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Original Research Paper

General Medicine

AN EYE OPENER - ACUTE LOW-DOSE METHOTREXATE TOXICITY

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ABSTRACT Methotrexate is a dihydrofolate inhibitor given in both low dose 5-25mg/week in rheumatological conditions including rheumatoid arthritis, psoriasis etc and high dose 500mg/m2 i.v given in malignancies which may result in Methotrexate toxicity due to various reasons. Here we discuss a case of 70 year old male patient presented with mucocutaneous ulcerations due to accidental low dose Methotrexate toxicity.

KEYWORDS : Acute Methotrexate toxicity, Acute renal injury, oral ulcerations, skin ulcerations, leucovorin

INTRODUCTION

Methotrexate (MTX) acts by antagonizing folic acid required for deoxyribonucleic acid (DNA) synthesis of cells andinhibits mitosis of the cells. After it enters the cell, MTX inhibits dihydrofolate (DHF) reductase, which is responsible for the conversion of DHF to tetrahydrofolate (THF). Therefore, there is a reduction in thymidylate and purine biosynthesis. DNA synthesis will eventually halt 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] Salicylates and nonsteroidal anti-inflammatory 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.[2]

CASE REPORT

A 70 year male patient came with complaints of oral and buccal ulceration, difficulty of swallowing and speaking, ulceration and itching all over body, constipation for 4 days. He also had history of low grade fever for 2 days.

He is a known case of dermatitis and eczema from 15 years of age and was on topical treatment intermittently. No history of any co morbidities. Patient was prescribed Tab. folic acid 5mg OD, Tab. Methotrexate 7.5 mg once weekly and Tab. hydroxyzine 10 mg OD 1 week before. Patient accidentally took Tab Methotrexate 7.5 mg OD daily for 7 days, totally 52.5 g in 7 days.

On examination: Patient was conscious, oriented, afebrile. His vitals were BP: 120/80 mmHg, PR:80/min, CBG: 110mg/dl, RR: 18 breaths/min. Systemic examination were normal. On local examination of Oral cavity, multiple well defined erythematous erosions were present in buccal mucosa (fig: 1a) and hard palate (fig:1b). Multiple new ill-defined erosions were present on the already pre-existing dermatitic lesions (fig: 1c) (hyper pigmented skin of the dorsum of both foot, extensor aspect of bilateral hands and forearms).

Figure 1: On day of admission (day 1)

Figure:1a

Figure: 1b

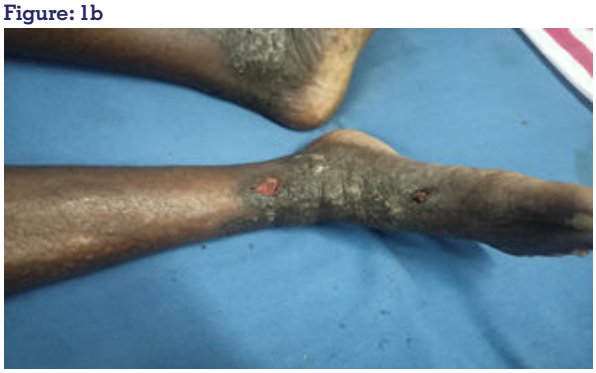

Figure: 1c

Investigations at the day of admission showed increased renal parameters: Blood urea-54 /mg/dl, Sr. creatinine-2.2 mg/dl; Complete Blood Count parameters were: Hb- 12.1gm , TC-3800 cells/mm^3, Platelet-1,98,000 cells/mm^3; Sr electrolytes showed hyponatremia of 129 mEq/L (normal value:135-145 mEq/L); LFT Parameters, urine examination, ECG, Chest X-ray revealed normal findings.

Based on clinical and laboratory findings he was provisionally diagnosed as Acute Low dose Methotrexate Toxicity / Acute Kidney Injury / Dyselectrolytemia and was treated with Inj .Leucovorin 15mg (diluted in 10ml distilled water over 5 minutes) Q 6 hourly for 4 days; i.v fluids, steroids, antibiotics, analgesics, Silver sulfadiazine (SSD) for L/A, mouth gargle [prednisolone 5ml +gelusil 5ml +Benadryl 5 ml] twice daily as advised by dermatologist.

On Day 7: Patients complaints improved; His vital were stable.

Complete blood count was normal. Renal Parameters

resolved (blood urea: 35mg/dl; sr.Creatinine: 0.8mg/dl). Review dermatology opinion was obtained and was advised to continue Steroids, SSD, Mouth gargle, analgesics and T. Folic acid 5 mg every 12 hourly.

Figure 2 : Day 7 of admission

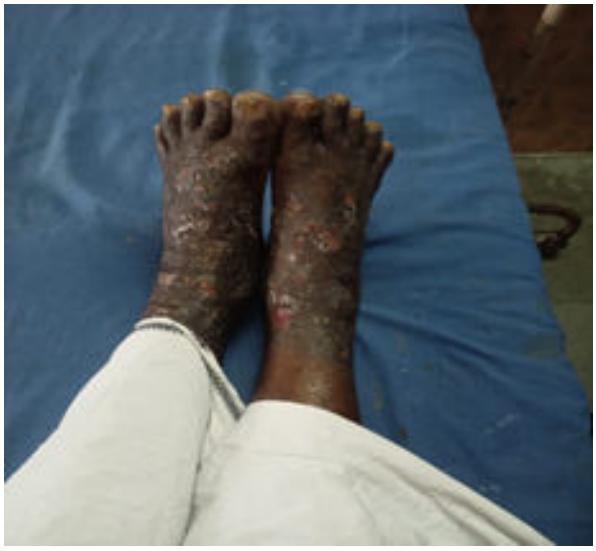

Figure: 2a

Figure: 2b

Figure: 2c

On day 9: Patients complaints improved, His vitals were stable. On Local examination: healing mucocutaneus lesions was present. Blood investigations including complete hemogram, RFT were normal.

