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Accidental methotrexate overdose leading to multisystem toxicity: A case report

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ABSTRACT

Background: Methotrexate (MTX) is an extensively used chemotherapeutic agent with well-characterized toxicity profiles. This case report describes the clinical presentation, management, and outcome of a patient presenting with severe MTX toxicity.

Case Presentation: A 35-year-old Bangladeshi female was admitted on March 9, 2024, with severe mucosal ulcerations, painful skin lesions, and gastrointestinal bleeding after ingesting Methotrexate daily for 12 days by mistake instead of the medication prescribed to her. On physical examination, there was severe injury involving skin and mucosa. The laboratory results showed severe pancytopenia and liver and kidney function in derangement. There was gradual improvement with the prompt withdrawal of Methotrexate, Folinic Acid therapy, and supportive therapies; most of the laboratory values returned to normal by day 14.

Conclusion: This case was one of severe Methotrexate poisoning, leading to profound systemic toxicity. Thus, timely recognition, immediate drug withdrawal, and aggressive supportive care comprising Folinic Acid therapy and hydration played a major role in this patient's management.

1. Background

Methotrexate (MTX) is a folate antagonist that displays striking antiproliferative and immunosuppressive properties. It has been established as one of the most common therapeutic modality in a wide range of malignancies and autoimmune diseases. This drug inhibits the enzyme dihydrofolate reductase, thus interfering with the synthesis of purines and pyrimidines that are important for DNA replication and cell proliferation. This provides the rationale for the effectiveness of methotrexate in diseases like rheumatoid arthritis, psoriasis, and a number of malignancies due to its cytotoxic effects on rapidly dividing cells, which include malignant cells and activated lymphocytes.

Classically representing a drug with narrow therapeutic index, MTX is commonly associated with many dose-dependent toxicities and adverse effects despite the clear therapeutic benefits. Acute toxicity from methotrexate normally reveals manifestations related to multiple organ systems. Hepatic toxicity may cause elevations in liver enzymes, while steatosis and fibrosis are also potential outcomes. Renal toxicity related to methotrexate can result in acute kidney injury, tubular damage, and renal functional impairment. Additionally, MTX can cause hematologic issues such as pancytopenia and mucositis [1,2].

Most reported toxicities arise from high-dose MTX (500 mg/m^2), particularly in oncology, where prolonged infusions or doses above several grams per square meter are used. Evans et al. [3] found that plasma MTX levels above 10 μM at 24 hours post-infusion are strongly associated with toxicity.

In low-dose settings, toxicity often results from accidental overdose or prescription errors. Even a few days of low-dose MTX taken daily instead of weekly can cause significant toxicity, as noted in case studies [4,5]. Additionally, some patients may experience toxicities even at standard therapeutic doses due to genetic or metabolic differences, such as MTHFR polymorphisms affecting folate metabolism [6]. Age, sex, and regional factors have not shown a strong correlation with MTX toxicity, highlighting the importance of dosing patterns and individual susceptibility

In this context, we present a case report of a 35-year-old female who

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experienced multisystem toxicities following an accidental methotrexate overdose. This patient's clinical evolution, therapeutic approach, and outcome demonstrate the difficulties encountered in the management of methotrexate toxicity and emphasize the need for monitoring and early treatment, as well as close cooperation among different specialists to ensure the best possible outcome. This case is therefore useful in increasing the knowledge of healthcare practitioners about the side effects that result from methotrexate therapy and the importance of medication safety precautions in avoiding medication related errors and their consequences on patients.

2. Case description

A 35-year old woman with no significant past medical history was admitted to the medicine department of our hospital on March 9, 2024 with complaints of fresh per rectal bleeding and epistaxis. Upon detailed history taking, it was revealed that patient had been prescribed Montelukast but had mistakenly taken Methotrexate 10 mg daily for 12 consecutive days.

She reported extensive painful mucosal ulcerations in her mouth, which made eating and speaking difficult, and observed the development of multiple large, painful skin ulcerations on her extremities.

