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Case Series

Methotrexate toxicity-an alarming bell!

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ABSTRACT

Since its introduction in 1951, methotrexate (MTX) has been widely used as the primary anti-psoriatic agent. However, unsupervised dosing by patients or concurrent use of excessive nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to toxicity. Gastrointestinal symptoms are the most commonly observed manifestations, followed by cutaneous toxicity. In this retrospective study conducted at a tertiary care center in Gujarat, data from patients admitted for MTX toxicity between April 2017 and December 2019 were analyzed. A detailed history, including dosage, duration, signs and symptoms, investigations, treatment, and outcomes, was collected and evaluated. The study included 12 hospitalized patients (aged 35-70 years) with MTX toxicity. Among them, 10 patients had psoriasis, 1 had psoriatic arthritis, and 1 had rheumatoid arthritis with discoid lupus erythematosus. Eleven patients had taken daily oral MTX for one week along with painkillers, while one patient had taken an unknown amount without undergoing any investigations. Mucosal ulceration was observed in all cases, and skin necrosis was seen in 2 patients. Hematological investigations revealed myelosuppression in all patients, with altered renal function in 1 patient. Leucovorin (15 mg/ml) was administered to all patients, resulting in improvement for 10 patients, but 2 patients experienced persistent myelosuppression and succumbed to the toxicity. This study emphasizes the importance of pre-treatment investigations, proper monitoring, and strict avoidance of self-administration when administering MTX. Additionally, the co-administration of drugs such as NSAIDs should be judiciously managed. Folinic acid has shown usefulness in cases of MTX toxicity and overdose. In summary, this study underscores the significance of careful administration and monitoring of MTX, along with the avoidance of self-dosing. It highlights the need for judicious use of co-administered medications, and emphasizes the utility of folinic acid in managing MTX toxicity and overdose.

Keywords: MTX, Psoriasis, Mucositis, Cutaneous necrosis, Toxicity, Leucovorin

INTRODUCTION

Methotrexate (MTX) was introduced as an anti-psoriatic agent in 1951 and received FDA approval for the same in 1972. Structurally similar to folic acid, MTX is irreversibly linked to dihydrofolate reductase, exerting an anti-proliferative activity. It also induces apoptosis and increases the concentration of adenosine, resulting in anti-inflammatory and immune regulatory actions.[1]

MTX inhibits cell mitosis by antagonizing folic acid required for 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 reduction in thymidylate and purine biosynthesis, bringing DNA synthesis to halt.

Accidental overdose is the most common cause of acute MTX toxicity. Usually, folic acid tablets are co-prescribed with MTX to ameliorate the haematological and gastrointestinal adverse effects. However, many patients may make an error to distinguish between MTX and folic acid tablets because of similar appearance and thus land up with acute MTX toxicity.

Acute MTX toxicity presents as pancytopenia, gastrointestinal mucositis, cutaneous necrosis, hepatotoxicity, pulmonary toxicity and acute renal failure.[2,3] Predisposing factors for developing MTX toxicity include acute renal failure (decreased excretion of drug), hypoalbuminemia, and concurrent use of drugs known to interact with MTX. Salicylates and 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 a dihydrofolate reductase inhibitor.[4]

CASE SERIES

This case series included 12 patients, out of which 10 patients were of psoriasis, 1 of psoriatic arthritis and 1 of DLE (discoid lupus erythematosus) and rheumatoid arthritis. These patients had presented to our tertiary care hospital in Gujarat during the period of 2017-2019. Out of 12 patients, 11 patients had history of taking oral MTX (7.5 mg) daily for one week with pain killers and 1 patient had history of taking unknown amount of oral MTX without any prior investigations.

Detailed history and examination had been recorded in all cases to reach a diagnosis of acute MTX toxicity. All patients were admitted in dermatology department and routine investigations (including hemogram and blood biochemistry) were done. MTX was immediately stopped and all patients were treated with injection leucovorin (15 mg/ml) 2cc in 100ml normal-saline per day for 10 days. Intravenous fluids were given to the patients with severe mucosal ulceration. The routine investigations were repeated every 2 days.

In our study, there were 3 female and 9 male patients. Mean age of presentation was 53.41 years. All patients showed varying degrees of oral mucosal ulceration (Figure 1), 2 patients had cutaneous necrosis overlying pre-existing lesions (Figure 2). Myelosuppresion was seen in all cases at the time of presentation. Renal function was deranged in one patient. Rest of the routine investigations were normal (Table 1).

