

Severe Myelotoxicity Following an Initial Methotrexate Dosing-Frequency Error in a Patient Treated for Suspected Rheumatoid Arthritis: A Case Report

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Abstract

Introduction

Methotrexate is widely used as a disease-modifying antirheumatic drug and is generally prescribed as a once-weekly medication in inflammatory rheumatic diseases. A dosing-frequency error in which a weekly regimen is inadvertently administered on consecutive days can result in severe mucosal and hematological toxicity. We report severe methotrexate-associated myelotoxicity following an initial dosing-frequency error in a patient treated for suspected rheumatoid arthritis.

Case presentation

A 58-year-old man was admitted with odynophagia and dysphagia. He had recently been prescribed low-dose methotrexate for suspected rheumatoid arthritis, with an intended once-weekly regimen for four weeks. The patient subsequently took methotrexate for four consecutive days instead of once weekly. The clinical course was complicated by severe oral mucosal disease, documented oral candidiasis with suspected esophageal candidiasis, profound neutropenia, thrombocytopenia, and anemia. On 21 September 2026, the hemoglobin concentration was 8.4 g/dL, total leukocyte count was $1.78 \times 10^9/L$, absolute neutrophil count was $0.28 \times 10^9/L$, and platelet count was $80 \times 10^9/L$. On 25 September, the total leukocyte count was $2.41 \times 10^9/L$, with neutrophils of 9.4% and an absolute neutrophil count of approximately $0.23 \times 10^9/L$; platelet count was $62 \times 10^9/L$. Methotrexate was discontinued. Treatment included folinic acid, granulocyte colony-stimulating factor, antifungal therapy, antimicrobial/supportive treatment, intravenous fluids, and close hematological monitoring. Hematological recovery subsequently occurred, with hemoglobin 10.7 g/dL, total leukocyte count $5.83 \times 10^9/L$, and platelet count $314 \times 10^9/L$ documented during subsequent testing.

Conclusion

This case demonstrates that even low-dose methotrexate can cause clinically significant myelotoxicity when a weekly regimen is inadvertently administered on consecutive days. Early recognition of the characteristic combination of mucosal toxicity and cytopenias, immediate cessation of methotrexate, folinic acid rescue, supportive management, and meticulous patient education are critical to preventing potentially fatal complications.

Keywords: Methotrexate; medication error; myelotoxicity; pancytopenia; neutropenia

Introduction

Methotrexate is an established disease-modifying antirheumatic drug used extensively in inflammatory rheumatic diseases, particularly rheumatoid arthritis. In non-oncological indications, methotrexate is generally administered once weekly rather than daily. Although low-dose methotrexate is usually well tolerated, repeated administration at an incorrect frequency can produce severe toxicity, including mucositis, bone marrow suppression, pancytopenia, hepatotoxicity, renal injury, and life-threatening infection.

Medication errors involving daily administration of methotrexate prescribed for weekly use have been repeatedly reported. Published cases have described severe mucositis, pancytopenia, neutropenia, and sepsis following inadvertent daily dosing. A recent retrospective study of patients with methotrexate-associated pancytopenia also found that inadvertent daily rather than weekly administration was a major factor in early toxicity.

The present case illustrates severe hematological toxicity following an initial methotrexate dosing-frequency error in a patient who had been started on methotrexate for suspected rheumatoid arthritis. The case is particularly relevant to general physicians because the initial presentation was dominated by upper aerodigestive mucosal symptoms, while subsequent laboratory evaluation demonstrated severe neutropenia and thrombocytopenia. The case emphasizes the importance of actively asking about methotrexate dosing frequency whenever mucositis or unexplained cytopenias occur in a patient receiving low-dose methotrexate.

Patient Information

A 58-year-old man was admitted to Sree Balaji Medical College and Hospital on 18 September 2026 with a short history of odynophagia/dysphagia.

The patient had recently been prescribed methotrexate for suspected rheumatoid arthritis. The intended regimen was methotrexate once weekly for four weeks. However, the patient mistakenly took the medication on four consecutive days instead of once weekly.

The clinical record documents methotrexate exposure at a dose of 5 mg. The exact prescription wording and dispensing instructions should be retained with the source documents for verification at submission.

The available record did not establish a definitive diagnosis of rheumatoid arthritis; therefore, this manuscript refers to the underlying indication as suspected rheumatoid arthritis rather than confirmed rheumatoid arthritis.

