Multivisceral Damage Following Acute Methotrexate Intoxication By Dosing Error

Sirine Bouzid, Rim Karray, Amine Abdelhedi, Fadhila Issaoui, Olfa Chakroun, Noureddine Rekik.

Emergency Department, University Hospital Habib Bourguiba Sfax, Tunisia

Abstract

Background: Methotrexate (MTX) is a chemotherapeutic agent commonly used for the treatment of nonmalignant and malignant conditions. It remains the principal medication used to treat rheumatoid arthritis. High-dose MTX is known to cause significant injuries, including acute renal failure, hepatotoxicity, myelosuppression, and multiorgan failure.

Case presentation: Here we report a 65 years old female patient with rheumatoid arthritis who had developed oral and mucocutaneous ulceration after daily ingestion of MTX.

Conclusion: This case report highlights the importance of early follow-up and regular laboratory investigations of patients on methotrexate therapy.

KEYWORDS: Methotrexate; Intoxication; Dosing Error; Multivisceral Damage

INTRODUCTION

Methotrexate (MTX) is a folic acid used to treat autoimmune conditions and inflammatory diseases such as rheumatoid arthritis. Daily accidental ingestion instead of one dose per week is a common cause of acute MTX intoxication. Most of the publications state MTX's side effects, but there are very few revealing mortality (1).

Here we report a 65-year-old female patient with rheumatoid arthritis who had developed oral and mucocutaneous ulceration after daily ingestion of MTX.

CASE REPORT

A 65-year-old female was admitted to the emergency department for mucocutaneous ulceration after daily ingestion of MTX. She had hypertension and diabetes. She was recently diagnosed with rheumatoid arthritis 5 days ago, and she had a prescription for MTX. Upon review of the methotrexate dose administration, she reported that she had wrongly taken 15mg for the first 2 days and then 5 mg on the third day.

On physical examination, the patient was conscious and oriented. She had no respiratory nor hemodynamic distress. General examination noted conjunctivitis (figure 1).

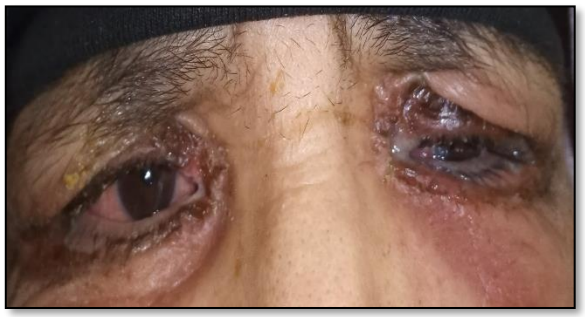

Figure 1: *Bilateral Conjunctivitis related to MTX intoxication*

She was febrile and in reduced general condition. Oral cavity examination showed ulcerated mucosa with bleeding (figure 2). Genital examination

revealed vaginal mucosa with per vaginal bleeding (figure 3).

Figure 2: *Ulcerated mucosa in oral cavity*

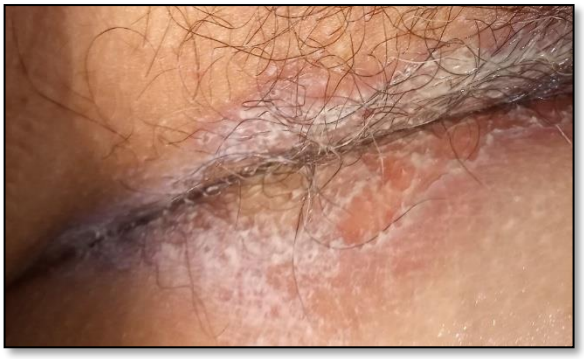

Figure 3: *Genital mucosa (figure 3).*

Blood counts and peripheral blood smear have shown pancytopenia: leucocyte count of 400/uL, Hemoglobin rate of 9.5 g/dl, and platelet count of 79.000/ uL. The liver functions tests showed slightly elevated liver enzymes, and she had acute renal failure (creatinine level of 250 µmol/L). A Biological inflammatory syndrome was detected (Reactive C protein 445g/L). Regrettably, we could not measure the blood level of MTX because of a lack of facilities.

