers, generalized weakness, nausea, vomiting, and skin lesions following accidental daily consumption of methotrexate instead of weekly dosing for 10 consecutive days. Laboratory investigations revealed severe pancytopenia, elevated liver enzymes, hypoalbuminemia, and acute kidney injury. Methotrexate toxicity was diagnosed based on clinical presentation, medication history, and laboratory abnormalities. Methotrexate was immediately discontinued, and the patient was treated with intravenous leucovorin rescue therapy, aggressive hydration, urinary alkalinization, broad-spectrum antibiotics, granulocyte colony-stimulating factor, blood transfusions, and supportive care. Gradual clinical and hematological recovery was observed during hospitalization. **Conclusion:** Methotrexate toxicity is a preventable but serious adverse drug reaction. Early diagnosis, prompt initiation of leucovorin rescue therapy, intensive supportive management, and regular laboratory monitoring are essential for favorable outcomes. Proper patient counseling regarding once-weekly dosing schedules remains crucial in preventing methotrexate-related medication errors and associated morbidity.

KEYWORDS: Methotrexate toxicity; Rheumatoid arthritis; Pancytopenia; Leucovorin rescue; Medication error; Mucositis.

INTRODUCTION

Methotrexate serves as the primary disease-modifying antirheumatic medication for rheumatoid arthritis treatment because it provides effective and economical treatment which maintains disease control over time. The chronic autoimmune inflammatory disorder rheumatoid arthritis leads to continuous joint damage together with symptoms of pain and swelling which result in complete loss of physical function.^[1] The drug methotrexate decreases disease activity by blocking folate-dependent enzymes which control both DNA production and inflammatory processes. Rheumatology guidelines recommend low-dose weekly methotrexate therapy as the primary treatment because patients generally tolerate it well. Methotrexate demonstrates a safe profile, but it causes serious gastrointestinal, liver, kidney, skin, and bone marrow adverse effects. Toxicity can develop through multiple pathways which include overdose, renal impairment, drug interactions, advanced age, hypoalbuminemia, and insufficient monitoring during extended therapy.^[2]

Medical professionals treat methotrexate toxicity as a critical emergency because it leads to life-threatening conditions through its development of severe pancytopenia and mucositis and sepsis and multiorgan dysfunction when medical staff fails to detect it at an early stage. The toxic effects primarily affect rapidly dividing cells which include bone marrow cells and gastrointestinal mucosa and epithelial tissues. Bone marrow suppression leads to anemia and leukopenia and thrombocytopenia and severe neutropenia which together make people more likely to experience infections and bleeding emergencies.^[3] The first signs of toxicity appear through oral mucositis and skin ulcerations which show that patients have reached dangerous levels of methotrexate in their bodies. The body experiences increased toxicity because renal dysfunction prevents methotrexate clearance and causes higher serum drug levels. The process of identifying warning signs requires medical professionals to begin treatment immediately which helps reduce both morbidity rates and mortality rates that result from methotrexate toxicity.^[4]

The primary reason for methotrexate toxicity in rheumatoid arthritis patients remains medication errors which continue to be a major problem. Patients who receive methotrexate prescriptions for weekly use might misinterpret their dosing instructions which leads to unintentional medication overdoses through daily consumption. Elderly individuals become especially susceptible to these issues because they experience both health literacy deficits and multiple health conditions and they take multiple medications.^[5] The combined use of nonsteroidal anti-inflammatory drugs with proton pump inhibitors and trimethoprim-sulfamethoxazole and nephrotoxic medications creates a higher risk for methotrexate accumulation and toxicity. The studies demonstrate that complete blood count and liver function tests together with renal function tests should be used as

standard laboratory tests which need to be conducted throughout methotrexate therapy. The combination of patient counseling and pharmacist-led medication review activities establishes essential methods for doctors to identify methotrexate-related serious adverse drug reactions.^[6]

The primary method for treating methotrexate toxicity requires doctors to stop the medication and use leucovorin rescue therapy while they provide patients with aggressive hydration and urinary alkalization and infection control and basic medical care. Leucovorin functions by enabling the body to bypass folate antagonism while it protects normal cells from toxic damage. The medical team needs to decide about blood transfusions and granulocyte colony-stimulating factor administration and nutritional support in addition to their current monitoring activities which will depend on how serious the toxicity conditions become.^[7] Early intervention helps improve clinical outcomes because it decreases the chances of developing complications. The current case report documents a patient with rheumatoid arthritis who experienced severe low-dose methotrexate toxicity after he mistakenly took his medication every day instead of following his prescribed weekly schedule. The report presents methotrexate-associated complications through clinical evaluations and laboratory data and treatment methods and patient education strategies and patient monitoring techniques.^[8]