There was no documented history in the available record of a previous hematological disorder. Renal function was preserved during the episode; serum creatinine was 0.79 mg/dL on subsequent biochemical testing. Liver biochemical parameters were not markedly abnormal in the available laboratory assessment.

The patient's relevant past history included previous orthopedic intervention for avascular necrosis, including hip replacement, as documented in the clinical record. Other historical details were not considered directly contributory to the methotrexate toxicity.

Clinical Findings

At presentation, the dominant symptoms were dysphagia/odynophagia and painful oral symptoms.

ENT examination documented mucosal abnormalities including oral lesions/stomatitis and white lesions involving the palate and oral cavity. Subsequent clinical documentation described oral candidiasis and suspected esophageal candidiasis.

The patient was repeatedly documented as conscious, oriented, and generally afebrile during clinical review. Cardiovascular, respiratory, abdominal, and neurological examinations were not remarkable for an acute systemic complication.

The combination of mucosal disease and profound cytopenias prompted consideration of drug-induced bone marrow toxicity. Once the history of incorrect methotrexate frequency was identified, methotrexate-associated myelotoxicity became the leading diagnosis.

Timeline

Date	Clinical event
Before admission	Methotrexate initiated for suspected rheumatoid arthritis. Intended regimen: once weekly for four weeks. Patient subsequently took methotrexate on four consecutive days.
18 September 2026	Admitted with dysphagia/odynophagia. Initial evaluation by ENT.
19 September 2026	Continued evaluation for odynophagia/dysphagia. Oral mucosal abnormalities documented.
21 September 2026	Severe cytopenias documented: Hb 8.4 g/dL, WBC $1.78 \times 10^9/L$, ANC $0.28 \times 10^9/L$, platelets $80 \times 10^9/L$.
24 September 2026	Clinical documentation identified methotrexate overdose/dosing error-associated bone marrow toxicity with pancytopenia, oral candidiasis and suspected esophageal candidiasis.

Date	Clinical event
25 September 2026	Persistent severe neutropenia: Hb 9.5 g/dL, WBC $2.41 \times 10^9/L$, neutrophils 9.4%, ANC approximately $0.23 \times 10^9/L$, platelets $62 \times 10^9/L$.
26 September 2026	Methotrexate remained discontinued. Folinic acid and supportive therapy continued. Filgrastim 300 µg was documented. Antifungal and antimicrobial therapy was administered.
26–27 September 2026	Hematological recovery documented. WBC increased to $5.83 \times 10^9/L$, with recovery of neutrophil count; platelet count subsequently increased to $314 \times 10^9/L$. Serum creatinine was 0.79 mg/dL.
Subsequent course	Clinical status improved with resolution/improvement of mucosal symptoms and recovery of blood counts.

Diagnostic Assessment

Hematological findings

The hematological abnormalities were consistent with severe bone marrow suppression.

Table 1. Representative hematological parameters during hospitalization

Date	Hemoglobin (g/dL)	Total WBC ($\times 10^9/L$)	Neutrophils (%)	ANC ($\times 10^9/L$)	Platelets ($\times 10^9/L$)
21 Sep 2026	8.4	1.78	15.7	0.28	80
25 Sep 2026	9.5	2.41	9.4	~0.23	62
26/27 Sep 2026	10.7	5.83	48.5	~2.83	314

The absolute neutrophil count was calculated from the reported total leukocyte count and differential where necessary.

Renal function remained preserved, with serum creatinine documented at 0.79 mg/dL on subsequent biochemical testing. This is clinically relevant because renal dysfunction is a recognized risk factor for methotrexate accumulation and toxicity, but significant toxicity occurred in this patient despite preserved renal function.

Diagnostic reasoning

The principal differential diagnoses considered for the mucosal disease and cytopenias included:

1. Drug-induced bone marrow suppression.
2. Infection-associated cytopenia.
3. Nutritional deficiency-associated cytopenia.
4. Hematological malignancy or primary marrow disease.
5. Severe systemic infection with secondary marrow suppression.

The temporal relationship between recent methotrexate initiation, incorrect repeated dosing, mucosal toxicity, and development of severe neutropenia and thrombocytopenia strongly supported acute low-dose methotrexate toxicity secondary to a dosing-frequency error.

The clinical record specifically documented the diagnosis as methotrexate-overdose-induced bone marrow toxicity/pancytopenia with oral candidiasis and suspected esophageal candidiasis.

No evidence in the available record suggested that renal failure was the precipitating factor.

Therapeutic Intervention

Methotrexate was immediately discontinued after recognition of toxicity.