On physical examination at admission, the patient appeared unwell and was in considerable distress. She was dehydrated and anemic without any evident jaundice or cyanosis. Her blood pressure was 140/85 mmHg with a pulse rate of 105 beats per minute. She was dyspneic with a slightly higher respiratory rate of 22 breaths per minute and a body temperature of 37.8°C. But she was otherwise conscious and well-oriented.

Examination of the integumentary system revealed multiple hyperpigmented plaques with the irregular border and several ulcerated lesions, limited to distal parts of both upper and lower extremities. Some of the skin lesions showed areas of necrosis with tissue breakdown: some had a black eschar and some had a raw, red base—the type of recent skin loss. Surrounding these were areas of crusting or scarring. Thickening and discoloration of the toenails were also noted. Mild soft tissue swelling around the affected areas was observed, which could be attributed to inflammation or possible infection [Figs. 1 and 2]. Besides that, the patient had facial erythema and hyperpigmentation particularly over the cheeks and forehead that depicted inflammation and skin damage. There was mild periorbital edema which could be an effect of inflammatory responses. There was conjunctival injection in the left eye signifying inflammation, similar to mucosal toxicity. Her lips were dry and cracked, reflecting mucositis.

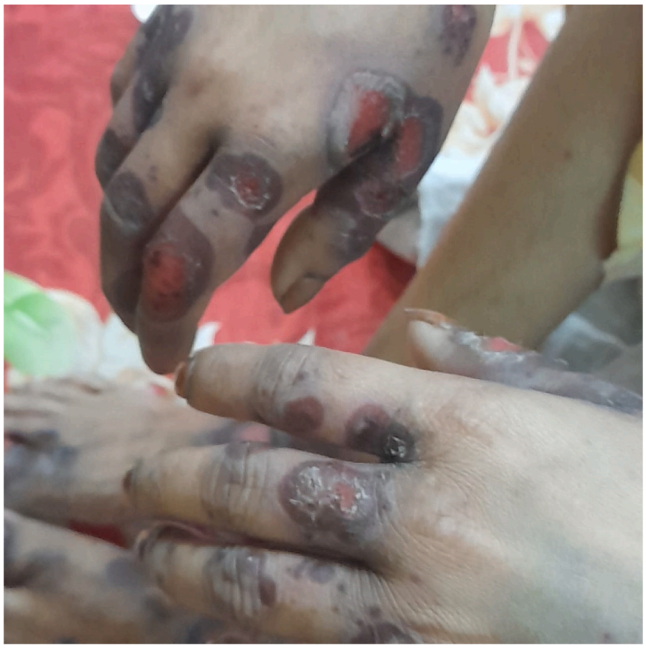

Fig. 1. shows the hands of the patient with visible skin necrosis and ulceration.

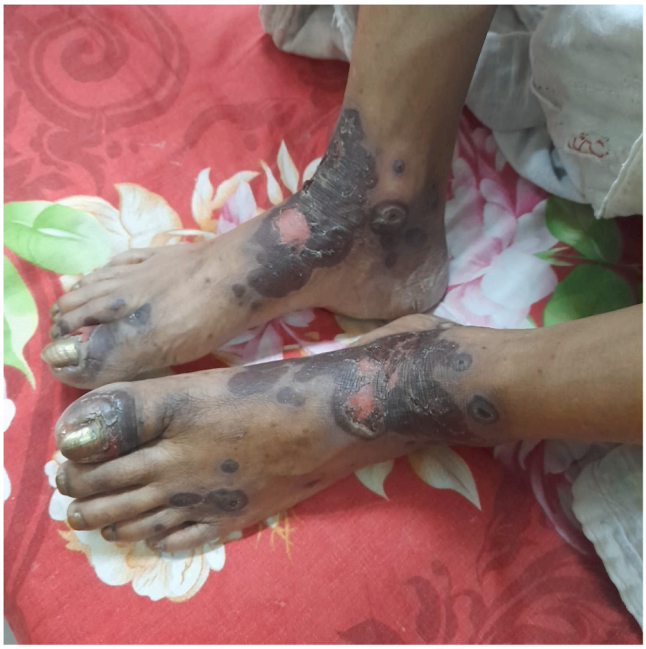

Fig. 2. depicts the feet of the patient with extensive areas of skin necrosis, ulceration with surrounding discoloration.

