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Case Report

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A Clinical Case of Methotrexate Toxicity

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Abstract

Methotrexate is a commonly prescribed immunosuppressant and chemotherapy agent, carefully monitored by healthcare providers due to its potential adverse effects. As a result, methotrexate toxicity is relatively rare. We present the case of a 79-year-old man followed in rheumatology for symmetrical polyarthralgia, who inadvertently took methotrexate 10 mg daily, instead of weekly, leading to methotrexate toxicity. The patient presented with erosive mucositis affecting the lateral tongue, buccal mucosa, and hard palate, as well as pustular lesions on the scalp (occipital and cervical regions) extending to the trunk. Laboratory findings revealed pancytopenia and transaminitis, and upper gastrointestinal endoscopy showed erythema and superficial ulcerations in the oropharyngeal region. Methotrexate was discontinued immediately, and the patient was treated with intravenous fluids, filgrastim, and supportive care. This case highlights the importance of early recognition of methotrexate toxicity, as well as the critical role of patient education. It underscores how easily a medication with numerous therapeutic benefits can cause serious adverse outcomes if not taken as prescribed. Effective communication between healthcare providers and patients is essential to ensure medication safety.

Keywords: Methotrexate toxicity; Myelosuppression; Pancytopenia

Introduction

Methotrexate (MTX) is a folic acid antagonist that has become a cornerstone in the treatment of numerous clinical conditions due to its potent antiproliferative and immunosuppressive properties [1, 2]. Since its introduction in 1947, MTX has been widely used in oncology, rheumatology, dermatology, and gynecology. It exerts its effects by inhibiting the enzyme dihydrofolate reductase (DHFR), leading to the depletion of tetrahydrofolate, a cofactor essential for the synthesis of purines and pyrimidines. These nucleotides are critical for DNA and RNA synthesis, and their inhibition causes the arrest of the cell cycle in the S phase. At high doses, MTX effectively suppresses rapidly proliferating malignant cells, whereas at low doses, it modulates immune responses, making it effective in chronic inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease [1, 3, 4].

However, despite its proven clinical efficacy, MTX carries a substantial risk of toxicity. Its non-selective mechanism of action means that, in addition to targeting pathological cells, MTX also affects healthy rapidly dividing cells, such as those in the bone marrow, gastrointestinal mucosa, and skin. This explains the breadth and severity of its potential adverse effects. Toxicities associated with MTX may be dose-dependent or idiosyncratic and can occur even at standard therapeutic doses, especially in the presence of risk factors such as renal impairment, hypoalbuminemia, drug interactions, or errors in dosing schedules [5-7].

Hematologic toxicity is among the most serious and potentially fatal adverse effects of MTX. Myelosuppression may present as leukopenia, anemia, or thrombocytopenia and can lead to pancytopenia in severe cases. These effects are usually reversible upon drug discontinuation but require prompt recognition and intervention. The risk of myelosuppression increases in patients with renal dysfunction due to impaired clearance of MTX, leading to drug accumulation and heightened toxicity [2, 3, 7, 8].

Gastrointestinal toxicity is also common and may range from mild nausea and anorexia to severe mucositis and enteritis. Oral mucositis and mucocutaneous ulcers often serve as early warning signs of systemic MTX toxicity. In some patients, mucositis may involve the entire gastrointestinal tract, resulting in diarrhea, malabsorption, weight loss, and dehydration. Hepatotoxicity is another well-recognized complication of MTX use. Although elevations in liver enzymes are common and usually transient, chronic use may lead to hepatic fibrosis and, rarely, cirrhosis. The risk increases with cumulative dosing above 1.5 g, but liver injury has also been reported at lower doses in patients with additional risk factors such as alcohol use, obesity, diabetes, and concomitant hepatotoxic drugs [1, 4, 7].

Pulmonary toxicity, although less frequent, can be life-threatening. MTX-induced lung injury may present as interstitial pneumonitis or pulmonary fibrosis and can occur independently

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of the cumulative dose or duration of treatment. Importantly, this toxicity may be reversible with early drug withdrawal and corticosteroid therapy, but delayed diagnosis can lead to irreversible lung damage or respiratory failure [5, 8-10].

