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Case Report

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METHOTREXATE TOXICITY (CUTANEOUS ULCERATION) TO BE ADDRESSED CAREFULLY IN PSORIASIS TREATMENT: CASE REPORT

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ABSTRACT

Methotrexate (MTX) continues to be one of the most widely used systemic immunosuppressive agents in dermatology. In addition to the important well characterised adverse effects such as hepatotoxicity and myelosuppression, MTX may induce a number of rare cutaneous adverse reactions including MTX induced cutaneous ulceration. Here the case of MTX induced cutaneous ulceration in a patient with scalp psoriasis for which he consulted a self styled dermatologist who started him on oral 'daily medication of MTX' without any baseline investigation. Withdrawal of drug and appropriate skin care led to rapid healing of ulceration. Cutaneous ulceration typically precedes other markers of toxicity, hence early recognition, prompt cessation of MTX and appropriate treatment with folic acid may minimize the morbidity and mortality rate of MTX toxicity.

KEYWORDS: Methotrexate; Psoriasis; Cutaneous ulceration; Skin lesions.

INTRODUCTION

Methotrexate (MTX) introduced in the 1950s and continues to be one of the most widely used systemic immunosuppressive agents in dermatology.[1] MTX was introduced as anti-psoriatic agent in 1951 and approved by FDA (*Food and Drug Administration*) in 1972. Structurally similar to folic acid, MTX is irreversibly linked to dihydrofolate reductase, exerting antiproliferative activity. It induces apoptosis and increases the concentration of adenosine, resulting also in anti-inflammatory and immunoregulation action.[2]

Whilst awareness of important potential adverse events such as hepatotoxicity, myelosuppression and pulmonary fibrosis are reflected in robust guidelines for dosing and monitoring of treatment, other adverse events including cutaneous ulceration remain rarely reported and poorly characterized.[3] Cutaneous ulceration may play a crucial role as an early clinical sign of impending systemic toxicity. Although rare, it is of primary importance that dermatologists remain alert to cutaneous indicators of methotrexate toxicity.[4]

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, but it supposed to be three time a week of 2.5 mg dose. Folic acid tablets are prescribed on other non-MTX days. In India, many of patients may make an error to distinguish between MTX and folic acid tablets as they look similar in its appearance, thus may land up with acute MTX toxicity.[5]

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.[5]

Case study

A 70 year old, male obese patient with a symptom of skin lesions over trunk and B/L extremities. Detailed past history suggested that the patient had scaly lesions over scalp (scalp psoriasis) for which he consulted a self styled dermatologist who started him on oral weekly medications of methotrexate without any baseline investigation (Contraindications of Methotrexate toxicity in obese patients). Patient was apparently asymptomatic since last 15 days, and then he developed erosions over trunk which was insidious in onset and gradually progressed to involve B/L extremities (Fig. 01). Again 5 days back patient developed oral ulcers. The patient was immediately admitted to dermatology department of the hospital, and then the Patient was diagnosed as methotrexate toxicity after a systemic patient medication history interview.

Systemic and local examination reveals
Cutaneous: Multiple erosions with crusts overlying, few erosions present over B/L extremities, gluteral region, lower back and abdomen. Multiple plaques with loosely adherent silvery white scaling + over scalp.
Mucosa: Multiple + erosions over buckle mucosa.
Nail: Beaus lines present over right 4th finger nail, longitudinal ridges + over figs and forenails.
Hair: normal.
Other: CVS, CNS, RS normal.

On the first day of hospitalization, routine blood test demonstrated a marginal elevation of ESR (80 mm/hr), decrease in HB (10.6%), slight decrease in platelet count (1.45 lakhs/cmm), PCT is decreased (0.14%). Other tests like RBS (89 mg/dl), urea (26 mg%), Sr.creatinine (0.9 mg%), total bilirubin (0.4 mg/dl), conjugated bilirubin (0.2 mg/dl), unconjugated bilirubin (0.2 mg/dl), albumin (3 mg/dl), A/G ratio (1:1), SGOT (14 µ/l), SGPT (33 µ/l), ALP (68 Iu/l) are normal.

Patient suffered co-morbidities including HTN and COPD and on regular medication. Not a known case of DM/BA/PTB/ epilepsy. Multiple therapies were prescribed to the patient, mainly injection Vitcofol was given intramuscularly once a day until the day of discharge. T. Bact (Mupirocin) ointment was prescribed and it was applied on the lesions twice a day for daily. Along with these he was been prescribed with antihypertensive (Telmisartan) agents for hypertension, a combination of Clopidogrel+Atarvostatin twice a day, Tab.Deriphylline was given twice a day for breathlessness along with these nebulizers like Duolin (Salbutamol+Ipratropuim bromide) and Budecort (Budesonide) is given as the patient was known case of chronic obstructive pulmonary disease. The gastro intestinal symptoms were managed symptomatically with histamine 2 receptor blockers (H_2). Intravenous fluids dextrose 500 ml was given 8th hourly for all the days as supportive therapy. On the 2nd day of treatment the patient was started with Candid mouth paint for lesions in the oral cavity.