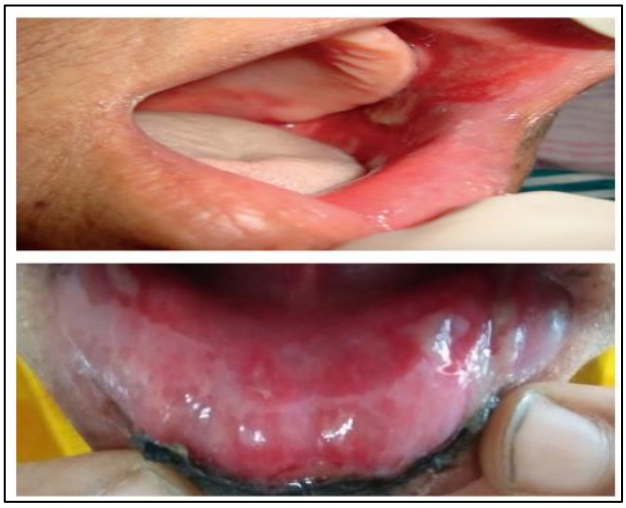

Figure 1: Varying degrees of mucosal ulceration

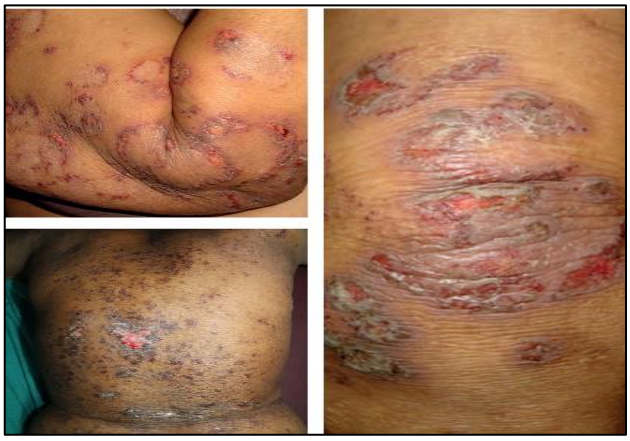

Figure 2: Varying degrees of cutaneous necrosis over psoriatic plaques.

Table 1: Haemogram and blood biochemistry of all patients.

Investigation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Hb (g/dl)	10	6.9	10.1	8.4	7.6	8.2	9.6	12.1	7.8	9.2	10.4	8.6
WBC (/mm^3)	2780	1200	3200	3600	1300	1600	3450	2200	2850	3340	1800	2000
APC (/mcl)	1,03,000	69,000	3,29,000	2,08,000	2,01,000	1,06,000	78,000	1,01,000	82,000	2,03,000	1,09,000	95,000
Bilirubin (mg/dl)	1.0	0.85	0.8	0.7	1.01	0.85	0.75	0.9	0.8	1.0	0.95	0.7
SGPT (U/L)	30	32	28	27	25	34	26	30	28	32	27	34
S. Alkph (IU/L)	132	125	142	140	135	145	128	130	138	132	144	140
S. Creat (mg/dl)	0.85	0.7	0.65	0.8	1.0	4.8	0.9	0.8	0.75	1.0	0.6	0.7
Urea (mg/dl)	20	22	25	27	28	72	24	30	26	20	28	22

After 10 days of treatment, all patients showed improvement in cutaneous and mucosal ulceration. myelosuppression improved in all patients except 2 in whom hemoglobin, total leucocyte count and platelet counts kept on decreasing. One of them showed deterioration of liver function with increased bilirubin level (8.1 mg/dl) and succumbed to acute respiratory failure on the 10th day. The second patient who had altered renal function at the time of presentation, showed further deterioration towards end of treatment. He was given platelet transfusions and taken for dialysis for two days, during which he succumbed. Rest of the patients improved clinically as well as hematologically.

DISCUSSION

MTX is approved by the FDA for moderate to severe psoriasis and for cutaneous T cell lymphomas, but it is also commonly used to treat autoimmune bullous diseases, autoimmune collagen diseases and other inflammatory dermatologic conditions.[5] The usual dose in dermatologic indications ranges from 7.5 to 25 mg once weekly. These low doses, compared to those used in oncologic indications, may also have direct anti-inflammatory effects by increasing adenosine levels via intracellular formation of MTX polyglutamates.[6]

Epidemiology of MTX adverse events

The most common adverse event is gastrointestinal intolerance, which is a mild adverse event. The most common severe adverse event is bone marrow toxicity. Psoriatic plaque ulceration is a characteristic but rare adverse event.[7] The mortality associated with the use of MTX in patients with psoriasis is low and it is mostly due to pancytopenia.[8] Although there seems to be an under-reporting of severe adverse events, data from long-term studies in psoriasis suggest that MTX is a safe drug when used at weekly low-dose regimens.[9,10]

Classification of MTX adverse events

Adverse events that have been associated with low-dose MTX can be classified into four categories: category A or dose-dependent effects, category B or idiosyncratic effects, category C or effects due to cumulative dose, and category D or delayed effects after discontinuation of the drug.[11] Category A includes mucocutaneous and gastrointestinal toxicity and eventually pancytopenia, which can also be due, however, to idiosyncratic effects (category B). Cumulative dose adverse events (category C) classically include chronic hepatic and pulmonary toxicity. Furthermore, some patients may develop pulmonary toxicity with low MTX doses, suggesting an idiosyncratic mechanism. As delayed adverse events (category D) include teratogenicity, MTX is contraindicated during pregnancy and should be avoided during lactation.[12] In this report we discuss only acute MTX toxicity, which basically includes the side effects of categories A and B.