The last one is dermatologic manifestations that range from mild rashes to severe exfoliative dermatitis. A particularly concerning finding is the development of cutaneous ulcerations. These lesions may precede systemic toxicity and, thus, require urgent assessment. Additionally, MTX has been associated with photosensitivity and alopecia, both of which can affect patient adherence and quality of life [1, 3, 5].

Although most toxicities are predictable and dose-dependent, medication errors represent a preventable and critical cause of MTX-related complications. MTX is typically prescribed as a once-weekly dose for inflammatory diseases; however, it is not uncommon for patients or caregivers to mistakenly administer the drug daily, leading to acute toxicity. Such errors are often due to inadequate patient education, poor communication, or ambiguous prescription instructions. Daily ingestion can quickly lead to severe toxicities, including pancytopenia, mucositis, hepatotoxicity, and skin ulceration, and may be fatal if not promptly recognized [4, 7, 10, 11].

Given the narrow therapeutic window of MTX, monitoring protocols are essential to ensure patient safety.

Routine laboratory evaluations, including complete blood counts, liver function tests, and renal function monitoring are standard practice. The concurrent administration of folinic acid (leucovorin), the most specific antidote to MTX toxicity, is often recommended, particularly in high-dose regimens or in the setting of toxicity. Nonetheless, even with these precautions, vigilance remains paramount [4, 7, 10, 11].

In this context, we report the case of a 79-year-old Caucasian male who developed significant hematologic and dermatologic toxicity following the inadvertent daily intake of 10 mg of MTX instead of the prescribed weekly dose. The patient presented with thrombocytopenia, oral mucositis, and progressive skin ulcerations, illustrating the dangers of dosing errors and the potential severity of MTX toxicity. This case underscores the importance of clear prescribing practices, effective communication, and thorough patient education in the prevention of adverse drug events associated with MTX.

Case Report

We report the case of a 79-year-old Caucasian male with a past medical history of symmetrical polyarthralgia, followed by the rheumatology department, who had been receiving MTX at a prescribed dose of 10 mg weekly. He also had a history of arterial hypertension but was not on any antihypertensive medication. He had no known drug allergies and denied the recent use of nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics. The patient presented to the emergency department with a 2-day history of progressive skin rash involving the scalp, chest, and neck. He denied fever, gastrointestinal symptoms, respiratory complaints, or other systemic manifestations. Upon further evaluation, it was revealed that the patient had been mistakenly taking MTX daily instead of weekly for the previous 6 consecutive days, indicating a dosing error and probable drug intoxication. He was autonomous in managing his own medication, and the error resulted from a misinterpretation of the prescription and insufficient explanation from the prescribing physician.

The patient is a retired businessman and remains fully independent in his activities of daily living. There was no relevant family medical history. The clinical history was primarily obtained directly from the patient and confirmed with his wife and daughter to ensure completeness and accuracy. He was admitted to Hospital de Sao Joao, in Porto, Portugal, where he was evaluated and managed by internal medicine specialists and physicians undergoing specialty training in internal medicine.

On physical examination, he was alert, oriented, and hemodynamically stable, with a blood pressure of 122/75 mm Hg, heart rate of 85 beats per minute, and normal oxygen saturation (SpO_2 98%) on room air. He was afebrile and showed no signs of respiratory distress. His mucous membranes and skin were pink and well-hydrated, and no cyanosis or peripheral edema was noted.

Dermatological examination revealed erosive mucositis involving the lateral aspects of the tongue, buccal mucosa, and hard palate. Pustular lesions were observed on the scalp, particularly in the occipital and cervical regions, with extension to the anterior thorax. No ocular involvement or epidermal detachment was present. Cardiopulmonary auscultation was normal, and the abdominal examination showed no tenderness or peritoneal signs.

Initial laboratory investigations demonstrated normocytic anemia (hemoglobin 10.8 g/dL; mean corpuscular volume (MCV) 91.9 fL), leukopenia (2.80×10^9/L with neutrophils at 40%), and thrombocytopenia ($48{,}000 \times 10^9$/L), consistent with pancytopenia. Inflammatory markers were within normal limits. Renal function and coagulation profiles were unremarkable. Hepatic enzymes were elevated (aspartate aminotransferase (AST) 77 U/L, alanine aminotransferase (ALT) 88 U/L), with no evidence of cholestasis or hyperbilirubinemia. Albumin levels were normal.

