

Iatrogenic Methotrexate Toxicity Leading to Acute Oral Mucositis: A Rare Case Report

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ABSTRACT

Methotrexate (MTX) is a folate antagonist extensively employed in oral metronomic chemotherapy and the management of various autoimmune disorders. Despite its established therapeutic efficacy, its narrow therapeutic index predisposes patients to severe adverse effects following dosing errors or inappropriate administration. Oral mucositis represents one of the most debilitating manifestations of MTX toxicity and may be accompanied by significant haematological and cutaneous complications. This report describes a rare case of iatrogenic MTX toxicity in a 56-year-old male who inadvertently consumed MTX 7.5 mg daily instead of the prescribed mirtazapine for 10 consecutive days. The patient presented with extensive painful pan-oral ulcerations, purulent discharge, haemorrhagic crusting of the lips, de-papillated erythematous tongue, restricted mouth opening, and multiple necrotic cutaneous lesions involving the extremities and trunk. Haematological evaluation revealed severe anaemia, while peripheral blood smear, exfoliative cytology, and histopathological examination demonstrated features consistent with MTX-induced cytotoxic mucosal injury accompanied by chronic inflammatory cell infiltration. Following prompt recognition of the medication error, MTX was discontinued and supportive management comprising folic acid supplementation, haematinic therapy, topical corticosteroids and anti-inflammatory oral rinses was instituted. Progressive clinical improvement was observed within two weeks, culminating in complete resolution of oral and cutaneous lesions with normalisation of haematological parameters at two months. The present case highlights the potential for severe mucocutaneous and haematological toxicity even with short-term inadvertent exposure to low-dose MTX. Furthermore, it underscores the critical importance of medication reconciliation, patient education, attentive clinical observation and early recognition of oral manifestations to prevent avoidable iatrogenic morbidity and improve medical safety.

Keywords: Anti-metabolite, Drug toxicity, Folic acid, Medication error, Oral ulcer

CASE REPORT

A 56-year-old male patient visited the Oral and Maxillofacial Pathology OutPatient Department (OPD) with chief complaint of painful ulceration, pus discharge with pan-oral involvement and unable to eat since last seven days. He was suffering from neuropsychiatric disorder and was under medical supervision since last two years and no other significant systemic comorbidity was reported. His neuro psychiatrist prescribed three medications, Risperidone 10 mg (escitalopram oxalate), Lorazepam 2 mg (lorazepam), Mirtazapine 7.5 mg (mirtazapine) and this information was shared by him with documentation. Upon verification of the prescription and dispensed medication strips, it was revealed that, MTX 7.5 mg had been inadvertently dispensed by the pharmacist in place of the prescribed Mirtazapine 7.5 mg, likely due to similarity in generic names and dosage strengths, resulting in daily consumption of MTX for ten consecutive days. The discrepancy remained undetected because the patient and his family members were unable to verify the medication labels due to language barrier. His intra-oral findings included large ulcerated lesions involving bilaterally buccal and labial mucosa, commissure of the mouth multiple denuded areas with superficial sloughing with purulent discharge also found over the same region, crusting with areas of haemorrhage over both upper and lower labial mucosa, with pale lips and associated with tenderness and reduced mouth opening. Tongue appeared as depapillated, beefy red. According to the World Health Organization (WHO) Oral Mucositis Toxicity Scale, the condition was graded as Grade 3 mucositis, characterised by oral ulcers with extensive erythema, with the patient unable to swallow solid food and restricted to a liquid diet [1]. On examination, skin lesions were also found as hyperpigmented patches with centrally brownish necrotising crusty area in upper arm, elbow, calf, heel and upper chest [Table/Fig-1a-g]. After investigating routine haematological values, maximum parameters were within reference range, but few investigations yielded abnormal findings. Though haematological



[Table/Fig-1]: Pre-treatment clinical photographs of the patient on the day of his first visit to OPD: a) Extraoral photograph of the patient showing crusting with areas of haemorrhage over both labial mucosa with pale lips; b) Intraoral photograph of the patient showing ulcerated lesions involving bilateral buccal mucosa, bilateral labial mucosa, multiple denuded areas with superficial sloughing; c) Intraoral photograph of the patient showing ulceration in the commissure of the mouth and de-papillated, beefy red tongue with restricted mouth opening; d) Hyperpigmented patch with centrally brownish necrotising crusty area in upper arm noted; e) Skin manifestation showing small hyperpigmented patch over his upper chest area; f&g) Similar skin lesion over his elbow, calf and heel (All skin lesions are marked with black circle).

evaluation revealed severe anaemia; however, platelet count was within normal physiologic limits [Table/Fig-2]. General physical examination revealed he was moderately built and nourished, body weight and body mass index within normal limits for age. All vital parameters were within regular limits. Baseline biochemical investigations demonstrated normal renal and hepatic function levels [Table/Fig-2]. No other pre-existing nutritional deficiency, haematological disorder, individual susceptibility was identified at the time of the primary examination.

