

# A Case Report on Methotrexate Overdose Induced Pancytopenia and Mucocutaneous Ulcerations

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## ABSTRACT

Methotrexate (MTX) is commonly used in autoimmune conditions including rheumatoid arthritis, psoriasis, lupus, sarcoidosis and eczema due to its anti-inflammatory and immunosuppressive effect. The following report describes the case of a 55 year old female presenting with complaints of erythematous rashes over the limbs, oral and vaginal haemorrhagic mucositis. She was previously diagnosed with psoriasis and was on MTX 15mg weekly but the patient had taken it continuously resulting in toxicity. She was hospitalised, MTX withdrawn and treated with folic acid. Our case highlights the importance of counselling in order to ensure adherence to the correct MTX treatment regimen to prevent toxicity and its serious effects.

**Key words:** Methotrexate, Overdose, Psoriasis, Pancytopenia, Mucositis.

## INTRODUCTION

MTX is a folic acid antagonist, widely used in cancer therapy and several chronic inflammatory diseases because of its anti-inflammatory and immunosuppressive effects.<sup>1</sup> In lower doses MTX has been used in autoimmune diseases including rheumatoid arthritis, psoriasis, lupus, sarcoidosis and eczema.<sup>2</sup> It interferes with cellular proliferation thereby predominantly impacts cells with highest turnover or reduced half-life. Thus high doses can cause microsites, cytopenias with increased risk of bleeding, infections and macrocytic erythrocytes.<sup>3</sup>

Approximately, 78% of psoriasis patients treated with MTX develops adverse drug reaction (ADR). The commonest adverse reactions are nausea and vomiting; the other side effects include urticarial, pruritus, reversible alopecia, ecchymosis and in severe cases mucosal erosions, reactivation of phototoxic responses, acute ulcerations of psoriatic plaques and toxic epidermal necrolysis. Although leucopenia and thrombocytopenia can occur at any

stage of treatment, myelosuppression is a serious complication of MTX therapy. It has been shown that 1.4% of patients develop pancytopenia when treated with low dose MTX. To prevent adverse effects on the hematopoietic system and lessen hepatotoxicity, folic acid should be supplemented in patients on MTX therapy. Daily accidental ingestion instead of weekly dose is a common cause of acute MTX toxicity.<sup>4,5</sup> Here we report a 55 years old female patient of psoriasis who had developed pancytopenia and mucositis after daily intake of MTX.

## CASE REPORT

A 55 year old female patient with psoriasis had complaints of erythematous rashes over the limbs oral cavity and vaginal microsites with bleeding manifestations. She is a known case of psoriasis and she had wrongly taken MTX 15mg for 15 days consecutively. She also had history of parrot bite 14 days ago, consulted elsewhere and had received tab doxycycline. There after she noticed some rashes, when she consulted her physician again was advised amoxicillin plus clavulanic

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acid twice daily for 5 days; but she discontinued the antibiotics as she attributed the worsening erythematous rash to the antibiotics.

On the day of admission patient was conscious, oriented and her BP was 110/80mmhg. Oral cavity examination showed ulcerated reddish mucosa with bleeding, genital examination revealed reddish inflamed labial and vaginal mucosa with per vaginal bleeding; also reddish black lesions were present over both the upper and lower limbs (Figure 1 and 2). She was advised to stop MTX. Blood counts and peripheral blood smear were suggestive of pancytopenia [total leucocyte count (TLC) of 2300/uL, Hb- 10.3 g/dl, PCV -33.3% and platelet count of 96000/uL]. Her liver functions tests (LFT) showed mildly elevated liver enzymes. Renal function tests were normal. Urine routine showed pus cells and bacteria. Urine, blood and wound swab culture sent before antibiotics administration were sterile. Testing for HIV, Hepatitis B and hepatitis C viruses were negative. Ultrasound abdomen showed grade 1 fatty liver, no splenomegaly. Dermatologist opinion sought was advised local applicants.

