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Volume 6 Number 1, January – June 2021

Can Granulocyte-Monocyte Colony Stimulating Factor Prevent Fatality in Methotrexate Toxicity? A Case Series with Review of Literature

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How to cite this article:
DhvaniTushar Chaudhary, Ashka D Shah, Sejal H Thakkar, Raksha M Patel,Can Granulocyte-Monocyte Colony Stimulating Factor Prevent Fatality in Methotrexate Toxicity? A Case Series with Review of Literature. RFP Journal ofDermatology 2021; 6(1):27–30.

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Abstract

Introduction: Methotrexate (MTX) is a widely used immunosuppressive drug. Though being safe, it has some non-fatal and fatal side effects. Granulocyte-monocyte colony stimulating factor (GM-CSF) a hemopoietic growth factor, is an upcoming preventive and therapeutic modality to curb harmful effects of bone marrow suppressive drugs.***Case series:*** Herein, we narrate three cases of acute MTX toxicity. Two of these presented with cutaneous ulcerative lesions while one presented with only constitutional symptoms. Two patients had derailed liver function tests while one had altered renal function tests. All showed pancytopenia.GM-CSF was given in two cases which responded well, whereas one succumbed to death before administration.***Conclusion:*** Pre-treatment and periodic monitoring; strict avoidance of self-administration are of utmost importance when patient is on MTX. GM-CSF needs exploration in MTX toxicity treatment, and could be a pivotal drug in prevention of fatality in presence of pancytopenia.

Keywords: Methotrexate; Adverse Drug Reaction; Ulceration; Pancytopenia; Self-Medication.

Key Message: Methotrexate in spite of being a safe drug can lead to fatal outcomes. Self-medication, over dosage and improper monitoring are the contributory factors. Granulocyte-Monocyte Colony Stimulating Factor has been a known treatment of pancytopenia, and its role in methotrexate toxicity needs to be explored.

Introduction

Methotrexate (MTX) has been used since long in neoplasms and rheumatoid arthritis (RA) and has been approved by FDA as an anti-psoriatic agent since 1972.[1] While this wonder drug has shown excellent results in remitting psoriasis, it does come with its share of serious life-threatening side effects.[2,3]

Granulocyte monocyte-colony stimulating factor (GM-CSF), a hemopoietic growth factor has been in limelight since a few years.[4] It allows us to increase the dose and duration of chemotherapy by reducing serious side effects. GM-CSF now is also gaining momentum as a treatment modality for bone marrow toxic/suppressive drugs.[5,6]

Herein we narrate three cases with fatal MTX toxicity and role of GM-CSF in preventing fatality.

Case Report

Three cases with fatal MTX toxicity were noted. Their clinical profiles, history, examination and significant investigatory findings have been elaborated. (Table 1)

Table 1: Details of Cases diagnosed with Methotrexate (MTX) toxicity.