CASE PRESENTATION

Patient Demographics

A 58-year-old female presented to the emergency department of a tertiary care teaching hospital with complaints of painful oral ulcers, fever, generalized weakness, nausea, vomiting, and skin lesions. The patient was a known case of seropositive rheumatoid arthritis diagnosed eight years earlier. She belonged to a middle socioeconomic background and was moderately built and poorly nourished at the time of admission.

Chief Complaints

The patient presented with the following complaints:

- Painful oral ulcers for 5 days
- Fever for 4 days
- Generalized weakness and fatigue for 1 week
- Nausea and vomiting for 3 days
- Difficulty in swallowing for 4 days
- Skin rashes and peeling lesions over upper limbs for 3 days
- Reduced appetite and decreased oral intake for 1 week

History of Present Illness

The patient was apparently stable one month before admission and was on regular treatment for rheumatoid arthritis. She had been prescribed oral methotrexate 15 mg once weekly along with folic acid supplementation. Due to misunderstanding of prescription instructions, the

patient accidentally consumed methotrexate 15 mg daily instead of weekly for 10 consecutive days.

After approximately one week of excessive methotrexate intake, she developed severe oral ulcers associated with burning sensation and difficulty swallowing. This was followed by fever, generalized weakness, loss of appetite, nausea, and repeated episodes of vomiting. Two days later, she developed erythematous skin lesions with areas of peeling over the upper extremities and trunk.

Her symptoms progressively worsened, leading to inability to consume food properly and severe fatigue, following which she was brought to the emergency department by her family members. There was no history of hematemesis, melena, seizures, breathlessness, or altered sensorium.

Medication History

The patient had been receiving the following medications regularly:

Drug	Dose	Frequency	Indication
Methotrexate	15 mg	Once weekly	Rheumatoid arthritis
Folic acid	5 mg	Once weekly	Folate supplementation
Prednisolone	5 mg	Once daily	Rheumatoid arthritis
Pantoprazole	40 mg	Once daily	Gastric protection
Calcium supplements	500 mg	Once daily	Bone protection

On detailed questioning, it was identified that the patient consumed methotrexate daily for 10 days because she misunderstood the weekly dosing instructions.

Personal History

- Appetite: Reduced
- Sleep: Disturbed due to pain and fever
- Bowel habits: Normal
- Bladder habits: Normal
- Diet: Mixed diet

Vital Signs

Parameter	Finding
Temperature	38.6°C
Pulse Rate	108 beats/min
Blood Pressure	100/60 mmHg
Respiratory Rate	22 breaths/min
Oxygen Saturation	97% on room air

General Physical Examination

- Pallor: Present
- Icterus: Absent
- Cyanosis: Absent
- Clubbing: Absent
- Lymphadenopathy: Absent
- Pedal edema: Absent
- Dehydration: Present

Multiple painful oral ulcers with hemorrhagic crusts were noted over the buccal mucosa, tongue, and lips.

History of Past Illness

The patient was diagnosed with seropositive rheumatoid arthritis eight years previously based on clinical features and positive rheumatoid factor. She had intermittent episodes of joint pain and morning stiffness involving small joints of both hands and wrists. She had no previous history of methotrexate toxicity, chronic liver disease, tuberculosis, malignancy, or hematological disorders. There was no history of diabetes mellitus, hypertension, ischemic heart disease, or chronic kidney disease.

Family History

There was no significant family history of rheumatoid arthritis, autoimmune disease, malignancy, or hematological disorders.

General Examination

At presentation, the patient appeared toxic, dehydrated, pale, and weak.

Diffuse erythematous skin lesions with superficial desquamation were present over both upper limbs and trunk.

