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METHOTREXATE A BOON OR BANE : A CASE REPORT OF METHOTREXATE TOXICITY

General Medicine

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ABSTRACT

Methotrexate continues to be one of the most widely used systemic immunosuppressive agents in dermatology. In addition to the important, well-characterized adverse effects such as hepatotoxicity and myelosuppression, methotrexate may induce a number of rare cutaneous adverse events including methotrexate-induced ulceration. We present a case of methotrexate-induced cutaneous ulceration in a patient with chronic plaque psoriasis occurring during long-standing methotrexate therapy. Withdrawal of the drug and appropriate skin care led to rapid healing of the ulceration . Review of the literature demonstrates cases of this important rare adverse event, primarily occurring in patients with chronic plaque psoriasis, induced by triggers such as accidental overdose or introduction of an interacting agent. Cutaneous ulceration typically precedes other markers of toxicity. Active treatment with folinic acid (calcium leucovorin) may be required. Early recognition, prompt cessation of methotrexate, and appropriate treatment minimizes morbidity. Physicians and dermatologists need to be alert to the possibility of cutaneous adverse events associated with methotrexate therapy, aware of potential drug interactions, and confident in the management of methotrexate toxicity.

KEYWORDS

Methotrexate, Chronic Plaque Psoriasis, Calcium Leucovorin

INTRODUCTION

Methotrexate (MTX) inhibits mitosis of the cells by antagonizing folic acid required for deoxyribonucleic acid (DNA) synthesis of cells. Once in the cell, MTX inhibits dihydrofolate (DHF) reductase, an enzyme responsible for the conversion of DHF to tetrahydrofolate (THF).

Consequently, there is a reduction in thymidylate and purine biosynthesis. DNA synthesis eventually halts and cells can no longer divide. Polyglutamination of MTX prolongs its intracellular presence. Hence, cells with the capability of effective polyglutamination such as leukemic myeloblasts, synovial macrophages, lymphoblasts, and epithelia are more susceptible to the action of MTX.[1] Acute MTX toxicity presents as pancytopenia, gastrointestinal (GI) mucositis, hepatotoxicity, pulmonary toxicity, and acute renal failure.[2,3]

The most common cause of acute MTX toxicity is an accidental overdose of MTX tablets by the patient or physician's prescription error. MTX is prescribed by many physicians as three consecutive dosages of 2.5 mg at an interval of 12 h. Folic acid tablets are prescribed on other non-MTX days. In India, many of our patients may make an error to distinguish between MTX and folic acid tablets and thus may land up with acute MTX toxicity.

Predisposing factors for developing MTX toxicity include acute renal failure, hypoalbuminemia, and concurrent use of drugs known to interact with MTX. Salicylates and nonsteroidal anti-inammatory drugs (NSAIDs) can decrease the renal elimination and the tubular secretion of MTX while trimethoprim/sulfamethoxazole (Septran®) can enhance the cytotoxic effects of MTX as trimethoprim is an antifolate reductase inhibitor.[4] Concomitant use of MTX and NSAIDs, increase the risk of MTX toxicity as Methotrexate (MTX) inhibits mitosis of the cells by antagonizing folic acid required for deoxyribonucleic acid (DNA) synthesis of cells. Once in the cell, MTX inhibits dihydrofolate (DHF) reductase, an enzyme responsible for the conversion of DHF to tetrahydrofolate (THF). Consequently, there is a reduction in thymidylate and purine biosynthesis. DNA synthesis eventually halts and cells can no longer divide. Polyglutamination of MTX prolongs its intracellular presence. Hence, cells with the capability of effective polyglutamination such as leukemic myeloblasts, synovial macrophages, lymphoblasts, and epithelia are more susceptible to the action of MTX.Acute MTX toxicity presents as pancytopenia, gastrointestinal (GI) mucositis, hepatotoxicity, pulmonary toxicity, and acute renal failure.The most common cause of acute MTX toxicity is an accidental overdose of MTX tablets by the patient or physician's prescription error. Folic acid tablets are prescribed on non-MTX days. In India, many of our patients may make an error to distinguish between MTX and folic acid tablets and thus may land up with acute MTX toxicity. Predisposing factors for developing MTX toxicity include acute renal failure, hypoalbuminemia, and concurrent use of drugs known to interact with MTX. Salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the renal elimination and the tubular secretion of MTX while trimethoprim/sulfamethoxazole can enhance the cytotoxic effects of MTX as trimethoprim is an antifolate reductase inhibitor. Concomitant use of MTX and NSAIDs, increase the risk of MTX toxicity as , NSAIDs inhibits MTX clearance and displace MTX from protein binding sites .