At the time of admission, blood count revealed profound pancytopenia. However, a general upward trend of hematologic values was observed in the next few days with elevation of Hemoglobin, RBC, WBC, Platelet count from their lower base line. With regards to liver function tests, the ALT value was elevated, and marked the parameter's highest point on Day 3, but gradually started decreasing afterward. The renal function was also impaired initially and showed increased serum creatinine and BUN, both of which have shown maximum values on third day of the study and then becoming normal by the end of second week of the study. Serum bilirubin and LDH were also increased in the first day and showed a gradual declining trend during the days of hospitalization. Serum albumin was on declining on the third day but the level rose thereafter. For the most part, the patient's electrolytes were within normal range during the patient's hospitalization except during 3rd to 7th days showing a higher potassium level [Table 1].

As part of management, methotrexate was discontinued immediately. Injection folinic acid was administered at a dose of 15 mg IV every six hours, continued until the recovery of clinical features and normalization of lab findings. Intravenous administration was chosen to ensure high bioavailability and rapid action, especially crucial given the patient's severe dysphagia due to extensive oropharyngeal mucosal ulceration. She was started on aggressive hydration with intravenous fluids to support renal function and enhance methotrexate clearance. Pain was treated with opioid analgesic and topical treatments and sterile dressing were applied for mucosal and skin ulcerations. Two units of blood were transfused. Antibiotic was added based on clinical judgement and supported by laboratory values. Regular monitoring of laboratory values were done. By days 8–10, her liver and renal functions began to stabilize, with ALT decreasing to 75 U/L, and serum creatinine and BUN improving to 1.3 mg/dL and 20 mg/dL respectively. Her white blood cell count and platelet levels started to recover, and her hemoglobin increased to 11.5 g/dL on day 14. LDH and bilirubin also showed a downward trend. By day 14, her condition had significantly improved, with most laboratory values approaching normal state.

Table 1
Trend of investigations.

Name of investigations	Day 1	Day 3	Day 7	Day 10	Day 14
Hemoglobin (g/dL)	6.8	8.3	9.9		11.5
RBC (million/mm^3)	2.93	3.43	4.18		4.88
WBC ($\times 10^9$ /L))	2.48 (Neutrophil−35.7 %)	14.57 (Neutrophil−79.7 %)	42.07 (Neutrophil−95.7 %)		12.58 (Neutrophil−74.6 %)
Platelet ($\times 10^9$ /L)	11	30	120		259
ALT (U/L)	85	140	105	75	45
Serum Creatinine (mg/dL)	1.5	2.5	1.6	1.3	1.0
BUN (mg/dL)	25	45	28	20	14
LDH (U/L)	300	450	300	230	180
Bilirubin (mg/dL)	1.5	2.5	1.6	1.1	0.7
Albumin (g/dL)	3.5	2.5	3.2	4.0	4.5
Sodium (Na+) (mmol/L)	138	136	135	138	140
Potassium (K+) (mmol/L)	4.8	5.2	5.0	4.7	4.5
Chloride (Cl-) (mmol/L)	100	98	96	98	100
Bicarbonate (HCO3-) (mmol/L)	22	20	18	22	24

3. Discussion

In this case report, we present a 35-year-old female who developed a severe cutaneous and mucosal reaction following an accidental overdose of Methotrexate, a medication she was mistakenly taking instead of Montelukast. This case highlights the critical importance of medication adherence and the potential severity of adverse drug reactions, particularly when it comes to drugs with a narrow therapeutic index like Methotrexate.