Based on the clinical appearance of the patient differential diagnoses including erythema multiforme, Stevens–Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and oral vesiculobullous disorders were considered because of the extensive painful oral ulcerations

Test description	Pre-treatment result	Post-treatment result
Haemoglobin (gm/dL)	6	13
Red blood cell count (million/cu mm)	2	5.66
Total leucocyte count (/cu mm)	5,400	5,700
Platelet count (lac/cu mm)	1.85	1.92
ESR (mm)	96/1 st hour	07/1 st hour
Total bilirubin (mg/dL)	0.7	0.34
Globulin (gm/dL)	2.1	2.3
Alkaline phosphatase (U/L)	87	91
Serum urea (mg/dL)	26	22
Serum creatinine (mg/dL)	1.19	0.89

[Table/Fig-2]: Comparative distribution of the laboratory investigated parameters of the patient in pre and post-treatment time.

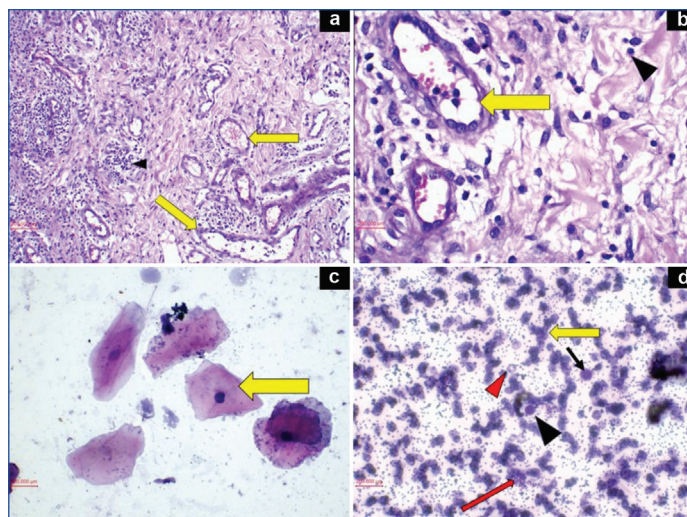
and mucosal sloughing. Erythema multiforme was ruled out due to the absence of characteristic target lesions, and a preceding history of infection or drug trigger typically associated with the condition. SJS and TEN were excluded owing to the lack of widespread cutaneous involvement including eye and genital mucosa, epidermal detachment, and a positive Nikolsky sign. Oral vesiculobullous disorders were ruled out based on the acute onset of lesions following inadvertent MTX administration, absence of preceding vesicles or bullae, and lack of characteristic histopathological or immunological findings. The clear temporal association with MTX overdose, accompanying haematological abnormalities, and prompt clinical improvement after drug withdrawal supported the diagnosis of MTX-induced oral mucositis.

To corroborate clinical diagnosis, few diagnostic procedures were performed (peripheral blood smear, scrape cytology and incisional biopsy from representative site). Leishman-stained blood smear revealed multiple reticulocytes in rouleaux formation, less erythrocytes, few White Blood Cells (WBCs). Papanicolaou (PAP) stained smear showed scattered clumps of desquamated cells with prominent nucleus and non-specific inflammatory cell infiltrate in the background. Haematoxylin & Eosin (H&E) stained histopathological section demonstrated discontinuous atrophic epithelium, flattened rete ridges, dense infiltrate of chronic inflammatory cells and numerous proliferative blood vessels engorged with RBCs [Table/Fig-3a-d].

For treatment the offending drug was immediately suspended. Patient was prescribed haematinic for four months, with a combination of 100 mg elemental iron and 1.5 mg folic acid, administered twice daily, prescribed to compensate for RBC breakdown. Another 5 mg folic acid supplement was advised twice daily so that daily therapeutic dosage of it would maintain. Triamcinolone (0.1% w/w) gel was advised for local application. Anti-inflammatory mouth rinse containing benzydamine 0.15% w/v was advised to alleviate patient discomfort. Patient was recalled after 15 days for the first follow-up and after two months for the second follow-up. First follow-up presentation showed regressing ulcer, no crusting, reestablished normal mouth opening. Second follow-up revealed no further sign of ulceration, healing mucosal barrier, papillary regrowth in tongue and ability to have regular diet. All his previous skin patches have been healed with depigmentation [Table/Fig-4a-f]. Routine haematological and biochemical tests were reinvestigated on the second follow-up to rule out hepatotoxicity; all values were within normal range comparing previous values [Table/Fig-2].