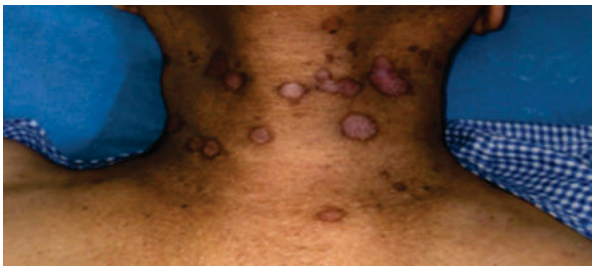
Case Report

A 65 year old male ,a resident of an old age home presented with chronic plaque psoriasis of 10 years presented with ulceration and bleeding over pre-existing psoriasis plaques and erosions over the glans and scrotum since four days. For his plaque psoriasis he was on long term therapy with tacrolimus ointment, but due to recent flare up of his psoriatic plaques he was prescribed oral methotrexate 5 mg on Saturday and Sunday (10 mg /week) for eight weeks .However, he mistakenly took the drug consecutively for 10 days following which he developed the present symptoms and presented to the hospital . Examination revealed erythematous to hyperpigmented, scaly and crusted plaques over both lower limbs, upper limbs and the gluteal region, inguinal region and glans penis. There were multiple ulcers over these plaques, some of them showing hemorrhagic crusts . There were multiple erosions over the glans and prepuce. Along with there were multiple oral ulcers on examination of oral cavity. His total lymphocyte count (TLC) was 2000/mm^3, with an ANC (absolute neutrophil count – 800). Other haematological abnormalities included thrombocytopenia with a platelet count of 30,000. Based on the clinical and haematological findings a clinical diagnosis of methotrexate toxicity was made. Other routine tests included liver function tests, kidney function tests, blood and urine cultures which turned out to be in normal limits. Enzyme-linked immunosorbent assay for human immunodeficiency virus was negative.

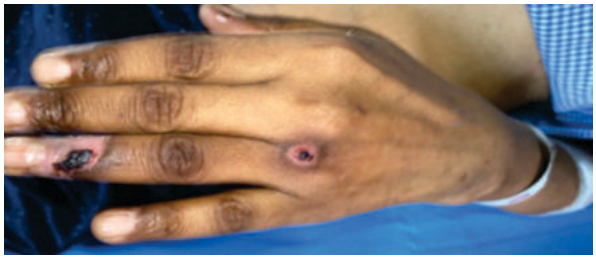
An immediate dermatology opinion was sought, advice to with hold methotrexate, and start topical mupirocin ointment. Patient was started on injection calcium leucovorin 30 mg(folinic acid) stat dose was given followed by 15 mg every 6 hourly for 12 doses. Empirical treatment against gram negative bacteria was started as injection piperacillin and tazobactam 4.5 g tid and tablet fluconazole 200 mg for 7 days. the ulcerated lesions began to heal in 5 days of admission. Patient was kept in isolation room and strict aseptic precautions were followed in view of severe neutropenia. Management of neutropenia for this patient also included injection filgrastim 300 ug subcutaneously, till ANC was more than 1500/mm3 for 48 hours. Eventually patient was discharged 10 days after admission with an ANC of 2000 and wbc count of 3000/mm3 .

Table 1 : Investigations

	10/11	13/11	16/11	20/11
Hb	12.3	11.5	11.5	11.4
Wbc	2000	2500	2800	3000
ANC	800	800	1800	2000
Plts	30000	32000	42000	75000
Creat	0.64	0.65	0.72	0.68
SGOT	55	54	55	42
SGPT	24	21	22	28



Picture:1



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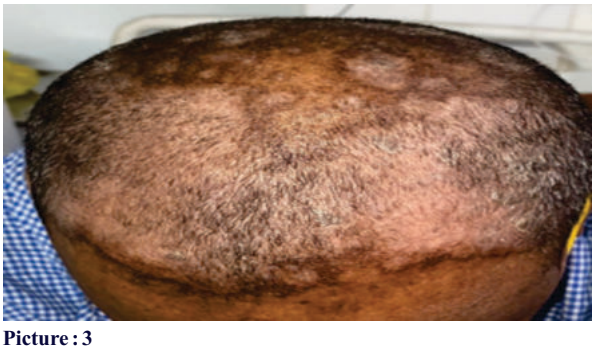

