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# A Life-Threatening Methotrexate Intoxication Associated with End-Stage Renal Disease Resolved by Late Administration of Glucarpidase: Case Report

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**Keywords:**

Methotrexate Toxicity; Glucarpidase; Renal Failure; Psoriasis; Nephrotoxicity

**Abbreviations**:

AKI: Acute Kidney Injury; DAMPA: 4-Deoxy-4-Amino-N10-Methylpteroic Acid; FA: Folinic Acid; HDMTX: High-Dose Methotrexate; MTX: Methotrexate.

## 1. Abstract

Methotrexate (MTX) is a folate inhibitor drug used to treat rheumatologic diseases and, at higher doses, as antineoplastic medication. Due to its potential toxicity, MTX must be administered upon medical prescription; indeed, improper intake may be potentially lethal, also at dosages below 500 mg/m2, defined as "high dose Methotrexate" (HD-MTX). Our case presented skin involvement, genitourinary and gastrointestinal mucositis, kidney injury, and myelosuppression as the main collateral effects of MTX intoxication. Considering its kidney elimination, MTX toxicity is higher if renal function is impaired, particularly in patients with an estimated glomerular filtration rate<30 ml/min. The management of MTX intoxication was based on three main goals: facilitating the kidney elimination of the drug through urine alkalinization and hydration, reducing the serum concentrations using levopholinic acid treatment, and treating the organ damage with supporting therapies and prophylactic antibiotics. A specific Methotrexate antidote (Glucarpidase) is indicated in case of high plasma MTX concentrations and delayed elimination within a maximum timing of 90 hours for administration from the toxic dose. We report the case of an incorrect self-intake of Methotrexate leading to life-threatening systemic intoxication solved after the administration of Glucarpidase for use beyond the time limit indicated for its maximum efficacy. This case underscores the efficacy of glucarpidase even beyond 90 hours after methotrexate intake.

## 2. Learnings Points

- Methotrexate (MTX) intoxication is a potentially life-threatening condition characterized by skin and mucosal involvement, kidney injury, myelosuppression, and encephalopathy.
- Glucarpidase is an MTX antidote with the best efficacy if given within 90 hours from the toxic MTX dose
- In our patient, the delayed administration of glucarpidase, after 8 days from the first dose, resolved a life-threatening case of

MTX intoxication.

## 3. Introduction

Methotrexate is a drug frequently used to treat neoplastic and rheumatic diseases by interfering with the metabolism of folic acid. Unfortunately, it has a narrow therapeutic index. It may lead to various collateral effects when administered at different dosages, particularly at higher doses. It is crucial to recognize Methotrexate intoxication as a medical emergency, necessitating the prompt administration of antidotes. Additionally, especially in the case of acute renal failure, the accurate management of the complications and prompt administration of the antidote glucarpidase is essential for ensuring a successful outcome. Little is known about the beneficial effects of glucarpidase in case of late administration outside the recommended therapeutic time window.