DISCUSSION

Mucositis is the inflammation and ulceration of the mucous membranes involving gastro-intestinal tract. Patients over 50 years of age are prone to suffer from mucositis because of insufficient Deoxyribonucleic Acid (DNA) repair. Salient factors for mucositis are nutritional deficiencies, poor oral hygiene, certain medications, pre-existing conditions, chemotherapy, and radiation therapy.



[Table/Fig-3]: Photomicrographs of all operative procedures: a) 10X magnification view of H&E stained histopathological section showing connective tissue stroma with dense infiltrate of chronic inflammatory cells (black arrowheads) and numerous proliferative blood vessels (yellow block arrows); b) 40X magnification view of H&E stained histopathological section of connective tissue stroma showing non-specific chronic inflammatory cells (black arrowheads) and multiple proliferative blood vessels with plump endothelial cells and engorged with RBCs (yellow block arrows); c) 40X magnification view of PAP stained cytologic section showing scattered clumps of desquamated cells with prominent nucleus (yellow block arrows); d) 10X magnification view of Leishman stained peripheral blood smear showing multiple reticulocytes in rouleaux formation (yellow block arrows), erythrocytes (red arrowheads), neutrophil (black arrow), lymphocyte (black arrowhead), platelets (red block arrows).



[Table/Fig-4]: Post-treatment clinical photographs of the patient on follow-up day: a) Extraoral photograph of the patient showing normal facial appearance; b) Intraoral photograph of the patient showing healing mucosal barrier, no sign of further ulceration; c) Papillary regrowth on the tongue and patient can open his mouth to maximum extent; d-f) All skin lesions are healed with depigmentation shown in upper arm, upper chest and heel area (black arrows marked).

Cytotoxic drugs associated with severe mucositis are MTX (high-dose), Etoposide, and Melphalan. Methotrexate (MTX) is an anti-metabolite drug commonly administered during chemotherapy and as an immunosuppressant for autoimmune diseases. According to WHO, oral mucositis has been graded into Grade-1 to Grade-4 [1]. In International Classification of Diseases-10 (ICD-10), K12.3 is the code for oral mucositis (ulcerative), which refers to inflammation of the oral mucous membrane, often with ulcer formation. Changes in the oral environment result in oral microbiota dysbiosis, which can cross through the damaged and ulcerated mucosa, interacting with immune cells and enhancing inflammatory responses. Folic acid, a synthetic, oxidised, water-soluble form of folate used therapeutically, was prescribed as part of the supportive management following MTX discontinuation. Although leucovorin (folinic acid) is the standard rescue therapy for MTX toxicity [2], supportive folic acid supplementation was administered in the present case based on clinical judgment, with subsequent complete clinical recovery. MTX induces DNA damage and causes the release of reactive oxygen species, leading to epithelial cell death. Oral ulcer occurs in 11-17% patients receiving low doses of MTX [3]. A systematic review reported a mean healing time of 19.9 days (approximately three weeks) following MTX discontinuation, with most studies

Parameters	Aadithya et al., (2024) [13]	Kumar RR et al., (2021) [14]	Smedra A et al., (2023) [15]	Quan Soon KL et al., (2024) [16]	Present case
Patient age/sex	67-year-old male with psoriasis	74-year-old male patient	Case series (paediatric patients)	54-year-old female	56-year-old male
Cause of toxicity	Accidental daily intake instead of weekly dosing	Iatrogenic overdose due to medication error	Medication-related overdose	Inadvertent Methotrexate (MTX) exposure	Dispensing error resulting in accidental substitution of MTX for mirtazapine
MTX exposure	Low-dose MTX	Low-dose MTX	Low-dose MTX	Low-dose MTX	7.5 mg daily for 10 consecutive days
Primary intra-oral findings	Severe oral mucositis	Extensive oral ulceration	Oral mucositis	Oral mucositis with ulceration	Grade 3 pan-oral mucositis with purulent ulcerations, haemorrhagic lip crusting, de-papillated tongue
Cutaneous manifestations	Ulceration of psoriatic plaques	Present	Present	Mucocutaneous lesions	Multiple necrotic cutaneous lesions over extremities and trunk
Haematological abnormalities	Bone marrow suppression (anaemia, leukopenia, thrombocytopenia)	Pancytopenia	Myelosuppression	Pancytopenia with hepatotoxicity	Severe anaemia without leukopenia or thrombocytopenia
Liver/Renal involvement	Not significant	Variable	Variable	Hepatotoxicity reported	Renal and hepatic function remained normal
Management	MTX withdrawal, folinic acid, supportive care	MTX withdrawal, leucovorin, supportive therapy	MTX withdrawal, folinic acid, supportive care	MTX withdrawal, folinic acid, G-CSF, antibiotics, blood products	MTX withdrawal, high-dose folic acid, haematinic therapy, topical corticosteroid, benzydamine mouth rinse, supportive care
Clinical outcome	Complete recovery	Favourable recovery	Recovery in all cases	Complete recovery	Marked improvement within 15 days with complete oral, cutaneous, and haematological recovery at 2 months

