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Case Report

Internal Medicine Section

A Case of Severe Methotrexate Toxicity: Clinical Insights and Management

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ABSTRACT

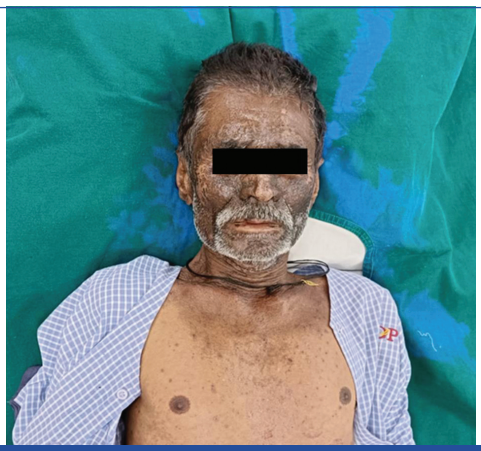
Methotrexate (MTX), first synthesised in 1947, originated as a derivative of aminopterin, a medication initially used to treat acute leukaemia in children. It shares similar properties with aminopterin and has since demonstrated remarkable efficacy in managing a wide array of complex dermatological and rheumatological conditions. Despite its therapeutic benefits, MTX toxicity, though rare, can lead to severe and potentially fatal consequences. This case report describes a 62-year-old male who developed erythematous lesions over his scalp, face, upper limbs, and torso following an excessive intake of MTX (120 mg/week for one month). The patient exhibited symptoms consistent with severe MTX toxicity, including mucositis, pancytopenia, and neutropenic sepsis. Despite timely initiation of leucovorin rescue therapy, intravenous hydration, urine alkalinisation, and aggressive management of neutropenic sepsis the patient's condition deteriorated. Respiratory support was provided, but he ultimately succumbed to multi-organ dysfunction, underscoring the challenges associated with managing High-Dose MTX (HDMTX) toxicity. This report highlights the mechanisms of MTX toxicity, including its impact on folate metabolism and cell division, resulting in widespread tissue damage and immunosuppression. It emphasises the critical need for early recognition of toxicity symptoms, such as mucositis and bone marrow suppression, to promptly initiate life-saving interventions. Furthermore, it underscores the importance of patient education on MTX dosing and monitoring to prevent such adverse outcomes, illustrating the necessity for vigilant clinical management in patients receiving MTX therapy.

Keywords: Immunosuppression, Rheumatology, Rheumatoid arthritis, Sepsis

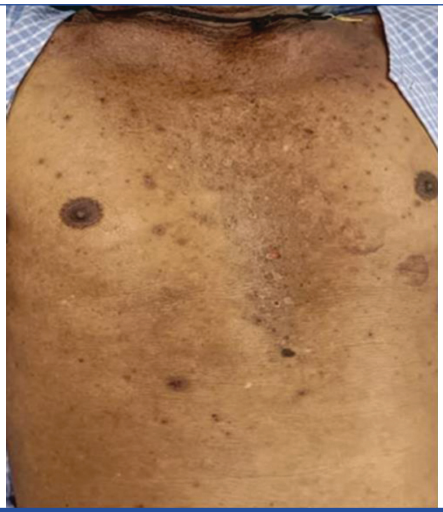
CASE REPORT

A 62-year-old male farmer arrived at the emergency room with symptoms of a high-grade fever accompanied by chills, chest pain, hoarseness of voice, and a gradual worsening of itching on the face, upper limbs, chest, and trunk over four days. Further evaluation revealed that the patient also had four days of dysphagia and bloody stools. The patient was recently diagnosed with Rheumatoid Arthritis (RA) and prescribed MTX tablets at a dose of 7.5 mg twice daily for one month, Prednisolone tablets at a dose of 10 mg once daily, and Aceclofenac tablets at a dose of twice daily for one month. The patient gave no history of known allergies.