An upper gastrointestinal endoscopy revealed erythema and superficial ulcerations in the oropharynx and the esophagus and stomach appeared normal.

No further investigations, such as chest computed tomography (CT), were deemed necessary to exclude MTX-induced pneumonitis.

The diagnosis of unintentional MTX intoxication was established, with manifestations involving cutaneous, hematologic, and hepatic systems and the patient was admitted to the Internal Medicine ward for supportive care and close monitoring. He remained hospitalized for 20 days.

Therapeutic management included the initiation of oral corticosteroids (prednisone 40 mg/day), followed by gradual tapering. Dermatologic and hepatic abnormalities improved rapidly under this regimen.

Due to persistent pancytopenia, filgrastim (granulocyte colony-stimulating factor (G-CSF)) was administered, resulting in a progressive recovery of all three hematopoietic lineages. By discharge, the patient's blood tests showed hemoglobin of 11.1 g/dL, leukocytes of 6.01×10^9/L, and platelets of $139{,}000 \times 10^9$/L.

Leucovorin was not administered in this case. The decision was based on clinical assessment: the patient presented 2 days after the last MTX dose, with toxicity signs already established but not life-threatening. In addition, leucovorin was not immediately available in the hospital pharmacy at the time.

Folic acid and vitamin B12 were not administered during hospitalization, as there was no clinical or laboratory evidence of vitamin deficiency. The patient showed no signs of megaloblastic anemia, neurological impairment, or other features typically associated with folate or B12 deficiency. Additionally, MTX toxicity cannot be reversed by folic acid or vitamin B12, as the drug inhibits the enzymatic conversion of folic acid into its active form. Leucovorin (folinic acid), which bypasses this metabolic blockade, is the most specific antidote and remains the treatment of choice. However, given the patient's stable clinical course, absence of neurological symptoms, and preserved renal function, leucovorin was ultimately not deemed necessary. It is nonetheless important to recognize that MTX also disrupts the methylation cycle via inhibition of S-adenosyl-methionine, and prolonged interference in this pathway may result in neurological complications, including spinal cord demyelination. At follow-up, blood counts had normalized, and MTX was permanently discontinued [2, 4, 11].

Upon discharge, the patient was referred to the outpatient Internal Medicine consultation for follow-up. MTX was discontinued permanently, as there was no further indication for its use.

Discussion

MTX is a folic acid antagonist that was initially developed as an anti-cancer agent but is now widely used as an immunotherapy drug in a broad range of autoimmune and inflammatory conditions, such as rheumatoid arthritis and psoriasis. In diseases of the connective tissue, such as rheumatoid arthritis, MTX is commonly administered over prolonged periods. When used at low doses (7.5 - 10 mg per week), MTX has been shown to be generally well tolerated, with only minimal disturbances in liver function tests. Moreover, the concurrent administration of folinic acid, an MTX antidote, has been shown to significantly reduce adverse effects [2, 10].

Although MTX was introduced in the 1950s, it did not gain widespread use in the treatment of rheumatoid arthritis until the 1980s. Clinical trials during this period demonstrated that MTX was significantly more effective than placebo in patients with severe and persistent disease. Due to its ability to inhibit DNA synthesis and cell replication, MTX has since become a standard treatment in hematologic, rheumatologic, and oncologic practice. However, these same mechanisms are responsible for the drug's toxic potential, highlighting its dual role as both a therapeutic agent and a possible cause of serious complications [1, 2].

MTX is absorbed through the gastrointestinal tract and eliminated primarily by the kidneys. This pharmacokinetic profile makes renal function a critical determinant in MTX safety. Pre-existing renal impairment, commonly observed in patients with rheumatologic diseases, may reduce MTX clearance, increasing its plasma levels and toxicity [2, 11, 12].

Furthermore, the most frequent cause of MTX toxicity in adults is accidental daily ingestion instead of the prescribed weekly dose - a preventable error that underscores the need for precise dosing instructions [2, 6, 11, 12].