Figure 3: Day 9 of admission

DISCUSSION

Low dose MTX rarely produces toxicity, and most of such cases occur due to failure to adhere to the recommended guidelines [3] .The ulcerations are limited to the skin lesions as they are hyperproliferative and have higher uptake of Methotrexate. Acute Methotrexate toxicity presents with mucositis (Graded according to WHO as shown in Table 1), acute renal injury, hepatotoxicity, gastrointestinal (GI), pulmonary toxicity and pancytopenia[4,5]. Methotrexate induced nephrotoxocity is due to direct tubular toxicity and crystal nephropathy[6,7]. Investigations including CBC, LFT, RFT, Sr.electrolytes, Chest x-ray, Input/ output chart, serum Methotrexate levels are measured to provide appropriate management. However Sr. Methotrexate level is not necessarily monitored for low dose Methotrexate toxicity.

Table 1: The WHO Oral Mucositis Scaling

Grade	Description
I (mild)	Oral soreness, Erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcer ,liquid diet tolerated
IV (life threatening)	Oral alimentation impossible

Leucovorin (Folinic acid) is the antidote and decreases the toxicity by increasing the intracellular storage of reduced folic acid. The dosage of IV folinic as shown below (Table 2).Since 90% is renal excretion, adequate hydration and diuresis should be maintained. Alkalinization of urine with 40–50 mEq of sodium bicarbonate per liter of IV fluid decreases the crystallization of Methotrexate and it's metabolite (2, 4-diamino-N(10)-methylpteroic acid [DAMPA]) in the renal tubules. Urine pH must be >7 and output should be approximately 2 L/m2/day until MTX levels are 0.2 □mol/L or below.[8]

Table 2: MTX plasma concentration (□mol/L) and dosages of Folinic acid

Timing After Last MTX Dose of Folinic Acid	MTX Plasma Concentration (□mol/L)				
	<0.2	0.2-0.7	0.71-2	0.21-19	20-100
24 H	NONE	15 mg/m2	15 mg/m2	15 mg/m2	60 mg/m2
		6 hourly	6 hourly	6 hourly	6 hourly
48 H	NONE	15 mg/m2	15 mg/m2	150 mg/m2	300 mg/m2
		6 hourly	6 hourly	6 hourly	3 hourly
72 H	NONE	30mg/m2	150 mg/m2	750 mg/m2	3000 mg/m2
		6 hourly	6 hourly	3 hourly	3 hourly

If serum MTX levels are more than 100 (□mol/L) the dose of folinic acid can be calculated using the formula below:

Upper limit of serum methotrexate: µmol/L.

At 24 h is 20 µmol/L.; At 48 h is 2 µmol/L; At 72 h is 0.2 µmol/L.

Total daily dose of folinic acid =Patients actual Sr. MTX x standard daily dose of folinic acid
Upper limit of serum MTX

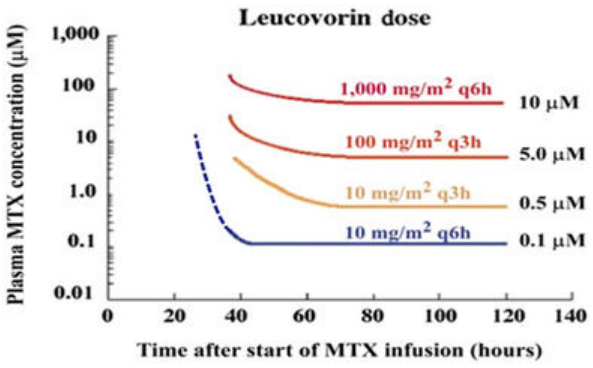

Figure: 4 Leucovorin Rescue Based on Plasma Methotrexate levels (after high-dose MTX)

Glucarpidase (carboxypeptidase, recombinant form of CPDG2 enzyme) was approved by the United States Food and Drug Administration in the treatment of plasma MTX concentrations (>1 □mol/L) in patients with delayed MTX clearance [9] . It acts by metabolizing circulating MTX to inactive metabolites Glutamate and DAMPA. It is given if serum MTX concentration ≥10 □mol/L and rise in creatinine of 100% or more .It decreases the level of Sr. MTX levels by 97% within 15 min. Each vial should be reconstituted with 1 ml NaCl 0.9% and administered I.V over 5 mins. Folinic acid and its active metabolite, are substrates for glucarpidase. Therefore folinic acid should be given 2 h before or after a dose of glucarpidase.[9]

Pancytopenia and neutropenia are high risk for infections and sepsis, hence broad spectrum non- nephrotoxic antibiotics, Packed red blood cell and platelet transfusion, Recombinant granulocyte colony-stimulating factors (G-CSFs) can be given. Oral care for mucositis is given by Pandya's formula: Mix 5 ml each of syrup prednisolone (5mg/5 ml), syrup Gelusil® and syrup Benadryl®. This mouthwash is rinsed for 2 mins; sucralfate suspension, Folinic acid mouthwash, Syrup viscous lignocaine, Oral saline rinses.

CONCLUSION:

The Methotrexate toxicity is mainly because of accidental intake due to lack of understanding and communication to the patients. Proper communication and explanation about the schedule of the drug in both verbal and written form is necessary to decrease the incidence of these cases. As Methotrexate is given once weekly and folic acid tablet on other days, In India, patients may make an error in differentiating both the drugs, resulting in Methotrexate toxicity. Proper instructions and counselling should be given to patients regarding self administration of any other drugs along with Methotrexate. Baseline investigations should be done to rule out the predisposing factors leading to Methotrexate toxicity.

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