Treatment consisted of:

- Folinic acid (leucovorin) rescue, documented as oral folinic acid 1-1-1 in the clinical treatment chart.

- Filgrastim 300 µg, documented during management of severe neutropenia.
- Antifungal therapy, including intravenous fluconazole, for documented oral candidiasis with suspected esophageal candidiasis.
- Antimicrobial therapy as clinically indicated.
- Intravenous fluids.
- Symptomatic treatment for mucosal disease and odynophagia.
- Local oral treatment, including candidal mouth preparation and topical oral analgesic therapy.
- Serial complete blood counts and clinical monitoring.

The treatment strategy was directed toward removal of the offending agent, restoration of folate-dependent cellular metabolism, recovery from severe neutropenia, treatment/prevention of infection, and supportive management.

Folinic acid is used in methotrexate toxicity because it bypasses the inhibition of dihydrofolate reductase and restores intracellular folate-dependent biochemical pathways. Leucovorin rescue is an established component of management of clinically significant methotrexate toxicity, although dosing regimens vary according to the clinical context.

Follow-up and Outcomes

The patient demonstrated progressive hematological recovery following discontinuation of methotrexate and institution of rescue and supportive therapy.

The total leukocyte count increased from $1.78 \times 10^9/L$ on 21 September to $5.83 \times 10^9/L$ during subsequent testing. The absolute neutrophil count recovered from a severely neutropenic level of $0.28 \times 10^9/L$ to approximately $2.83 \times 10^9/L$. Platelet count increased from $62\text{--}80 \times 10^9/L$ during the period of severe cytopenia to $314 \times 10^9/L$.

The patient's mucosal symptoms and oral lesions also improved with treatment of the mucosal candidiasis and supportive care.

No persistent renal dysfunction was documented; serum creatinine was 0.79 mg/dL during subsequent assessment.

The rapid improvement in blood counts after cessation of methotrexate and administration of folinic acid and filgrastim further supported the diagnosis of methotrexate-associated marrow toxicity.

Discussion

Methotrexate is a folate antagonist whose therapeutic effects in inflammatory disease are achieved at substantially lower doses than those used in oncology. In rheumatoid arthritis and other non-oncological indications, the medication is generally prescribed as a weekly dose. This unusual dosing frequency is itself a recognized source of medication errors.

The pathophysiology of methotrexate toxicity involves inhibition of folate-dependent cellular processes, with rapidly dividing tissues being particularly vulnerable. Bone marrow suppression and mucosal injury are therefore characteristic manifestations of clinically important toxicity.

In the present patient, the intended regimen was once weekly for four weeks, but methotrexate was taken on four consecutive days. This resulted in repeated exposure over a short interval and was followed by mucosal disease and severe hematological toxicity. The clinical association is strengthened by the characteristic temporal sequence and subsequent recovery after drug withdrawal.

The severity of the hematological toxicity is noteworthy. The absolute neutrophil count fell to $0.28 \times 10^9/L$, representing profound neutropenia, while the platelet count fell to $62 \times 10^9/L$. The patient also developed anemia. Thus, the toxicity involved multiple hematopoietic lineages rather than isolated leukopenia.

Mucosal manifestations are an important clinical clue to methotrexate toxicity. Previous case reports have described mucositis, oral ulceration, stomatitis, and gastrointestinal mucosal injury occurring together with pancytopenia following incorrect daily administration. In this patient, the initial clinical presentation was dominated by odynophagia and dysphagia, and the presence of oral candidiasis/suspected esophageal candidiasis further complicated the clinical picture.

A particularly important aspect of this case is that the toxicity occurred despite preserved renal function. Renal impairment is an important risk factor for methotrexate toxicity because methotrexate is predominantly eliminated through the kidneys; however, repeated administration at an incorrect frequency can itself produce

clinically significant toxicity. A 2026 retrospective study similarly found that inadvertent daily rather than weekly dosing was associated with early toxicity, whereas renal failure, advanced age, and hypoalbuminemia were associated with delayed toxicity.

Several published reports demonstrate the potentially severe consequences of methotrexate frequency errors. A 45-year-old woman with rheumatoid arthritis developed pancytopenia and mucositis after taking 10 mg daily for two weeks instead of weekly therapy and recovered after methotrexate withdrawal and leucovorin rescue. Another report described a patient who mistakenly took 5 mg every eight hours for four days, subsequently developing pancytopenia and neutropenic sepsis. An Indian case report described a patient who inadvertently took 5 mg of methotrexate daily for four days after confusing methotrexate with folic acid, resulting in pancytopenia and multiorgan toxicity.

