

Case Report

Acute methotrexate toxicity with severe cutaneous ulcerations in a patient of chronic plaque psoriasis

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ABSTRACT

Methotrexate continues to be one of the most widely used systemic immunosuppressive agents in chronic plaque psoriasis. In addition to the important well characterized adverse effects such as hepatotoxicity and myelosuppression, methotrexate may induce a number of mucocutaneous adverse events including methotrexate induced mucocutaneous ulcerations. We present a case of methotrexate induced severe cutaneous ulcerations in patient with chronic plaque psoriasis. 45 year old male known case of chronic plaque psoriasis on methotrexate therapy manifested as methotrexate toxicity leading to acute kidney injury with painful ulcerated plaques with active bleeding over previously psoriatic plaques over extremities and trunk with mucosal ulcerations responding effectively to leucovorin therapy. Dermatologists need to be alert to the possibility of cutaneous adverse events associated with methotrexate therapy especially ulcerations of psoriatic plaques.

Keywords: Methotrexate Toxicity, Psoriasis, Leucovorin

INTRODUCTION

Introduced in 1950s, methotrexate is one of the most widely used systemic immunosuppressive agents in dermatology. It is commonly used antimetabolite drug in chronic plaque psoriasis with dose ranging from 7.5 mg–30 mg per week.¹ It acts by inhibiting the deoxyribonucleic acid (DNA) synthesis of T lymphocytes and epidermal keratinocytes.² Higher dose of methotrexate can often have toxic effect on different system causing pancytopenia, deranged liver function and mucocutaneous necrosis. The mechanism of methotrexate toxicity is by inhibiting DNA synthesis in rapidly proliferating cells i.e., gastrointestinal tract, haematopoietic cells and keratinocyte cells of psoriatic plaque. Acute methotrexate toxicity commonly causes nausea, vomiting, mucosal ulcers, decrease blood counts, deranged liver functions and black stools. Pulmonary fibrosis and skin ulceration with or without active

bleeding are among the rare ones. It is of primary importance that dermatologists remain alert to cutaneous indicators of methotrexate toxicity and must be aware of risk factors that may affect its drug metabolism. We present a case of acute methotrexate toxicity manifesting as severe cutaneous ulcerations with acute kidney injury in a patient of chronic plaque psoriasis.

CASE REPORT

A 45 year old male known case of chronic plaque psoriasis receiving methotrexate therapy since last 5 years (cumulative dose = 2.5 gm) came with multiple painful ulcerated lesions on previously psoriatic plaques over upper and lower extremities and also over trunk since last 3 days. He was a hypertensive on medications and chronic alcoholic since last many years. On day 1, patient presented with multiple well defined erythematous plaques of various sizes with painful

ulcerated lesions with active bleeding over the ulcerated sites over bilateral upper limb, lower limb (extensor >flexor) and trunk with sparing over uninvolved psoriatic sites. Few mucosal ulcerations were present on buccal mucosa and angle of mouth. He mentioned history of receiving injectable methotrexate from private clinic. Patient was indoored for further management. Blood sample was sent for assessment of various parameters. Serum methotrexate level was found to be 0.2 micromol/l on day 1. Patient was immediately started on day 1 with injection leucovorin 50 mg over 6 hours for two doses followed by 25 mg over 6 hour duration for total of four doses on day 2 and day 3 along with injectable antibiotic and supportive treatment consisting of local care of the ulcers, topical antibiotic, anta acids and intravenous fluids. His blood parameters started improving after three days of leucovorin treatment. His vitals were monitored strictly along with urine input/output charting and dose of injection leucovorin was adjusted till the blood parameters and serum methotrexate level (0.01 micromol/l) came to normal. His blood investigations are mentioned in the table.



Figure 1: Multiple erythematous plaques with cutaneous ulcerations and active bleeding over trunk on day 1 of presentation.

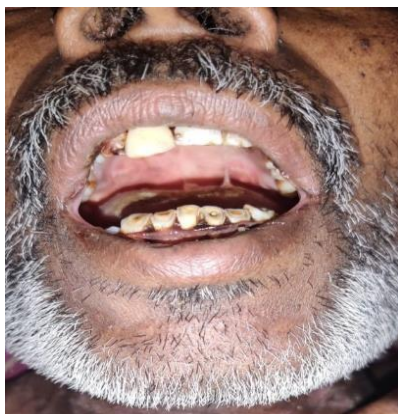


Figure 2: Mucosal ulcerations on gingiva and angle of mouth on day 1 of presentation.



Figure 3: Multiple erythematous resolving ulcerated plaques on day 7 of presentation.

Table 1: Blood investigations.

	Day 1	Day 2	Day 3	Day 4	Day 7
Hb (gm%)	8.5	8.7	9.9	11	11.5
TLC	1000	3000	3000	5000	13000
Platelets	20000	30000	1.27	1.69	1.71
Sr creatinine	1.5	1.7	1.6	2.6	2.9
Urea	48	55	57	58	47
T. bilirubin	1.89	1.07	1.04	0.82	0.80
SGOT	31	31	40	49	45
SGPT	25	25	26	33	32
Sr protein	7.4	7.1	6.2	5.3	5.5
ALP	136	136	104	76	69

Hb: haemoglobin, TLC: total leucocyte count, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, ALP: alkaline phosphatase.

DISCUSSION

Methotrexate is affordable and one of most effective systemic antimetabolite drug prescribed for chronic plaque psoriasis. It inhibits cellular mitosis by inhibiting dihydrofolate (DHF) reductase, an enzyme responsible for the conversion of DHF to tetrahydrofolate leading to reduction in thymidylate and purine biosynthesis. It gets polyglutaminated to active form inside cell and thereby it stays in cell for a long period when taken daily or in divided doses. The cells that effectively polyglutamate methotrexate includes leukemic myeloblasts, macrophages, lymphoblasts and dividing epithelial cells.¹ Methotrexate toxicity is rare with low dose and can be avoided with correct scheduling of the dose and adherence to the recommended guidelines.⁴ Acute methotrexate toxicity manifests in various multiple systemic forms including hepatotoxicity, pulmonary toxicity, acute renal failure, stomatitis, ulceration/erosion of the gastrointestinal tract and pancytopenia.² Treatment of methotrexate toxicity is usually by folinic acid (leucovorin) rescue therapy. The dose of folinic acid is usually decided according to level of serum methotrexate and duration of overdosing.³ However, facility of

measuring serum methotrexate level is not cost effective and also not available in resource poor settings.

The common reported precipitating factors for methotrexate toxicity are an alteration in its dosage and the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).⁶ Psoriasis patients commonly use NSAIDs for joint pain and co-administration of NSAIDs with methotrexate increases its level in blood by inhibition of renal tubular secretion of methotrexate.⁷ Other factors contributing to its toxicity include renal insufficiency, (the drug Methotrexate is excreted by renal system), infection, alcohol consumption, pustular psoriasis and age >55 years. In our case patient had renal insufficiency and alcohol consumption as a precipitating factor.

From the present case report, our observation suggests that counselling regarding dosing schedule of methotrexate and consequence of its overdosing should be mandatory for all patients of psoriasis. Especially in countries where drug regulation is not strict, patient often buy medications over-the-counter and resort to self-medication. This case is reported to make the physicians to have high index of suspicion in Indian patients with the different challenges of acute methotrexate toxicity due to overdosing and contributory precipitating factors.

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