Misinterpretation of Prescription Leading to Acute Methotrexate Toxicity: An Avoidable Accident

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Abstract

Low-dose oral methotrexate (MTX), as used for several dermatological and rheumatological indications, is generally a safe medication. Overdose of MTX may cause acute toxicity, which results in oral mucositis, skin ulceration, and pancytopenia.

A 40-year-old man presented with a 3-day history of oral mucosal ulceration along with pustular eruption, painful bullae, and skin erosion. He also had a passage of black, tarry stool for 2 days. Another patient, A 50-year-old female presented with oral mucosal ulceration and per-rectal bleeding. Both were recently started on low-dose oral MTX for seronegative arthritis. Misinterpreting the physician's prescription, they took MTX daily instead of weekly. Their blood count revealed a variable degree of pancytopenia. They were treated with intravenous or oral Leucovorin, along with other supportive therapy. Patients started responding within a few days after treatment and were discharged after a week.

Proper education of the patient regarding the dosage is fundamental for prescribing MTX and reducing the chance of developing toxicities. MTX-induced acute toxicity is a medical emergency requiring prompt and proper intervention.

Keywords: *Methotrexate, leucovorin, toxicity.*

INTRODUCTION

For many years, methotrexate (MTX) has been used widely to treat various rheumatological and dermatological diseases [1, 3]. When administered orally at dosages no more than 25 mg per week, it is regarded as a safe medication [4, 5]. Potentially lethal toxicity of MTX should be prevented by adequate selection and monitoring of patients [6]. The drug is primarily excreted through the kidney. The rate of excretion is dependent on the route of administration and dosage. It is affected by the concurrent use of certain protein-bound drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), barbiturates, and sulfonamides. If the dosage guidelines of MTX use are not followed properly, severe drug toxicity can occur, which may even lead to death. It is essential to monitor renal function, complete blood count, and carefully examine the skin and mucosal surfaces for any erosion or ulceration for early identification and prevention of MTX-induced acute toxicity [7]. Here, we discuss the cases of two Bangladeshi patients who developed MTX-induced acute toxicity.

CASE SUMMARY

Case-1

A 40-year-old man presented with 3-day-history of oral mucosal ulceration (**Fig. 1**), erosion on groins and at the junction of penis and scrotum, pustular eruption on the lower abdomen, painful bullae on the sole and erythema on the palm along with pain on swallowing. He also complained of passing black, tarry stool and a burning sensation during micturition for 2 days. He was taking MTX 10 mg weekly along with prednisolone 20 mg/day and naproxen 500 mg/day for seronegative arthritis without any complications for 1 month. However, following a follow-up visit 4-days back, he thought that there was a change in dosage schedule and started to take MTX daily. All his features developed on the 4th day of daily intake of MTX 10 mg. With the newly developed cutaneous, mucosal, and gastrointestinal symptoms, he was admitted to the hospital. After admission, he complained of the passage of fresh blood during defecation.

Fig. (1): Oral mucosal ulceration of the patients; (a) First patient, (b) Second patient.

The patient was afebrile, conscious, and responding to commands. He had the lesions mentioned above on the skin and oral mucosa. Urgently done blood count revealed bi-cytopenia in the form of leukopenia (1.56x10^9/L) and thrombocytopenia (70X10^9/L). His C-reactive protein

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(CRP) and erythrocyte sedimentation rate (ESR) were elevated (73.7 mg/L and 55 mm in 1st hour, respectively). The occult blood test (OBT) of stool was positive. The serum level of MTX could not be measured due to a lack of facility. Based on history, clinical features, and laboratory investigations, a diagnosis of MTX-induced acute toxicity was made.

Intravenous Leucovorin was started at a dose of 15 mg 8 hourly for 3 days, then shifted to oral Leucovorin 15 mg 8 hourly for another 7 days. Intravenous dexamethasone and Meropenem were also started to control the adverse effect of MTX and to control superadded bacterial infection, respectively. For gastrointestinal complications, proton pump inhibitors and Sucralfate solution were used. The patient was transfused two bags of whole blood and 2 bags of platelet for agranulocytosis and thrombocytopenia. Triamcinolone acetonide oral paste was given for oral lesions, and a topical steroid was used for cutaneous lesions. The patient started showing a response 2 days after treatment and was discharged from the hospital after 10 days.