Systemic Examination

Musculoskeletal Examination

- Bilateral tenderness and swelling of metacarpophalangeal and proximal interphalangeal joints
- Morning stiffness lasting approximately 45 minutes
- Mild restriction of joint movements due to pain

Cardiovascular System

- S1 and S2 heard normally
- No murmurs

Respiratory System

- Bilateral air entry present
- No added sounds

Central Nervous System

- Conscious and oriented

Laboratory Investigations**Complete Blood Count**

Parameter	Patient Value	Normal Range
Hemoglobin	7.8 g/dL	12–15 g/dL
Total Leukocyte Count	3,200 cells/mm ³	4,000–11,000 cells/mm ³
Platelet Count	68,000 cells/mm ³	150,000–450,000 cells/mm ³
Neutrophils	28%	40–70%

Renal Function Tests

Parameter	Patient Value	Normal Range
Serum Creatinine	2.1 mg/dL	0.6–1.2 mg/dL
Blood Urea Nitrogen	48 mg/dL	7–20 mg/dL

Liver Function Tests

Parameter	Patient Value	Normal Range
AST	96 U/L	<40 U/L
ALT	88 U/L	<40 U/L
Serum Albumin	2.8 g/dL	3.5–5.0 g/dL

Additional Investigations

- Rheumatoid factor: Positive
- C-reactive protein: Elevated
- Blood cultures: No bacterial growth
- Chest X-ray: Normal
- Urine analysis: Mild proteinuria

DIAGNOSIS

Based on the patient's clinical presentation, detailed medication history, physical examination findings, and laboratory investigations, a diagnosis of severe low-dose methotrexate toxicity was established. The patient had a documented history of rheumatoid arthritis and had accidentally taken methotrexate every day for 10 days instead of her prescribed weekly dosage. Clinically she exhibited the typical symptoms of methotrexate toxicity which included painful oral mucositis and fever and general weakness and nausea and vomiting and erythematous skin lesions that showed skin peeling. The hematological tests showed that the patient had severe pancytopenia because of bone marrow suppression which resulted in anemia and leukopenia and neutropenia and thrombocytopenia. The biochemical tests showed that the patient had elevated liver enzymes which indicated hepatotoxicity and raised serum creatinine levels which showed acute kidney injury. The patient developed severe methotrexate toxicity which included pancytopenia and mucositis and hepatotoxicity and

- No focal neurological deficits

Abdomen Examination

- Soft and non-tender
- No hepatosplenomegaly
- Bowel sounds present

nephrotoxicity because of her excessive methotrexate intake that began with her first symptoms.

TREATMENT AND MANAGEMENT

Day 1: After admission, methotrexate was stopped immediately and the patient was shifted to the intensive care unit for monitoring. Intravenous leucovorin 15 mg every 6 hours was started as antidote therapy. Intravenous normal saline at 100 mL/hour and sodium bicarbonate infusion were administered for hydration and urinary alkalinization. Piperacillin-tazobactam 4.5 g intravenously every 8 hours was initiated for febrile neutropenia. Ondansetron 4 mg intravenously twice daily and pantoprazole 40 mg intravenously once daily were prescribed. Baseline investigations including complete blood count, liver function tests, renal function tests, and electrolytes were performed. Strict monitoring of vital signs and urine output was maintained throughout the day.

Day 2: The patient continued to have severe oral ulcers, fever, and poor oral intake. Leucovorin 15 mg every 6 hours and intravenous fluids were continued. Filgrastim 300 mcg subcutaneously once daily was started because of persistent neutropenia. Chlorhexidine mouthwash twice daily and topical lignocaine viscous gel before meals were prescribed for mucositis management. Intravenous paracetamol 1 g every 8 hours was administered for fever. High-protein liquid nutritional

supplementation was initiated. Daily complete blood count and electrolyte monitoring were performed. Neutropenic precautions including strict hand hygiene and restricted visitors were maintained to prevent secondary infections.

Day 3: On the third day, the patient developed worsening anemia and severe weakness. One unit of packed red blood cells and one unit of platelet concentrate were transfused after hematology consultation. Leucovorin rescue therapy and filgrastim injections were continued. Piperacillin-tazobactam therapy was maintained due to ongoing febrile neutropenia. Intravenous potassium chloride supplementation was administered for hypokalemia correction. Skin lesions were treated with sterile saline dressing and liquid paraffin application twice daily. Renal function showed slight improvement with hydration therapy. The patient remained under continuous monitoring for sepsis, bleeding manifestations, and worsening pancytopenia.