## 4. Case Presentation

We report a particularly complex case of a male patient in his sixties (BMI 22 kg/m²) with acute methotrexate intoxication. The clinical history revealed just arterial hypertension under pharmacological treatment and a thirty-year-lasting diagnosis of psoriasis, just occasionally treated with steroid therapy. In February 2023, the patient reported the appearance of numerous dyskeratotic lesions on the limbs, subsequently extended centripetally and to the face, and symptoms such as dysuria, watery diarrhea, vomiting, and dysphagia for solid and liquid food. For this reason, he accessed the emergency area of the Policlinico P. Giaccone in Palermo, where he performed blood tests that showed a significant increase in creatinine levels with hyperkalemia and metabolic acidosis. He underwent an urgent hemodialysis session and was admitted to our ward afterward. Upon admission, an objective examination was performed with evidence of erythematous/desquamative lesions extended to the trunk, limbs, scalp, and face, (Figure 1) and erosions of the genital mucosa and oral cavity. At the same time, the thoracic, abdominal, cardiovascular, and neurological objectivity was normal. In addition, no third spacing i.e., ascites, pleural effusion, or edema was noted on examination. Blood chemistry at the entrance showed increased renal function indices, white blood count, and liver function indices were within normal limits. After a careful interview, the patient admitted he had arbitrarily administered, five days before, overdose therapy with methotrexate subcutaneously at a dosage of 15 mg for four consecutive days, in the absence of a medical prescription. No other interacting drugs were reported. Therefore, considering the reported information and the clinical manifestations characterized by signs of mucositis of the gastrointestinal and genitourinary tracts, skin involvement, and acute renal damage suggestive of methotrexate intoxication, after a telephonic consultation with the Poison Control Centre of Pavia, high-dose levopholinic acid therapy was promptly undertaken. In addition, hydration and sodium bicarbonate therapy for the alkalinization of urine to promote the renal elimination of the drug was practiced. On the second day of hospitalization, we witnessed the appearance of pancytopenia at blood tests, with “nadir” of blood count with severe neutropenia (0/mcl), severe anemia, and thrombocytopenia (<20000/mcl) on the third day of hospitalization, so granulocyte and erythroid growth factors and antimicrobial prophylactic therapy was administered and the patient placed in spatial isolation considering the high risk of infection. However, despite the undertaken therapy and the further increase of the dosage of levopholinic acid up to 1 gram/day, high plasma levels of methotrexate were dosed by chromatographic analysis using ultra-high performance liquid chromatography. The clinical findings were also superimposed on the appearance of ideo-motor slowdown and visual hallucinations attributable to encephalopathy. Therefore, given the worsening of the patient’s status burdened by a high risk of mortality and the persistence of severe renal dysfunction necessitating hemodialysis that compromised an adequate elimination of methotrexate, the specific antidote Glucarpidase, not present in our region (Sicily), was shipped in few hours from Northern Italy and administered for off-label use, although beyond the time limit indicated (more than 96 hours from the administration of the methotrexate) for its optimal effectiveness [1]. Following the administration of Glucarpidase in a single dose of 50 IU/kg, MTX concentrations promptly dropped and the patient’s condition gradually improved with the resolution of the skin lesions and erosions of the oral and genital mucous membranes, the resolution of diarrhea, and the progressive increase of platelet and granulocyte count up to the normalization of blood parameters (Figure 1). Contextually, the patient referred the patient reported improvement in coenaesthesis, reduction in asthenia, the disappearance of itching, and improvement in the quality of night sleep. The hemodialysis treatment was temporarily interrupted for 48 hours, to avoid the possible elimination of the antidote by hemodialysis, closely monitoring the renal function indices, electrolytes, and blood gas parameters. At the same time, however, the patient developed a SARS-COV2 infection and concurrent pneumonia which was associated with persistent renal failure. Unfortunately, hemodialytic treatment continuation was necessary considering the persistence of the renal damage secondary to acute tubular necrosis by methotrexate. Hence, at the stabilization of the clinical status, the patient was discharged at home with the strong advice not to take medication without previous specialistic consultation.

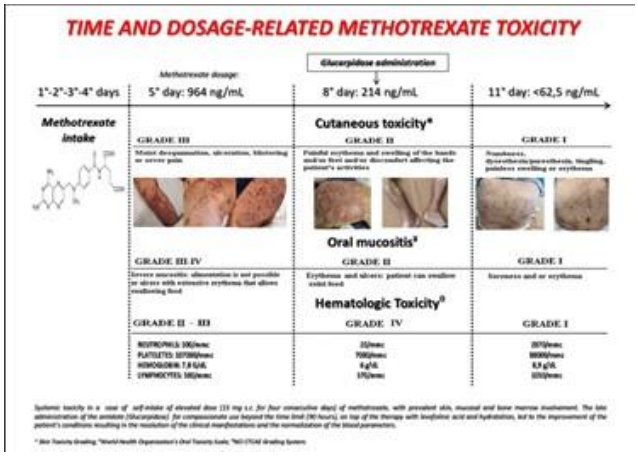


**Figure 1**: Upon admission, an objective examination was performed with evidence of erythematous/desquamative lesions extended to the trunk, limbs, scalp, and face.