The patient had benefited from hyperhydration and intravenous folinic acid at a dose of 15 mg and was given six hourly (1 mg/kg). Unfortunately, two days after her admission she developed acute respiratory distress for which she was sedated and intubated. Despite aggressive therapy, her blood tests worsened and she developed a multi-organ failure. She deceased four days after admission.

DISCUSSION

This case describes the clinical features of a rare case of acute MTX intoxication. Toxicity from low-dose MTX is uncommon. Most cases are due to failure to follow the prescribed recommendations. (1)

Methotrexate is a chemotherapeutic agent commonly used to treat nonmalignant and malignant conditions. It remains the principal medication used to treat rheumatoid arthritis (2). In therapeutic doses, MTX has anti-inflammatory and immunosuppressive action. Renal excretion is the primary route of elimination, which is influenced by the route of administration and the dosage (3).

As described in several studies, MTX toxicity has an impact on the skin, gastrointestinal mucosa, liver, kidneys, and bone marrow (3,4). High-dose MTX is known to cause significant injuries, including acute renal failure, hepatotoxicity, myelosuppression, and multiorgan failure.

Furthermore, pancytopenia can be one of the complications of methotrexate use whether in low or high doses (5). The mechanism of development of pancytopenia in MTX intoxication is not clear. It is commonly seen in therapeutic doses when the patient presents some risk factors such as dehydration, renal failure, or hypoalbuminemia (6). In the same wavelength, Calvo Romero discovered that pancytopenia caused by a therapeutic dose of methotrexate is more likely to

progress in the presence of renal failure (7). Grissinger reported one such similar case where the patient took the drug daily instead of weekly (8). In our case, with no history of renal failure, our patient had developed pancytopenia. Concerning thrombocytopenia, Paul et al have demonstrated that MTX could promote the apoptosis of platelet and cause mitochondrial damage (9).

Furthermore, our patient developed acute renal failure. It has been proven that the most commonly described mechanism of MTX nephrotoxicity is the crystallization of MTX in the renal tubular lumen (10). This acute kidney injury can be seen in 2% to 12% of patients (10). Renal failure may be also precipitated by concomitant ingestion of some drugs, which are protein bound like sulfonamides, nonsteroidal anti-inflammatory drugs (NSAIDs), and barbiturates. (4)

Skin lesions are reported to be more common in patients with psoriasis. As hyperproliferative psoriatic plaques absorb more methotrexate than normal skin, skin ulcerations caused by MTX toxicity are limited to the psoriatic plaques (11). In our case, we describe oral and vaginal ulceration in a previous normal skin. According to the literature, skin lesions due to acute MTX toxicity are still infrequent and can include ulcers, Stevens-Johnson syndrome, and toxic epidermal necrolysis (12)

In addition to the abovementioned signs, our patient has developed conjunctivitis, which is uncommon. Cases using therapeutic doses usually described symptoms of ocular burning and pruritus (13).

Pulmonary toxicity due to MTX has also been proven. It can be fibrosis, interstitial pneumonitis, or diffuse alveolar damage (14). In our case, the patient has developed respiratory distress.

Regarding the management of MTX intoxication, it is based mainly on hyperhydration, which was used in our case. Folinic acid (also known as leucovorin) is used as an antidote in case of overdoses(15). It has been proven that it competes with MTX to enter cells and allows the replacement of intracellular folate (16). Even though we used it, the outcome was fatal, which can be explained by the delayed consultation.

CONCLUSION

This case report highlights the importance of early follow-up and regular laboratory investigations of patients on MTX therapy. Thus, face-to-face advice and supplemental written information should be provided, especially to elderly patients. Avoiding self-administration of MTX is essential, as is never combining it with another medication without a doctor's approval.

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