Day 4: By day four, fever frequency reduced and oral pain improved slightly. Leucovorin 15 mg every 6 hours and filgrastim 300 mcg daily were continued. Intravenous normal saline infusion rate was reduced to 75 mL/hour as hydration status improved. Chlorhexidine mouthwash and topical lignocaine gel were continued regularly. Laboratory investigations showed mild improvement in leukocyte counts. The patient tolerated small amounts of semisolid diet. Piperacillin-tazobactam therapy was continued for infection prophylaxis. Daily monitoring of blood counts, renal parameters, liver enzymes, and vital signs was maintained. Nutritional supplementation and supportive nursing care continued throughout the day.

Day 5: On the fifth day, the patient became afebrile and oral ulcers started healing gradually. Leucovorin dosage was reduced to 15 mg every 8 hours because of improving hematological parameters. Filgrastim injections were continued. Intravenous fluids were tapered gradually while encouraging oral hydration. Pantoprazole was shifted from intravenous to oral administration at 40 mg once daily. Complete blood count showed improvement in leukocyte and platelet counts. Nutritional support and topical oral care were maintained. Physiotherapy-assisted mobilization was encouraged to improve muscle strength. No new skin lesions or bleeding manifestations were observed during clinical examination.

Day 6: Significant clinical improvement was observed on day six. White blood cell count and platelet levels improved considerably. Filgrastim therapy was continued for one additional day. Leucovorin frequency was reduced to 15 mg every 12 hours. Skin lesions showed healing with decreased erythema and desquamation. Sodium bicarbonate infusion was

discontinued after normalization of renal function parameters. Piperacillin-tazobactam therapy was continued to complete the planned antibiotic course. The patient tolerated oral semisolid diet without difficulty. Daily monitoring of blood counts, liver function tests, and serum creatinine levels continued to assess further recovery and prevent complications.

Day 7: By the seventh day, hematological recovery was evident with improved hemoglobin, leukocyte, and platelet counts. Filgrastim injections were discontinued after neutrophil recovery. Intravenous leucovorin therapy was replaced with oral folic acid supplementation. Piperacillin-tazobactam was continued until completion of the antibiotic course. Oral ulcers healed significantly and skin lesions resolved gradually. The patient tolerated normal oral diet and became ambulatory without support. Counseling regarding weekly methotrexate dosing, folic acid supplementation, and regular laboratory monitoring was provided to both patient and caregivers. Plans for rheumatology follow-up and future disease-modifying therapy modification were discussed before transfer to the general ward.

Days 8–14: During days 8 to 14, the patient showed steady clinical and hematological recovery without development of new complications. Oral folic acid 5 mg twice daily was continued for ongoing folate supplementation, and intravenous medications were gradually shifted to oral formulations. Piperacillin-tazobactam therapy was completed after seven days and discontinued as fever subsided completely and blood cultures remained negative. Oral pantoprazole 40 mg once daily and multivitamin supplementation were continued. Daily complete blood count, liver function tests, and renal function tests demonstrated progressive normalization of hemoglobin, leukocyte count, platelet count, serum creatinine, and liver enzymes. Nutritional rehabilitation with high-protein diet and oral hydration was encouraged. Regular oral care with chlorhexidine mouthwash was maintained until complete healing of mucositis. Skin lesions resolved significantly with topical emollient therapy. The patient received repeated counseling regarding proper once-weekly methotrexate administration, importance of folic acid supplementation, and regular follow-up monitoring. She was discharged on day 14 in stable condition with advice for rheumatology follow-up and temporary discontinuation of methotrexate therapy.

Discharge Medications

At the time of discharge, the patient was clinically stable with improved hematological and biochemical parameters. Methotrexate therapy was withheld temporarily until reassessment by the rheumatology department. The following medications were prescribed at discharge:

Drug	Dose	Frequency	Duration	Indication
Folic Acid	5 mg	Once weekly	4 weeks	Folate supplementation
Pantoprazole	40 mg	Once daily before food	2 weeks	Gastric protection
Multivitamin Tablets	1 tablet	Once daily	4 weeks	Nutritional supplementation
Chlorhexidine Mouthwash	10 mL gargles	Twice daily	7 days	Oral mucosal care
Topical Lignocaine Gel	Local application	Before meals	5 days	Relief from oral ulcer pain
Calcium + Vitamin D3	500 mg + 250 IU	Once daily	1 month	Bone protection
Prednisolone	5 mg	Once daily	As advised	Rheumatoid arthritis symptom control

The patient and caregivers were counseled extensively regarding strict once-weekly methotrexate dosing, avoidance of self-medication, importance of regular blood investigations, and early reporting of symptoms such as oral ulcers, fever, bleeding, or severe weakness. Follow-up with the rheumatology outpatient department was advised after one week for reassessment and future disease-modifying antirheumatic drug planning.