Acute oral low-dose MTX poisoning generally has a very benign course due to saturable absorption and rapid renal elimination. Severe toxicity may result from taking methotrexate on a daily basis rather than the suggested weekly schedule or from staggered dosages. Toxic effects can result from doses as low as 5–15 mg consumed for three or more days in a row [7]. Our patient took MTX for 14 consecutive days, resulting in multisystem toxicities.

Dermatological involvement in MTX toxicity is relatively common. The manifestation can range from mild rash and mucositis to severe manifestations like Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) [8,9] This toxicity is thought to result from its effects on rapidly dividing cells in the skin and mucous membranes. The drug's impact on folate metabolism and cellular turnover can lead to increased sensitivity and damage to these tissues. In our patient, extensive mucocutaneous involvement was a prominent finding. Early recognition and appropriate management can lead to effective resolution of these findings.

Gastrointestinal toxicity is another serious effect of MTX toxicity. Methotrexate-induced gastrointestinal toxicity may stem from DNA strand breaks in rapidly dividing intestinal cells, oxidative stress, and a cascade of inflammatory events triggered by direct cell injury [10,11]. This damage likely disrupts the intestinal mononuclear phagocyte system—composed mainly of dendritic cells and macrophages—which normally maintains gut homeostasis. Such disruption can create a self-sustaining inflammatory cycle, worsening tissue injury and inflammation [12]. Common manifestations include nausea, vomiting, and mucositis. These can have detrimental impact on Nutritional Status, hydration and electrolyte Balance and Quality of Life. Severe mucosal damage may lead to gastrointestinal bleeding, which is a serious and potentially life-threatening complication. Our patient had also evidence of multiple ulcers in oral cavity as well as evident GI bleeding.

Hematological toxicity is a major concern in MTX toxicity because it affects bone marrow function and blood cell production. Hematological toxicity mainly results from inhibition of dihydrofolate reductase, disrupting DNA synthesis in rapidly dividing bone marrow cells. This leads to in anemia, leukopenia, and thrombocytopenia, manifesting as higher the risks of infection, bleeding, and fatigue [13]. This type of toxicity usually develops within days to weeks after starting therapy [14,15]. Although the incidence of MTX-induced pancytopenia is low, i.e., 1.4 % [16], the resultant pancytopenia poses the patient at increased risk of Infection and bleeding tendency. In severe cases of pancytopenia, blood transfusion may be necessary to correct anemia, thrombocytopenia, and neutropenia. Granulocyte colony-stimulating factor (G-CSF) can be adjunctively used to stimulate neutrophil production and enhance host defense mechanisms [17]. Our patient also developed pancytopenia, which improved gradually after blood transfusions and the discontinuation of methotrexate.

Hepato-renal toxicity from Methotrexate poses significant risks, including liver damage and acute kidney injury which was also evident in our case. Methotrexate nephrotoxicity likely involves oxidative stress and mitochondrial dysfunction. In studies, MTX administration led to elevated serum markers of kidney injury (BUN, creatinine), increased reactive oxygen species, lipid peroxidation, and depleted antioxidant defenses in the kidneys. Additionally, MTX disrupted mitochondrial function, evidenced by reduced mitochondrial membrane potential, dehydrogenase activity, glutathione, and ATP content, alongside increased lipid peroxidation and mitochondrial permeability[18,19].On the other hand, Methotrexate hepatotoxicity is primarily due to the accumulation of its metabolite, MTX-polyglutamate (MTX-PG), which triggers oxidative stress, inflammation, steatosis, fibrosis, and apoptosis in liver cells. MTX-PG induces reactive oxygen species and inhibits antioxidant defenses, activates inflammatory cytokines (e.g., TNF-α, NF-κB, IL-6), depletes folate, disrupts RNA and DNA synthesis [20].

Recent studies have shown that luteolin has a protective effect against methotrexate-induced hepato-renal toxicity [21,22]. Regular monitoring of liver and renal function, dose adjustments, and preventive measures such as hydration and avoidance of additional hepatotoxic or nephrotoxic substances are crucial for managing these toxicities effectively [23].