Case Details	Case 1 Chronic Plaque Psoriasis	Case 2 Rheumatoid Arthritis	Case 3 Psoriatic Erythroderma
Age/Sex	40 years/Male	66 years/Male	64 years/Female
Co-morbidities	Hypertension	Hypertension	Hypertension
Patient presentation	Worsening of existing skin lesions changing into ulcerations for 3 days.	Skin Lesions scattered over body for 7 days. Difficulty in swallowing for 4 days.	Known case of psoriatic erythroderma, hospitalized for 3 weeks for the same
Drug history	Tab. MTX 5mg daily for 10 days.	Tab. MTX 15mg/week for 3 weeks.	Tab. MTX 7.5mg/week for 3 weeks.
H/O Self Medication/ Over dosage	Present	Absent	Absent
Past history	History of seasonal exacerbation of psoriasis every winter for three years. Each relapse episode was treated with Tab. MTX 15 mg per week for 6-12 weeks as and when required.	Tab. MTX was taken since 3 weeks.	Known case of Psoriasis for 7 years. Past history of Tab. MTX ingestion off and on before this episode.
Cutaneous examination	Cutaneous ulcerations of existing Psoriatic plaques all over the body. Bleeding- present. No mucosal lesions.	De novo ulcerations scattered over scalp, chest, abdomen, feet and groin. Bleeding present. Buccal mucosa-ulcerations present.	Findings suggesting psoriatic erythroderma present.
Constitutional symptoms	Absent	Absent	Fever, weakness for 2 days
Hemogram	Hb- Within Normal Range. WBC count- 2100/µL Count- 50,000/µL	Hb-8.6 g/DL WBC count- 500/µL Platelets- 22.00/µL	Hb- 7.6 g DL WBC Count-600/µL Platelet Count- 52,000/µL
LFT	T. Bilirubin- 2.4 mg/dl D. Bilirubin- 1.4mg/dl	Within Normal Range	SGOT-115 IU/L SGPT- 177 IU/L
RFT	Within Normal Range	S. Creatinine -2.1mg/dl S. BUN- 146mg/dl	Within Normal Range
S. electrolytes	Within Normal Range	S. Sodium- 132 mmol/L S.Potassium-6.1 mmol/L	Within Normal Range
Differential diagnosis	Stevens-Johnson Syndrome	Stevens-Johnson Syndrome	-
Diagnosis	MTX induced ulcerations with pancytopenia and hepatotoxicity.	MTX induced ulcerations with pancytopenia and nephrotoxicity.	MTX induced pancytopenia and hepatotoxicity.

Two cases presented with cutaneous ulceration (Figure 1a) with /without mucosal involvement and derailed lab reports while third case had only constitutional symptoms along with altered laboratory parameters. To determine level of MTX was not feasible due to financial constraints and lack of suitable laboratories.

All three patients were diagnosed with serious MTX toxicity on the basis of cutaneous lesions, pancytopenia and renal/hepatic involvement. They were managed accordingly.

Management- MTX was withdrawn in all the above cases and they were hospitalized and treated with injectable steroids, intravenous fluids, systemic broad-

spectrum antimicrobial therapy and anti-hypertensive medications. Along with this standard treatment, they were given injection leucovorin calcium 15 mg every 6 hours. Cutaneous lesions were taken care of by judicious cleaning with povidone iodine and dressing with liquid paraffin gauze pieces. For the patient with oral ulcerations, topical anesthetic gel, antiseptic gargles and antifungal mouth paint were given additionally.

Fig. 1A: Case of Psoriasis showing pre-treatment cutaneous ulcerations on pre-existing psoriatic lesions with acute methotrexate toxicity.

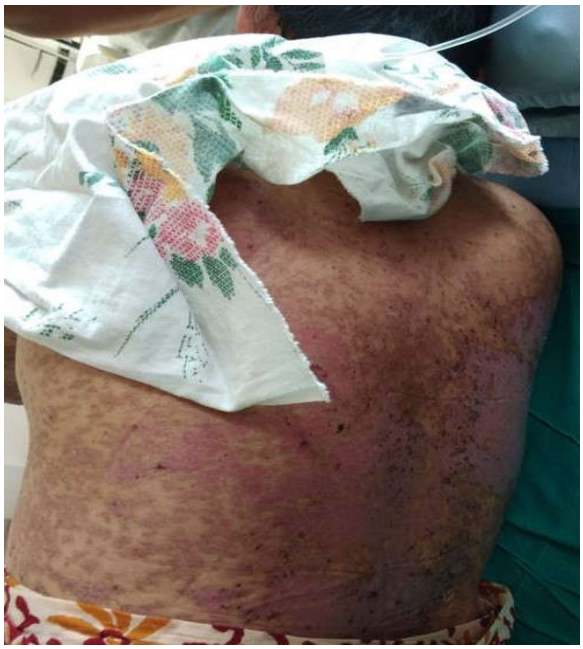

Fig. 1B: Case of Psoriasis showing healing of cutaneous ulcerations on pre-existing psoriatic lesions after treatment.

Effect of GM-CSF in preventing fatality was weighed in these patients.