DISCUSSION

Methotrexate is considered the anchor drug in the management of rheumatoid arthritis because of its efficacy and long-term disease control. However, low-dose methotrexate toxicity remains a serious clinical concern, especially in elderly patients and in cases of dosing errors. In the present case, the patient accidentally consumed methotrexate daily instead of weekly, leading to severe pancytopenia and mucositis. Similar findings were reported by Lim, Gaffney, and Scott, who described methotrexate-induced pancytopenia as an under-recognized but potentially fatal complication in rheumatoid arthritis patients. In another study, Kivity et al. identified incorrect dosing schedules, renal impairment, hypoalbuminemia, and advanced age as major predictors of methotrexate toxicity. The present case strongly correlates with these findings and emphasizes the importance of patient education regarding weekly dosing schedules and medication safety.^[9,10]

Bone marrow suppression is one of the most severe manifestations of methotrexate toxicity and may result in fatal infections, bleeding tendencies, and multiorgan complications. In the current patient, severe anemia, leukopenia, neutropenia, and thrombocytopenia were observed after excessive methotrexate intake. Gutierrez-Ureña et al. reported that pancytopenia secondary to low-dose methotrexate therapy is more common in patients with renal dysfunction and folate deficiency. Similarly, Gutierrez-Ureña and colleagues emphasized that delayed diagnosis may increase mortality in rheumatoid arthritis patients with methotrexate toxicity. Another study by

Salliot and van der Heijde highlighted that hematological adverse effects are preventable with regular blood count monitoring and appropriate folic acid supplementation. In the present case, prompt discontinuation of methotrexate, blood transfusions, leucovorin rescue therapy, and granulocyte colony-stimulating factor administration resulted in successful hematological recovery.^[11,12]

Mucositis and nephrotoxicity are important indicators of systemic methotrexate accumulation and usually occur due to impaired elimination of the drug. In the present case, the patient developed painful oral ulcers, dehydration, and acute kidney injury following repeated daily methotrexate administration. Widemann and Adamson explained that reduced renal clearance significantly increases methotrexate serum concentrations, thereby worsening toxicity manifestations including mucositis and pancytopenia. Howard et al. further emphasized that early hydration, urinary alkalization, and leucovorin rescue therapy are essential in reducing methotrexate-induced organ damage and mortality. The management protocol followed in the current patient closely resembled these recommendations and resulted in gradual normalization of renal function and complete healing of mucosal lesions. Early supportive therapy played a major role in preventing progression to septic shock and multiorgan dysfunction.^[13,14]

Prevention of methotrexate toxicity requires regular laboratory monitoring, clear prescription instructions, and continuous patient counseling. In the present case, inadequate understanding of weekly methotrexate dosing was identified as the primary cause of toxicity. Visser and van der Heijde reported that routine monitoring of liver enzymes, renal function, and hematological parameters significantly reduces methotrexate-related adverse effects in rheumatoid arthritis patients. Additionally, Singh et al., in the American College of Rheumatology guidelines, recommended periodic blood investigations and patient education as essential

components of methotrexate therapy monitoring. The current case further highlights the crucial role of pharmacists and healthcare professionals in preventing medication errors through proper counseling and follow-up. Effective communication and regular monitoring remain essential to ensure safe and effective long-term methotrexate therapy in rheumatoid arthritis patients.^[15,16]

CONCLUSION

Methotrexate toxicity is a rare but potentially life-threatening complication in patients receiving low-dose methotrexate therapy for rheumatoid arthritis. The present case highlights how accidental daily administration instead of weekly dosing can result in severe pancytopenia, mucositis, hepatotoxicity, and acute kidney injury. Early recognition of clinical symptoms, prompt discontinuation of methotrexate, initiation of leucovorin rescue therapy, aggressive hydration, hematological support, and infection control measures were crucial for successful patient recovery. This case also emphasizes the importance of regular laboratory monitoring, patient counseling, and clear prescription instructions to prevent medication errors. Multidisciplinary involvement of physicians, pharmacists, and nursing staff plays a significant role in ensuring safe methotrexate therapy and minimizing treatment-related morbidity and mortality in rheumatoid arthritis patients.

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