Keeping with the history, clinical presentation of mucocutaneous lesions with pancytopenia and elevated liver enzymes, MTX toxicity was suspected. Patient was treated with intravenous broad spectrum antibiotics (piperacillin/tazobactam), analgesics and antacids, anti-histamines, intravenous fluids, multivitamins and potassium supplements, oral anti-viral and local applicants liquid paraffin, fucidic ointment and oral hygiene with chlorhexidine mouth wash and local lignocaine use. Rheumatologist and Haematologist consulted and patient was given injection Folinic acid 15mg qid for 3 days and granulocyte colony stimulating factor (G-CSF) 300MU/day subcutaneously till the TLC increased above 4000/cumm. Bone marrow examination showed hyper cellular

marrow, immature platelets. On 4<sup>th</sup> day, there was a significant drop in platelet with bleeding manifestation hence the patient was shifted to MICU and one pint of single donor platelet was transfused. After consulting the Rheumatologist and Haematologist, injection Romiplostim 180µg (3µg/kg) single dose was given subcutaneously. On day 6, patient's blood counts and LFT gradually improved, also the bleeding was controlled; there after she was monitored in the ward. She showed good improvement, the skin lesions were better and mucosal bleeding subsided. She was discharged on day 12 with follow up for psoriasis with the Dermatologist.

## DISCUSSION

Methotrexate in low weekly doses is a first-line therapy for inflammatory diseases such as moderate to severe psoriasis and rheumatoid arthritis due to its effectiveness, low cost and ease of use. It is generally administered at doses ranging from 7.5-25mg/week.<sup>6,7</sup> However, several adverse events such as pancytopenia, pneumonitis, mucositis and cutaneous ulcerations may develop.<sup>8</sup> Cutaneous ulcerations being rarely reported and poorly characterised, play a crucial role as an early signifier of impending systemic overdose and pancytopenia.<sup>9</sup>

Pancytopenia is a rare systemic complication of MTX therapy. It is mostly seen in patients with risk factors such as daily MTX dosing, dehydration, hypoalbuminemia, renal failure, high mean corpuscular volume, low folic acid level, lack of folic acid supplementation, advanced age, infection and polypharmacy. Prolonged exposure of drug has more toxic effects on the tissues rather than the peak level of the drug achieved at one time. In our case daily intake of MTX instead of weekly, lack of folic acid supplementation and concomitant antibiotics use possibly resulted in toxicity.



**Figure 1: Oral mucosal inflammation with ulceration and bleeding.**



**Figure 2: Erythematous lesions over the limb with scaling and ulceration.**

MTX induced haematological toxicity can be managed by stopping the drug followed by supportive treatment to give adequate hydration, intravenous leucovorin, recombinant growth factors, transfusion of blood and its components along with antibiotic and antifungal coverage due to high risk of infection. The maintenance of dental care, mucocutaneous and rectal hygiene is also essential. In our patient MTX was stopped and was started on intravenous folic acid 6 hr. Additionally, G-CSF was given in view of worsening leucopenia. The severe thrombocytopenia and haemorrhage was treated with platelet transfusion and injection Romiplostim. Rumi *et al.* in their studies reported patients who were managed similarly.<sup>10</sup> The serum MTX levels are not good indicators of cellular toxicity as it is retained in a polyglutamated form in the cells.<sup>11</sup> Hence rescue measure should be initiated as soon as toxicity is suspected irrespective of the blood MTX levels. In our patient the blood MTX level was not high but the clinical features were pointing towards MTX toxicity and patient responded well to treatment. Poor understanding of the disease, drug interactions and non-adherence to treatment regimen can lead to serious complications including death. Pradhan S *et al.* in their case series highlight the significance of patient education regarding the disease, dosing schedule and the possible risks of toxicity with high or daily dosing of MTX. Also, the primary care physicians should be aware of the various attributing factors for toxicity as majority of them are preventable by regular monitoring and appropriate guidance.<sup>12</sup>

## CONCLUSION

MTX toxicity is rare with low dose, correct dose scheduling and adherence to the recommended guidelines. Therefore detailed counselling regarding the course of disease, dosing schedule and consequences of MTX overdosing is mandatory for all patients receiving MTX therapy to reduce possible side effects and unnecessary medical expenses.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest

## ABBREVIATIONS

**MTX:** Methotrexate; **ADR:** Adverse Drug Reaction; **G-CSF:** Granulocyte Colony Stimulating Factor; **TLC:** Total Leukocyte Count; **LFT:** Liver Function Test.

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