During the general examination, the patient's pulse rate was recorded as 110 beats per minute, blood pressure as 110/70 millimetres of mercury, oxygen saturation as 98% while breathing normal air, and respiratory rate as 18 breaths per minute. Erythema with blackish discoloration was noted on the head, face, chest, and trunk [Table/Fig-1], along with erosion of the oral mucosa, broken papules, and scratches over the chest [Table/Fig-2]. Auscultation revealed crackles in the bilateral infrascapular areas.



[Table/Fig-1]: Blackish discolouration of the face, chest and head.



[Table/Fig-2]: Blackish discolouration and ruptured vesicles on the trunk.

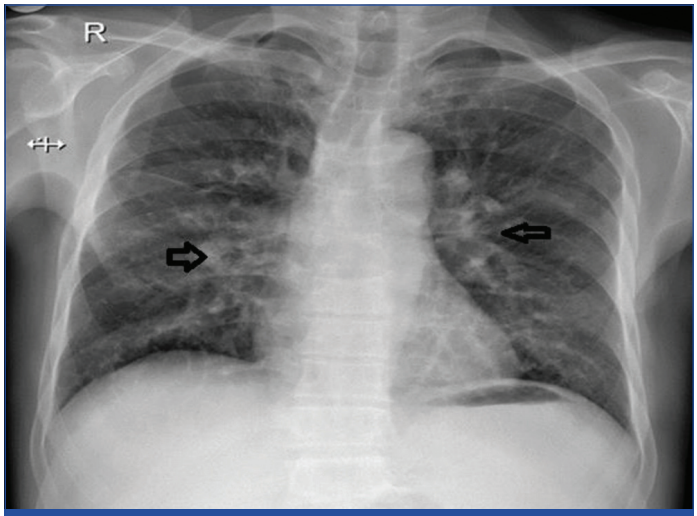
Laboratory investigations revealed bi-cytopenia, deranged liver function tests, elevated C-reactive protein and erythrocyte sedimentation rate, and elevated procalcitonin levels [Table/Fig-3]. The serum MTX concentration was 11 µmol/L at 48 hours. An electrocardiogram showed sinus tachycardia. The echocardiography and ultrasonography of the abdomen and pelvis were normal.

Investigation	Investigations on Day 0 (before starting on MTX)	Investigations on presentation	Investigations on Day 3
Haemoglobin	12.4 gm%	12 gm%	6.6 gm%
Total leucocyte count	5600/microlitre	300/microlitre	600/microlitre
Platelets	198000/mm^3	154000/mm^3	4000/mm^3
Total bilirubin	1.2 mg/dL	1.16 mg/dL	4.74 mg/dL
Direct bilirubin	0.6 mg/dL	0.65 mg/dL	3.81 mg/dL
Indirect bilirubin	0.6 mg/dL	0.51 mg/dL	0.93 mg/dL

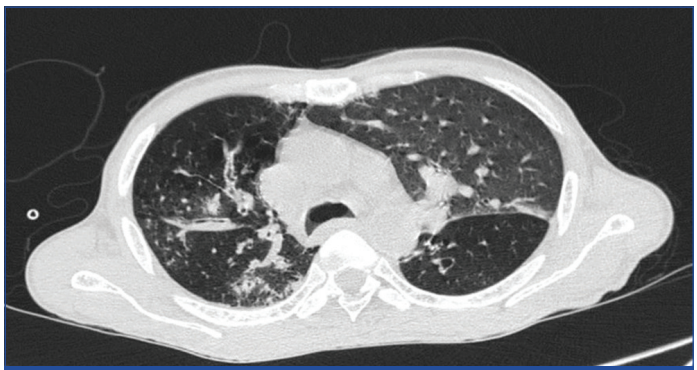
Aspartate transaminase	48 U/L	102 U/L	9 U/L
Alanine transaminase	43 U/L	1367 U/L	17 U/L
Alkaline phosphatase	77 U/L	57 U/L	46 U/L
Urea	25 mg/dL	49 mg/dL	20 mg/dL
Creatinine	0.5 mg/dL	0.76 mg/dL	0.9 mg/dL
Serum sodium	147 mEq/L	134 mEq/L	141 mEq/L
Serum potassium	3.5 mEq/L	4.8 mEq/L	4.3 mEq/L
Prothrombin time	1	20	24.6
International normalised ratio	1.1	1.1	2.2
ESR	19 mm/hr	98 mm/hr	101 mm/hr
CRP	24 mg/L	188 mg/L	194 mg/L
Procalcitonin	0.01 ng/mL	3.13 ng/mL	12.4 ng/mL
Urine routine microscopy	Normal	Normal	Normal
Proteins, pus cells	Nil	Nil	Nil
RBCs	2-3	6-8	3-4
D-dimer	440 mg/L	530 mg/L	7230 mg/L
Fibrinogen	156 mg/dL	100 mg/dL	>500 mg/dL
Ferritin	240 ng/mL	578 ng/mL	1117 ng/mL