## 5. Discussion

High-dose methotrexate (HDMTX) is burdened by high mortality [2]. It can lead to nephrotoxicity, creating a medical emergency due to delayed renal excretion and prolonged exposure to high concentrations of MTX. This condition can trigger life-threatening complications, including acute kidney injury (AKI) through crystal nephropathy [3]. Methotrexate is mainly eliminated by the kidneys (80%-90%). This medication can lead to vasoconstriction of the afferent arterioles, tubular precipitation, and direct injury to the tubules. Acute kidney injury (AKI) has been documented in 2% to 12% of patients undergoing high-dose methotrexate (HDMTX) treatment. In instances of significant renal impairment, glucarpidase may be utilized to facilitate non-renal elimination by converting extracellular MTX into its inactive metabolites, glutamate and DAMPA (4-deoxy-4-amino-N10-methylpteroic acid), which are eliminated by the liver. Supportive management, including aggressive hydration and urine alkalinization, is crucial in treating MTX toxicity, yet AKI occurs in 2–12% of patients despite such measures [4]. MTX plasma levels exceeding 10 μM at 24 hours pose a major risk for renal toxicity. Two recommended treatment options for reducing toxic MTX plasma levels are glucarpidase and high-flux hemodialysis, with the former being less invasive and more effective [3]. Glucarpidase, a genetically engineered enzyme, breaks down MTX outside cells into inactive byproducts, offering a rapid resolution of MTX-induced AKI, which is generally reversible, with most patients regaining normal kidney function. However, the long-term effects on nephron loss and the potential development of chronic kidney disease are not been extensively studied [3]. However, MTX crystalline nephrotoxicity represents a reversible form of AKI, characterized by peak creatinine elevations typically occurring within the first 5-6 days of treatment initiation. Subsequently, a return to baseline creatinine levels can be anticipated within up to four weeks [6]. These patients may either remain asymptomatic or experience decreased urinary output at the onset of AKI. Additionally, patients may exhibit a gradual decline in MTX levels due to AKI, which hampers the renal clearance of the drug. Individuals with AKI may require a median time of up to eight days for MTX clearance, compared to an average of five days for those with normal renal function. In our case, a patient administered glucarpidase showed improvement in all symptoms related to methotrexate toxicity, except for renal failure. Factors contributing to persistent end-stage renal disease included unknown pre-existing renal impairment, delayed administration of antidotes, and possible concomitant factors like the lack of folic acid supplementation during the arbitrary drug assumption or the concurrent SARS-COV 2 infection which can accompany AKI or worsen existing chronic renal failure in more than 25% of cases [5]. Despite the patient's methotrexate doses being lower than high doses, systemic toxicity could have been predisposed by these factors. Glucarpidase prevents further kidney damage and cannot resolve intracellular effects, necessitating leucovorin to protect normal cells from MTX toxicity [3]. Furthermore, in patients who require hemodialysis sessions due to acute renal failure, as in the case of our patient, the administration of glucarpidase should take place in an intradialytic window suitable to guarantee the correct action of the antidote. The molecule could be eliminated during the dialysis session, significantly dampening the antidotal action. Although the exceptional nature of the case does not allow us to generalize our conclusions about the habitual use of glucarpidase, it underscores the efficacy of glucarpidase even beyond 90 hours after methotrexate intake. The delayed administration of glucarpidase, nearly 8 days after the first MTX injection, resulted in the prompt resolution of cutaneous and bone marrow toxicity. Recognizing this extended temporal window for glucarpidase action could be crucial in case of delayed diagnosis for securing its urgent supply, given its limited availability in some countries and the need for individual patient requests [3,6].

## 6. Conclusions

In case of elevated concentration of MTX, it is fundamental to consider using the antidote glucarpidase promptly to address all symptoms. Nevertheless, glucarpidase may be considered as rescue therapy also in particular cases with late diagnosis or antidote supply even in patients with severe kidney damage as the one presented. Reassessing the effective timeframe for glucarpidase could be beneficial, potentially prompting its use in cases of late diagnosis of MTX toxicity.

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