Case-2

A 50-year-old female was admitted to the hospital with per-rectal bleeding and oral ulceration for 15 days. She took MTX 15 mg daily instead of weekly for the last 3 weeks. MTX was prescribed for arthritis. Her blood count revealed pancytopenia (hemoglobin 9.1 gm/dl, WBC $0.34x10^9$/L) and platelet $38X10^9$/L). Biochemical tests were normal; Serum MTX level could not be measured. The patient responded well to oral Leucovorin 15 mg 8 hourly, along with supportive therapy. She could leave the hospital within one week.

DISCUSSION

MTX competitively inhibits the function of dihydrofolic acid reductase, the enzyme needed to convert dihydrofolates to tetrahydrofolates. As the tetrahydrofolates are utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate, inhibition of the enzyme interferes with DNA synthesis and repair. The effect is more pronounced in rapidly proliferating cells, including stem cells, smooth muscle cells, and epithelial cells [8].

MTX is approved by the Food and Drug Administration (FDA) for use in several rheumatological and hematological conditions like rheumatoid arthritis, juvenile idiopathic arthritis, and particular types of leukemia and lymphoma. Although psoriasis and psoriatic arthritis are common indications of MTX in dermatology, several papulosquamous, allergic/immunological, dermatitic, blistering, vasculitic, and granulomatous dermatoses are also treated with MTX [9].

MTX, in low doses as used in psoriasis, rarely causes toxicity. Acute toxicity is primarily caused by patients' or doctors' disregard for the recommended dosage suggestion [10]. Rapidly proliferating cell populations, namely bone marrow and epithelium of the gastrointestinal tract and skin, are the major sufferers of the acute toxic effect of MTX, resulting in bone marrow suppression, pancytopenia, gastrointestinal manifestations, and skin ulceration [11, 12]. Mucosal cells are more susceptible to MTX than progenitor cells in the bone marrow owing to the increased accumulation and persistence of MTX in the intestinal epithelial tissue. The index cases had MTX-induced acute toxicity and developed mucocutaneous as well as gastrointestinal toxicity and pancytopenia. Mucositis typically develops 3-7 days after a single high dose of MTX administration, starting several days before leucocyte and platelet counts decline [11]. The index cases developed mucositis earlier than usual anticipation, within a few days after starting daily intake of MTX.

MTX-induced pancytopenia occurs in a dose-dependent fashion. However, it may also result from the characteristic effect of the antiproliferative action of MTX. Pancytopenia develops within the first 10 days of high-dose MTX treatment [5]. The side effects in our patients are mainly due to the inadvertent use of MTX and the concomitant use of NSAIDs. The first patient had taken naproxen once daily with a weekly dose of MTX without any side effects. But when he started to take naproxen twice daily along with a daily intake of MTX, he developed a mucocutaneous lesion at first and then gastrointestinal features. Concomitant use of naproxen and MTX causes cutaneous ulceration and pancytopenia [13]. Our patients also developed oral candidiasis due to poor oral hygiene and reduced immunity.

Leucovorin is a folate analog indicated in MTX toxicity, which does not need reduction by the enzyme dihydrofolate reductase [14]. It can be administered by oral or parenteral route. In MTX-induced acute toxicity, the intravenous route is preferred and should be started immediately. Where facilities are available, serum MTX levels can be measured to determine the dosage of Leucovorin. If facilities are unavailable, an empirical dosage may be used. The patient also needs all forms of supportive therapies.

Errors may happen when there is a lack of proper communication between physicians and patients. This is especially true for medications that require a special dosage schedule. Although prescribed for well-indicated conditions, serious life-threatening complications can result due to erroneous dosage of drugs like MTX. Nonetheless, reducing these types of incidents is not very difficult if physicians and patients exercise a little caution. Patients need to be well educated and given clear instructions in written format regarding the dosing pattern of MTX.

CONCLUSION

Acute toxicity of MTX is a medical emergency that may result in life-threatening pancytopenia and skin/mucosal ulceration. Appropriate education of the patient is integral

in prescribing MTX to reduce the chance of developing toxicities. Physicians need to ensure proper counseling and should provide written instruction regarding the dosing, adverse effects, and features of toxicity of MTX.

CONSENT FOR PUBLICATION

Written informed consent was taken from both patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

FQ and MB managed the patient and collected the data. MH prepared the first draft of the manuscript. FQ and MB revised the manuscript.

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