[Table/Fig-3]: Laboratory parameters at the time of Rheumatoid Arthritis (RA) diagnosis, at presentation, and on Day 3.

Chest radiography and High-Resolution Computed Tomography (HRCT) of the thorax revealed nodular and fibrotic infiltrates with cystic and cylindrical bronchiectatic changes in the right upper lobe, with a few air-fluid levels indicative of active infection [Table/Fig-4,5].



[Table/Fig-4]: Chest X-ray of the patient on presentation showing increased bronchovascular markings especially in the perihilar region.



[Table/Fig-5]: High-Resolution Computed Tomography (HRCT) thorax showing nodular and fibrotic infiltrates in both lungs.

High suspicion of an idiosyncratic reaction was considered due to a clinical history of drug intake followed by symptoms of fever, rash, itching and hoarseness of voice establishing a temporal relation with the drug, along with a supportive laboratory diagnosis of organ-specific damage. The patient was admitted and immediately started on a comprehensive treatment regimen, including Inj. Hydrocortisone 100 mg TDS, Inj. Pheniramine 22.75 mg TDS, and Inj. Leucovorin 15 mg/m^2 (25 mg/dose was given in this case) QID, along with intravenous fluids, antibiotics, folic acid, antidiarrhoeal drugs, and nebulisation therapy. The patient was closely monitored for clinical and biochemical responses. The antibiotic regimen was escalated due to persistent fever. Given thrombocytopenia, fresh frozen plasma and blood transfusions were administered to manage coagulation abnormalities. Additionally, the patient was started on injections of Filgrastim to stimulate white blood cell production.

Despite these measures, the patient's condition deteriorated significantly due to sepsis, presenting with severe pancytopenia, substantial derangements in liver function tests, elevated prothrombin levels, and markedly increased D-Dimer, fibrinogen, and ferritin levels. The patient was later intubated due to respiratory distress. Multiple transfusions of random donor platelets, fresh frozen plasma, and packed red cells were administered as required. Although the medical condition was severe, the patient's electrocardiogram showed no unusual findings, and both blood and urine cultures were negative for any bacterial growth. However, endotracheal tube secretions tested positive for Klebsiella pneumoniae. The antibiotic regimen was adjusted according to the drug sensitivity report, which showed intermediate sensitivity to colistin only. Unfortunately, despite all resuscitative measures, the patient went into cardiac arrest and succumbed to death.

DISCUSSION

Folate inhibitors have been crucial in developing treatments for various medical conditions, including cancer and autoimmune diseases [1]. MTX, a prominent folate inhibitor, works by inhibiting the enzyme Dihydrofolate Reductase (DHFR), thereby interfering with the conversion of dihydrofolate to tetrahydrofolate [1]. This inhibition reduces tetrahydrofolate levels, essential for synthesising purine nucleotides and thymidylate, both critical for DNA synthesis and cell replication [1]. MTX is widely used to treat autoimmune diseases such as RA, psoriasis, Systemic Lupus Erythematosus (SLE), and inflammatory bowel disease, as well as various cancers, including leukaemia and solid tumours [2]. However, despite its therapeutic efficacy, MTX can cause serious and life-threatening side effects, particularly in cases of overdose or impaired excretion [3]. These adverse effects can range from nausea and vomiting to more severe conditions such as acute renal failure, pulmonary toxicity, and hepatic failure. The Institute for Safe Medication Practices (ISMP) has categorised MTX as a "high-alert medication" as a result of these hazards [3].