Therefore, the novelty of the present case should not be stated as the first report of daily-for-four-days methotrexate administration. Rather, its educational value lies in illustrating the medication-safety problem in a patient at the initiation of therapy, presenting primarily with upper aerodigestive symptoms, and developing profound neutropenia and thrombocytopenia despite preserved renal function.

Management considerations

The first and most important intervention in suspected methotrexate toxicity is immediate discontinuation of methotrexate. Supportive management should be individualized according to the severity of cytopenias, mucosal disease, renal function, infection risk, and timing of exposure.

Folinic acid is used as a rescue agent because it bypasses methotrexate-mediated inhibition of dihydrofolate reductase. Published reports of low-dose methotrexate toxicity have used leucovorin together with supportive treatment, with improvement in hematological parameters after treatment.

Severe neutropenia requires careful infection surveillance and, where clinically appropriate, colony-stimulating factor support. In the present case, filgrastim was administered during the period of profound neutropenia. Antifungal therapy was also used because candidiasis was documented.

The case additionally illustrates the importance of distinguishing methotrexate toxicity from an isolated infectious process. Oral candidiasis can itself produce odynophagia, but the simultaneous presence of severe neutropenia and thrombocytopenia should prompt a careful medication history.

Medication-safety implications

Methotrexate is a high-alert medication in terms of dosing-frequency errors. Safety systems should therefore explicitly communicate the frequency rather than merely the numerical dose.

The following measures may reduce errors:

- Prescriptions should state "ONCE WEEKLY" prominently.
- The specific day of administration should be documented where appropriate.
- Daily oral methotrexate orders for non-oncological indications should trigger verification.
- Patients and caregivers should be verbally counselled regarding weekly rather than daily administration.
- The prescription and dispensing label should be reconciled before the first dose.
- Folic acid and methotrexate should be clearly differentiated during counselling.
- Early complete blood count, renal-function, and liver-function monitoring should be performed according to the treatment protocol.
- Patients should be instructed to report oral ulcers, severe sore throat, fever, unusual bruising, or other signs of marrow toxicity immediately.

ISMP specifically recommends systems that default oral methotrexate to weekly dosing and require verification of an appropriate oncological indication for daily orders.

Strengths and Limitations

Strengths

The major strength of this case is the clear temporal relationship between an identifiable methotrexate dosing-frequency error and subsequent severe mucosal and hematological toxicity. Serial blood counts demonstrate profound neutropenia and thrombocytopenia followed by recovery after withdrawal of methotrexate and administration of rescue/supportive treatment.

The case also highlights an important safety issue that can occur at the initiation of therapy and may initially present to a non-rheumatology department because of mucosal symptoms.

Limitations

This is a single-patient case and cannot establish causality beyond the strong clinical temporal association. The underlying diagnosis of rheumatoid arthritis was described as suspected in the available clinical history and was not independently confirmed in the record reviewed for this manuscript.

A serum methotrexate concentration was not documented in the available record. Similarly, a bone marrow examination was not documented. Consequently, the diagnosis is based on the medication history, characteristic clinical manifestations, cytopenia pattern, exclusion of obvious alternative explanations in the available record, and subsequent recovery following treatment.

The exact timing between the final erroneous methotrexate dose and initiation of folinic acid should be reconstructed from the medication administration record before journal submission.

Conclusion

This case demonstrates that a medication-frequency error involving low-dose methotrexate can produce severe and potentially life-threatening myelotoxicity even in the absence of renal failure. The combination of mucosal symptoms, oral candidiasis, profound neutropenia, thrombocytopenia, and recent repeated methotrexate exposure should prompt immediate consideration of methotrexate toxicity. Early discontinuation of methotrexate, folinic acid rescue, appropriate management of neutropenia and infection risk, and close hematological monitoring were associated with recovery in this patient. Most importantly, methotrexate prescribed for non-oncological indications should be clearly labelled and repeatedly counselled as a once-weekly medication, with systems designed to prevent inadvertent daily administration.

Ethics Statement

This manuscript describes a single clinical case. Institutional requirements regarding ethics committee approval or exemption should be confirmed with the institution and the target journal before submission.

Funding

No specific funding was received for this case report.

Data Availability

The clinical data supporting this case report are contained within the patient's medical record. Additional information is not publicly available because of patient confidentiality and privacy considerations.

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