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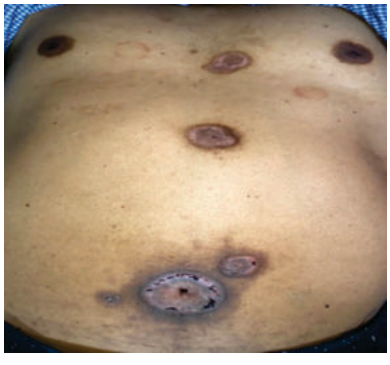

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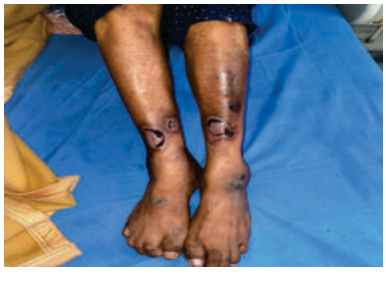

Picture :5

DISCUSSION

MTX toxicity targets vital organs and structures of the body namely skin, GI mucosa, kidney, liver, and bone marrow. Major toxic effects of MTX, such as hepatic, renal, pulmonary, and bone marrow disorders, occur less frequently than the minor effects but may be life-threatening. Signs and symptoms of acute MTX toxicity are based on extent and severity of organ involement.Common case scenario of acute MTX toxicity in psoriasis is a patient having long standing history of chronic plaque psoriasis presenting with sudden onset of erosions or ulcers in psoriatic plaques and sudden onset of severe mucosal ulceration in the oral cavity. A patient may present with fever secondary to infection. Paradoxically, the patient may have hypothermia due to the development of sepsis. Many-a-times, scaly psoriatic plaque may not be visible due to profound effects of MTX toxicity. Careful history from the patient or patient's relative should be obtained with regard to psoriasis and MTX use.Most of these patients are admitted to critical care setup or hospital; critical care physician needs to make a complete assessment of the patient to assess underlying sepsis or systemic disease **.** Ideally, the patient presenting with suspected signs and symptoms of MTX toxicity should be admitted in an intensive care setting, and reverse barrier nursing should be observed by treating staff.Three broad targets are involved in managing acute MTX toxicity: Folinic acid rescue, elimination of MTX from the body, and organ specific care **.**Folinic acid is the antidote of choice for treating MTX toxicity. This rescue regimen replenishes intracellular stores of reduced folate and attenuates the MTX toxicity. Ideally, the serum levels of MTX should be estimated in all cases of acute MTX toxicity, however; the facility for serum MTX measurement is not widely available, and most cases are managed on clinical grounds. Serum MTX levels give guiding schedule for folinic acid rescue therapy. The dose of IV folinic acid should be adjusted according to the MTX levels as shown in Table 2.Serum MTX levels should be measured every 24 h until the levels fall below 0.2 µmol/L. However, there is no rationale for MTX therapeutic drug monitoring in the setting of low-dose toxicity arising from weekly MTX dosing (5–25 mg/week).Elimination of methotrexate from the body. The vast majority of MTX is cleared by the kidneys (more than 90%). A satisfactory diuresis must be established (approximately 600 ml urine over 6 h, or 200 ml urine over 2 h) and **fl**uid input should be approximately 3 L/m2/day until MTX levels are 0.2 µmol/L or below, to maintain urine output and facilitate MTX excretion. Fluid balance should be monitored carefully to prevent renal toxicity and fluid overload. Aim for a urine output of approximately 2 L/m2/day until the MTX level has fallen to 0.2 µmol/L.MTX and its metabolites (2, 4-diamino-N(10)-methylpteroic acid [DAMPA]) are poorly soluble at acidic pH levels. An increase in urine pH from 6.0 to 7.0 increases the solubility of MTX and its metabolites by 5- to 8-fold and prevents crystal deposition. Urinary alkalinization with 40–50 mEq of sodium bicarbonate per liter of IV fluid reduces the risk of intratubular crystal formation. MTX and its metabolite 7-OH-MTX, which is seen predominantlywithhigh-dose MTX therapy, show, respectively, 20- and 12-fold increased solubility when pH increases from 5.0 to 7.0. Urine pH must be >7 to promote MTX excretion and prevent MTX crystallization. It should be maintained at this throughout the treatment period and until levels are 0.2 µmol/L or below.Managing delayed methotrexate excretion Glomerular filtration, tubular secretion, and tubular reabsorption all play a role in the renal clearance of MTX.

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