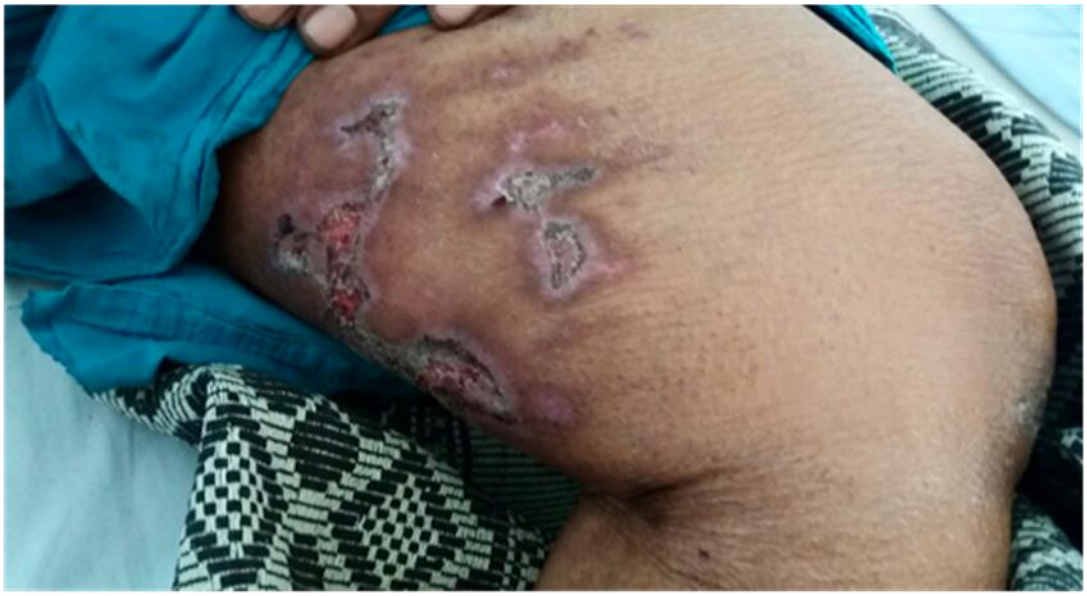

Fig. 01. Methotrexate Toxicity (Cutaneous Ulceration).

DISCUSSION
The exact mechanism of action of MTX in psoriasis vulgaris still remains unclear aside from antiproliferative and immunomodulatory actions. MTX can be administered orally, intramuscularly, or subcutaneously. It is primarily bound to serum albumin and excreted unchanged in urine. The exact mechanism of MTX induced skin ulceration is difficult to assess and also appears to be rare. In 1996 a literature review by Pearce and Wilson identified 47 cases of MTX induced skin ulceration reported between 1951 and 1967 and further 17 cases were reported between 1967 and 1996 including their own patients.[1]

Methotrexate is the mainstay of treatment for autoimmune conditions such as Rheumatoid arthritis and Psoriasis. Methotrexate has numerous side effects and, in rare circumstances, can lead to cutaneous ulceration. Stopping this medication can lead to complete healing of the ulcerated lesion. Cutaneous ulceration has been reported as a sign of Methotrexate toxicity. Even low doses of methotrexate can cause early onset pancytopenia and skin ulcers. Majority of cases of cutaneous and noncutaneous ulcers due to Methotrexate have been reported in patients with psoriasis.

Surprisingly, most of the cases of MTX induced ulceration have been reported in patients with low dose psoriasis treatments rather than those with high dose oncology regimens. Other cases where methotrexate induced skin ulceration without the history of psoriasis have been reported in patients with low dose treatment

for rheumatoid arthritis and in the patients who are undergoing treatment for fungoides and mycosis.[8] Patients with MTX toxicity may present with cutaneous lesions or with other signs of toxicity include mucositosis, liver dysfunction, and myelosupression. Early ulceration may be mistaken for flare of psoriasis and can leading to increase in MTX use either by patient or physician.

Diagnosing with biopsy is rarely required. However, methotrexate induced ulceration histological features include swollen keratinocytes with diminished cytoplasmic and nuclear staining. Dyskeratotic or vacuolated cells indicative of epidermal necrosis. Dermal changes include vascular dilation and lymphocytic infiltrates. Non specific ulceration may also be present. As with other MTX toxicity skin ulceration has described in the context of drug interaction when new medications are added to an existing methotrexate regimen. Examples include Trimethoprim, Amiadarone, Furosemide, Pencillin and NSAIDs. Other risk factors include renal impairment and diabetes mellitus.

Treatment of cutaneous lesions due to methotrexate toxicity in patients with psoriasis is mostly supportive because of these cutaneous erosions tends to heal quickly within one to two weeks of stopping or decreasing the dose of MTX. Patients recovered generally following with drawl of MTX and treatment with folic acid.

CONCLUSION

Methotrexate is an option of great therapeutic value for many conditions, and its use should be well guided by the physicians. This case illustrates the importance of recognising clinical signs of MTX toxicity and initiating therapy as soon as possible. This case also illustrates the importance of consideration of contraindications to Methotrexate toxicity and precautions in its use. Evidence of MTX toxicity includes the findings of skin lesions, histopathological findings and healing of the lesions following MTX withdrawal. Although low dose of MTX appears to be safe medication, acute MTX toxicity can be dangerous and life threatening. Awareness of possible MTX toxicity is still needed for its prevention, early diagnosis and management. Dermatologists need to be alert to the possibility of adverse reactions associated with MTX therapy, and also aware of potential drug interactions and should be confident in the management of MTX toxicity.

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