The cornerstone of management in methotrexate toxicity revolves around supportive care and mitigation of adverse effects. Folinic acid, a reduced form of folic acid, serves as a rescue therapy by bypassing the inhibitory effects of methotrexate on dihydrofolate reductase. Its administration replenishes intracellular folate levels and mitigates the cytotoxic effects of methotrexate on rapidly dividing cells [23].Glucarpidase, a recombinant bacterial enzyme with high affinity for methotrexate and folate analogues, rapidly lowers serum MTX levels by 90 %–95 % within 15 minutes and is increasingly recommended for MTX toxicities based on accumulating evidence. [24,25].

In this patient, methotrexate toxicity likely arose from the continuous administration of the drug over 12 consecutive days instead of the recommended weekly dosing schedule, leading to cumulative toxic effects. The extended duration without dose interruption allowed methotrexate polyglutamate to accumulate intracellularly, particularly in hepatocytes, leading to hepatotoxic effects such as oxidative stress,

inflammation, and potential liver injury.

In our case, prompt folinic acid rescue therapy resulted in gradual improvement across all affected organ functions. However, the severity of toxicity, the extent of organ involvement, and duration of methotrexate exposure are critical factors in determining the effectiveness of folinic acid alone. In this patient, with early intervention, the clinical and laboratory findings improved with folinic acid rescue, suggesting that this approach was sufficient for recovery.

4. Conclusion

This case report highlights the critical impact of Methotrexate toxicity on multiple organ systems, including the gastrointestinal, hematologic, hepatic, and renal systems. The patient experienced severe gastrointestinal symptoms, significant hematologic abnormalities, and both hepatic and renal dysfunction, underscoring the need for careful monitoring and prompt intervention. Early recognition of toxicity and tailored management strategies are essential to mitigate adverse effects and ensure effective treatment. This case emphasizes the importance of individualized care and regular monitoring to optimize patient outcomes and minimize the risks associated with Methotrexate therapy.

4.1. Guidelines

The case report presentation followed CARE guidelines [26].

4.2. Learning points for clinicians

For clinicians, several key learning points emerge from managing Methotrexate toxicity. Early recognition of Methotrexate-related adverse effects, including gastrointestinal symptoms, hematologic abnormalities, and liver and kidney dysfunction, is crucial. Regular and comprehensive monitoring of blood counts, liver function, and renal function can help detect toxicity early and guide timely interventions. Finally, long-term monitoring and follow-up are important to address any delayed effects and adjust the treatment plan as necessary.

4.3. Patient perspective

"I mistakenly took Methotrexate daily for 12 days instead of my prescribed medication. Soon after, I began experiencing severe pain in my mouth, which made eating extremely difficult. I also developed several ulcers on my skin and started feeling generally unwell. Breathing became a bit labored, and I felt quite distressed. I was admitted to the hospital, where the medical team provided intensive care. Over time, with their treatment and support, my symptoms gradually improved. Now, I can eat more comfortably and my breathing has returned to normal. The experience was challenging, but I am grateful for the care I received and the gradual recovery I am experiencing."

4.4. Consent

In accordance with ethical guidelines, informed consent was obtained from the patient for the publication of this case report and the accompanying images. The patient has given permission for the inclusion of her medical details, personal experience, and any relevant information in this report. A copy of the written consent is available for review by the Editor-in-Chief upon request. All identifying information has been anonymized to ensure patient confidentiality and privacy.

CRediT authorship contribution statement

Soumitra Roy: Writing – review & editing, Supervision, Resources. **Ranjon Kumer Roy:** Writing – review & editing, Supervision, Resources. **Sadia Satara Zaman:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Md Asaduzzaman:** Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Data curation, Conceptualization. **Md Rezaul Karim:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Data curation, Conceptualization. **Prionti Saha:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Md. Majharul Islam:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **M.M. Jahangir Alam:** Writing – review & editing, Supervision, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

Data will be made available on request.

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