Case 1 and Case 2 also received injection filgrastim (GM-CSF) at a dose of 5µg/kg/day subcutaneously until absolute neutrophil count reached 5000/µL. After 7 days of treatment both these cases had WBC count of 8600/µL and 6600/µL respectively. The ulcerative lesions started healing after 4-5 days. Ulcerative lesions of psoriasis took 16 days to heal. (Figure 1b) Ulcerative lesions of RA patient showed complete healing in 10 days. (Figure 2)

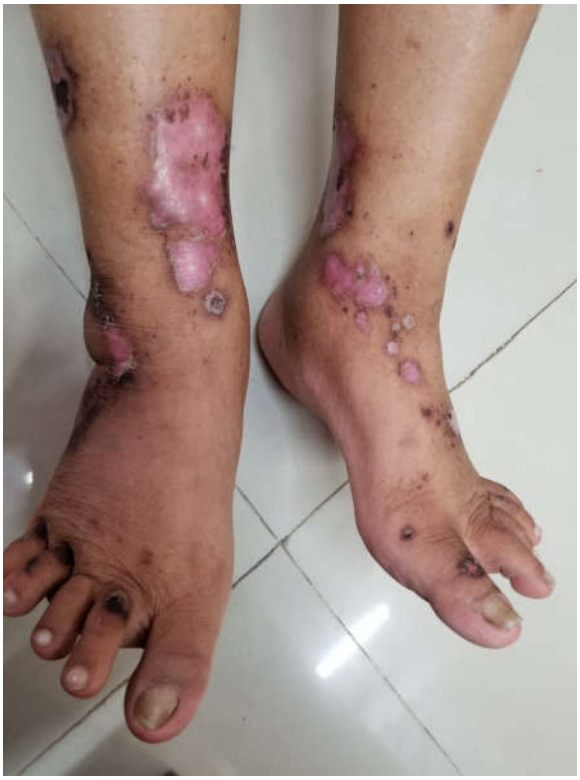

Fig. 2: Case of Rheumatoid Arthritis with acute methotrexate toxicity showing healed cutaneous ulcerations of de novo skin after treatment.

The case of psoriatic erythroderma succumbed to death on third day after diagnosis of MTX induced bone marrow suppression; before we could administer GM-CSF.

Discussion

Though MTX toxicity can present with a routine regime, it most commonly manifests due to over-dosage and self-medication.[2,3,6] As strengthened by past research self-medication along with over-dosage appears to be the tipping point in pushing this drug towards being toxic.[3,7] Case 1 presented with exacerbation of existing psoriatic lesions which was described as type 1 by Lawrence and Dahl, while case 2 was similar to type 2 where the patient showed lesions on non-psoriatic skin.[2,8] Ulceration of psoriatic plaque is comparatively a rare presentation though it was very well noted in our case and by a few others.[3] One of our patients presented with constitutional symptoms and pancytopenia without cutaneous ulcerations. Hence, toxicity cannot be ruled out in absence of obvious ulcerations.[6] All the cases in our report showed significant hematological

alterations specially pancytopenia as reported by others too.[9]

GM-CSF in MTX toxicity

GM-CSF has been studied in curbing the restrictive side effects of chemotherapy. It acts on progenitor cells and helps in hematological recovery. GM-CSF has an added beneficial effect when given with other drugs like leucovorin calcium.[4]

Treatment of choice for MTX induced bone marrow suppression is leucovorin calcium (folinic acid) which is administered orally or intravenously every 6 hours.[10]

Using GM-CSF and leucovorin calcium together were seen to have faster recovery of bone marrow suppression as was seen in the study by Kam et al where, pancytopenia could be reversed within 2-3 days of treatment.[6]

Two of our cases received GM-CSF and were revived from MTX toxicity. The patient, who did not receive GM-CSF, could not survive.

Conclusion

MTX must be monitored vigilantly for adverse reactions like cutaneous and mucosal ulcerations despite being safe. Fatal MTX toxicity can present even without cutaneous ulceration. There is crucial role of pre-treatment laboratory investigations as well as periodical monitoring when patient is on MTX therapy. Self-administration of MTX should always be discouraged with proper counseling.

Early administration of GM-CSF plays an important role in reviving the patients from MTX toxicity. In spite of being costly, it is a safe lifesaving treatment for acute MTX toxicity.

Acknowledgment: None

Conflict of interest: None

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