This case report details the experience of a 62-year-old male patient who developed MTX toxicity following the initiation of HDMTX (120 mg/week for 1 month) for RA. For RA, the typical MTX dosage ranges from 5 to 25 mg per week to balance efficacy and safety [2]. Nevertheless, higher dosages, commonly administered during cancer therapy or in severe instances, are linked to notable detrimental consequences, such as bone marrow suppression, lung toxicity, nephrotoxicity, and more susceptibility to infections. Research indicates that about 60% of individuals receiving HDMTX experience reversible hepatitis, and roughly 25% develop hyperbilirubinemia. Pancytopenia is a common complication, especially in patients with renal impairment, infections, folic acid deficiency, and the elderly [4]. Medications like trimethoprim can exacerbate MTX-induced myelosuppression [5]. A case series of 15 patients reported acute toxicity due to inadvertent daily intake of the prescribed weekly MTX dose for two or more days, leading to adverse events. Key findings included neutropenia in 80% of patients, gastrointestinal symptoms such as vomiting (60%) and diarrhoea (13.3%), and two deaths from bacterial sepsis. Similarly, this patient consumed HDMTX (120 mg/week), presenting with marrow toxicity, worsening sepsis, and gastrointestinal symptoms, consistent with the findings in this series [6].

In this case, the patient developed severe pancytopenia and multiple mucosal lesions, indicative of MTX-induced myelosuppression. The absence of purpura, ecchymosis, and schistocytes on the blood smear made conditions like Disseminated Intravascular Coagulation (DIC) or Thrombotic Thrombocytopenic Purpura (TTP) unlikely. The serum MTX concentration was 11 µmol/L at 48 hours, confirming MTX toxicity (Serum levels >10 µmol/L at 24 hours, >1 µmol/L at 48 hours, and >0.1 µmol/L at 72 hours are considered to be at high risk for impending toxicity [7]. Consequently, the patient was treated with leucovorin (15 mg/m^2), a known antidote for MTX toxicity [8]. Despite this and supportive treatments, the patient's condition deteriorated due to Klebsiella bacteraemia, leading to sepsis and septic shock. Elevated D-dimer and fibrinogen levels were attributed to the acute phase response in sepsis rather than direct MTX toxicity. MTX-induced immunosuppression an increased T-regulatory cells (Tregs), heightened susceptibility to secondary infections and poor outcomes. Leucovorin mitigates MTX toxicity by bypassing the inhibition of DHFR [9]. Investigational agents like thymidine may offer additional protection against MTX-induced damage [10]. Carboxypeptidase-G2 (CPDG2), a recombinant bacterial enzyme, has shown promise in rapidly metabolising MTX into inactive metabolites, reducing plasma levels by over 98% and potentially mitigating nephrotoxicity and other adverse effects associated with high MTX levels [11].

This case underscores the severe toxicity risk associated with HDMTX, particularly when compounded by infections, and highlights the importance of vigilant monitoring and timely intervention to manage MTX-related adverse effects.

CONCLUSION(S)

However, careful dose and patient education are crucial considering the possibility of significant adverse effects. Self-administration of such drugs should be avoided patients and relatives should be counselled regarding the treatment and associated adverse drug reactions. Given the narrow therapeutic window and the potential for severe toxicity, patients must be clearly instructed on the proper dosing schedule. Periodic follow-up and monitoring should be done by physicians to look for any early signs of toxicity. Co-prescriptions and drugs such as NSAIDS should be avoided during the course of treatment.

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