[Table/Fig-5]: Comparison of the present case with previously reported cases of low-dose methotrexate toxicity [13-16].

describing complete resolution of oral lesions within three weeks [3]. Oral mucositis pathophysiology is a complex multifactorial process involving direct and indirect injury pathways including DNA damage, oxidative stress, inflammatory responses, and bacterial translocation. The ulceration stage is very painful, since the protective barrier that covers the nerve endings at the lamina propria is lost. The resulting micro-coagulation and neutropenic state facilitate the Gram-negative bacteria and yeast colonisation with the production of secondary infection. Bacterial exotoxins aggravate the inflammatory reaction by inducing mononuclear burst with the release of more IL-1 β , TNF- α , and nitric oxide. Ulcerative oral mucositis was related to *Porphyromonas gingivalis*, *Candida glabrata*, and *Candida kefir* [4]. MTX is an antifolate antimetabolite widely used as a chemotherapeutic agent and immunosuppressant in the management of rheumatoid arthritis, refractory psoriasis, and several malignancies [5]. The drug is taken up into the cell by human reduced folate carriers (SLC19A1) and forms MTX-polyglutamate. This MTX-polyglutamate inhibit the enzyme dihydrofolate reductase, which catalyses the conversion of dihydrofolate into tetrahydrofolate, the active form of folic acid. Tetrahydrofolate is necessary to synthesise the nucleotides of both DNA and Ribonucleic Acid (RNA). MTX-polyglutamate also inhibits thymidylate synthase and purine synthesis, thereby preventing DNA synthesis. These separate actions combine to produce a cytotoxic effect, which is the primary reason MTX is prescribed as a cancer treatment [6,7]. Risk predictor genes for MTX- induced mucositis are MTX efflux transporter gene (ABCB1, ABCC4) and MTX influx transporter gene (SLC19A1, SLC01B1) [8]. Typically, MTX is started at a dose of 7.5–15 mg once weekly, and depending on the clinical response, it is gradually increased to the maximum tolerable and effective amount [9]. Adverse effects include hepatotoxicity, low WBCs, gastrointestinal bleeding, pancreatitis, bone marrow suppression, mucosal ulcers. The three primary treatments for MTX toxicity are folinic acid (leucovorin), thymidine, and glucarpidase [10,11]. Folinic acid is a naturally occurring reduced form of folic acid. Folinic acid is compounded with calcium in the form of leucovorin calcium and can be administered intramuscularly, intravenously or orally. After the initiation of MTX therapy, follow-up testing should include cell count, renal function, and liver function monitoring, which are recommended weekly for four weeks and then at least bi-monthly [12].

Several studies have reported severe MTX toxicity following low-dose administration due to dosing or dispensing errors. Aadithya

et al., described oral mucositis with bone marrow suppression, while Kumar RR et al., and Smedra A et al., highlighted the serious consequences of medication-related overdoses. Similarly, Quan Soon KL et al., reported mucocutaneous and haematological toxicity following inadvertent MTX exposure. In all cases, prompt drug withdrawal and supportive therapy resulted in favourable outcomes. The present case shares similar features with these reports and recovery following cessation of MTX and supportive therapy. However, the current case is distinctive because toxicity developed after accidental daily consumption of MTX [Table/Fig-5] [13-16].

CONCLUSION(S)

This case highlights that even short-term inadvertent exposure to low-dose MTX can result in severe oral mucositis and significant haematological toxicity due to medication dispensing errors. Oral ulceration may represent the earliest and most prominent clinical manifestation, underscoring the pivotal role of dentists in the timely recognition of MTX toxicity. Prompt identification of the offending drug, immediate discontinuation, and appropriate supportive management can result in complete clinical recovery and prevent potentially life-threatening complications. This report also emphasises the importance of meticulous medication reconciliation, pharmacist vigilance, and comprehensive patient education regarding the once-weekly dosing schedule of MTX. Strengthening multidisciplinary communication and medication safety practices is essential to minimise preventable iatrogenic adverse events and improve patient outcomes.

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