The adverse effect profile of MTX is extensive, ranging from mild to life-threatening reactions. The most severe complication is myelosuppression, which is the leading cause of the relatively rare fatalities attributed to MTX use. Other reported side effects include bone marrow suppression, liver fibrosis, pneumonitis, alopecia, hepatitis, nephrotoxicity, and gastrointestinal disturbances. MTX-induced hepatotoxicity may result in hepatitis or even cirrhosis, particularly in patients with other risk factors such as obesity, diabetes, or pre-existing liver disease. Notably, gastrointestinal toxicity is a dose-limiting factor, with patients often experiencing mucositis, nausea, abdominal pain, and cramping, which may lead to malabsorption, weight loss, and treatment discontinuation [4, 6, 9, 11].

MTX toxicity frequently results in pancytopenia, especially in cases of drug accumulation related to impaired renal clearance. This highlights the importance of regular laboratory monitoring and appropriate patient education. The atypical dosing regimen - weekly instead of daily - contributes to the risk of dosing errors. When MTX is inappropriately administered, hospitalization is often necessary, and treatment may involve folic acid supplementation, discontinuation of MTX, and supportive care [2, 10, 11].

Although folinic acid (leucovorin) is the established antidote for MTX toxicity, it was not administered in this case. The decision was based on the absence of clinical deterioration, preserved renal function, and a favorable trajectory of recovery with supportive measures alone. Folic acid and vitamin B12 were also not administered, as there was no clinical or laboratory evidence of deficiency. The patient showed no signs of megaloblastic anemia, neurological impairment, or other features typically associated with B12 or folate deficiency. Furthermore, MTX toxicity cannot be reversed by folic acid or vitamin B12, since MTX inhibits the conversion of folic acid into its active form. Leucovorin, by contrast, bypasses this enzymatic block, but its use is typically reserved for patients with severe or worsening toxicity [1-4].

In addition to inhibiting DHFR, MTX interferes with the methylation cycle by blocking S-adenosyl-methionine-dependent reactions. This secondary mechanism may contribute to neurologic complications, including spinal cord demyelination, particularly in cases of prolonged or cumulative exposure. Although no neurological symptoms were present in this patient, clinicians should remain aware of this potential late effect [13].

The case presented in this report exemplifies a medication error in which the patient received MTX daily instead of weekly, resulting in acute toxicity. Despite extensive documentation of MTX's risk profile, such errors persist in clinical practice. According to the literature, medication errors are defined as preventable events that may cause or lead to inappropriate medication use or patient harm. These events can occur at any stage of the medication process - from prescription and labeling to dispensing, administration, and monitoring. In our case, the error was classified as "action-based", meaning the action performed did not match the intended plan, suggesting a breakdown in patient instruction or system safeguards [9, 12, 14].

This case underscores the need for caution and diligence when prescribing high-risk medications like MTX. Safe prescribing practices, comprehensive patient education, clear labeling, and the implementation of electronic prescribing systems with built-in alerts may reduce the likelihood of such incidents. Regular follow-up and monitoring are critical to identifying early signs of toxicity and ensuring safe long-term use of MTX. Ultimately, this case serves as a reminder of the importance of communication, vigilance, and system-level safeguards in preventing potentially fatal medication errors.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Informed consent was obtained directly from the patient.

Author Contributions

Ana Cristina Peixoto was responsible for the identification and clinical management of the case, performed the literature review, and led the drafting of the manuscript. Rodrigo de Almeida Mota, Ana Luisa Maceda Rodrigues, and Margarida Miguel Paraiso contributed to the literature review and provided critical insights and suggestions for manuscript refinement. Leila Amaro Cardoso played a significant role in both the identification and clinical management of the case, contributed to the literature review, and offered substantive feedback to enhance the manuscript. Jorge Almeida was involved in the clinical management of the case and provided constructive recommendations to improve the manuscript. All authors have reviewed and approved the final version of the manuscript prior to submission and agree to be accountable for all aspects of the work.

Data Availability

The clinical data supporting the findings of this case report are confidential to protect patient privacy. However, they are available from the corresponding author upon reasonable request.

Abbreviations

DHFR: dihydrofolate reductase; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs

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