Presenting signs/symptoms of acute MTX toxicity

The acute side effects of MTX are mainly gastrointestinal intolerance, fever, arthralgias, myalgias, bone marrow and liver toxicity, mucositis, skin ulceration, rash, vasculitis and photosensitivity.[6,13] The presence of oral mucositis, skin ulceration and pancytopenia may suggest severe acute toxicity as the drug inhibits cells with a fast turnover, such as hematopoietic, gastrointestinal and cutaneous cells, which are mitotically more active and more prone to be affected by the anti-proliferative effect of MTX.[11] Pancytopenia may occur as a dose-dependent and rarely as an idiosyncratic side effect, usually presenting within the first 10 days of treatment.[10] Mucositis usually occurs within the first 7 days of drug administration, before the onset of pancytopenia, as the accumulation of MTX is higher in mucosal epithelial cells than in bone marrow stem cells.[14] Psoriatic plaque ulcerations are painful, and it has recently been suggested that they are more frequent on acral areas.[15] Skin ulceration has also been described in patients with mycosis fungoides receiving MTX as well as in patients without skin lesions receiving MTX.[16-20] Mucositis and cutaneous ulceration are considered dose-dependent and generally precede the onset of pancytopenia, serving as possible signs of severe MTX toxicity.[7,14,21]

Risk factors for acute MTX toxicity

The most common causes of acute MTX toxicity are errors in dosing and the concomitant use of medications, especially NSAIDs.[7] However other factors are renal function impairment, pharmacokinetics, high alcohol intake, infections and advanced age. Overdose due to errors in medication (daily instead of weekly dose) was the most common cause of acute MTX toxicity in our series. This drug should therefore be avoided in people with impaired cognition, elderly patients who take several medications or who live alone, patients with linguistic difficulties and psychiatric patients.[22] Parenteral administration might be less prone to administration errors in these populations. Renal insufficiency may increase MTX toxicity as its elimination depends on glomerular filtration and tubular secretion.[23] MTX pharmacokinetics are highly variable due to factors such as genetic mutations in intestinal transporters and efflux transporters that alter the concentration of intracellular MTX polyglutamates.[24] These mechanisms do not seem to alter the clinical outcome of psoriasis but are relevant in terms of toxicity.[25] The roots cause analysis for MTX toxicity in our patients identified presence all of the above risk factors in some way or the other in our patients.

Treatment of acute MTX toxicity

MTX should be discontinued at the earliest indication for possible toxicity and aggressive measures should be implemented. As it can be life-threatening, a multidisciplinary approach is needed with preferably

hospital admission. Folinic acid is used as an antidote and adequate hydration should be ensured to increase the renal elimination of MTX.[5,6] Acute MTX toxicity is usually temporary and MTX can be reintroduced, if needed, unless contraindicated.

Ideally, the serum levels of MTX should be estimated in all cases of acute MTX toxicity to guide the course of treatment (Table 2) but due to lack of availability of facility for serum MTX measurement, most cases are managed on clinical grounds.

Table 2: Folinic acid dose calculation when serum MTX levels are available.

Timing after first MTX dose	Dose of folinic acid according to MTX plasma concentration				
	<0.2 µmol/L	**0.2-0.7 µmol/L**	**0.71-2 µmol/L**	**0.21-19.9 µmol/L**	**20-100 µmol/L**
24 hours	None	15 mg/m^2, 6 hr	15 mg/m^2, 6 hr	15 mg/m^2, 6 hr	60 mg/m^2, 6 hr
48 hours	None	15 mg/m^2, 6 hr	15 mg/m^2, 6 hr	150 mg/m^2, 6 hr	300 mg/m^2, 6 hr
72 hours	None	30 mg/m^2, 6 hr	150 mg/m^2, 6 hr	750 mg/m^2, 6 hr	3000 mg/m^2, 6 hr

For MTX levels > 100µmol/L, the dose of folinic acid can be calculated as follows

Total dose of folinic acid=Actual serum MTX level×standard daily dose of folnic acid/Upper limit of serum MTX for the actual day and time.

CONCLUSION

Although low-dose MTX appears to be a safe medication, acute MTX toxicity can be a life-threatening emergency and both dermatologists as well as physicians should be aware of the presenting signs and symptoms. Patients should be carefully selected and adequate explanations and written or graphic instructions on prescription patterns should be provided to prevent errors in drug administration. Also, careful selection of patients is prudent to avoid prescribing MTX in patients with multiple medications or with renal insufficiency.

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