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## Methotrexate-Induced Mucositis Due to Accidental Overdose; a Case Report

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### ABSTRACT:

Methotrexate (MTX) is a major drug used in the treatment of rheumatoid arthritis (RA). Methotrexate can cause adverse effects such as mucositis, interstitial lung disease (ILD), infections, hepatotoxicity, and myelosuppression, even though it is useful for the treatment of rheumatoid arthritis. One well-known pernicious effect of methotrexate is dose-related mucositis. This study describes a 71-year-old female patient with Rheumatoid Arthritis (RA) who developed methotrexate-induced mucositis as a result of an unintentional overdose. Over the past week, she has developed subtle, progressive mouth ulcers and odynophagia. Early indications of bone marrow suppression were confirmed by her initial laboratory tests. Leucovorin calcium 50 mg was given to reduce the toxic effects of MTX, like bone marrow suppression. Benzydamine mouth wash was given to treat mouth ulcers. The patient, who was hospitalized for four days, was discharged with improved health and healed oral ulcerations. The MTX overdose was caused by taking a daily dose instead of a weekly dose. Thus, it is imperative to provide precise dosage guidelines and emphasize the vital function of folic acid in avoiding MTX toxicity.

**Keywords:** Methotrexate, Rheumatoid Arthritis, Mucositis, Overdose.

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## 1. Introduction

Methotrexate (MTX) is a folate antagonist that was initially created to treat cancers (Farber *et al.*, 1956). It has since been utilized as an immunosuppressive and/or anti-inflammatory medicine to treat non-neoplastic conditions.<sup>[1]</sup> Currently, MTX is the first-line disease-modifying anti-rheumatic drugs (DMARDs) for the management of RA (1985). In order to optimize therapeutic outcomes, MTX can be used as an anchor medication in patients who do not react to other DMARDs, as well as a first-line monotherapy in patients who have not responded to other DMARDs.<sup>[2]</sup> The recommended starting dose for RA using oral MTX is between 7.5 to 30 mg/week; however, due to pharmacokinetic variability and varying disease severity, each patient's optimal dose will be different.<sup>[3]</sup> After taking it orally, MTX reaches its highest blood levels in about an hour, and approximately fifty percent is protein-bound to serum albumin. MTX is found throughout extravascular tissue, parts including the liver, kidneys, and synovial fluid. MTX is changed into MTX-polyglutamates inside of cells, which have an increased intracellular half-life and are both more powerful and maintained by the cell membrane.<sup>[4]</sup> It is suggested that Folic acid supplements should be prescribed on a regular basis for all patients receiving MTX during their treatment of RA. There is not much evidence comparing the relative benefits of weekly versus daily folic acid consumption, although oral treatment with 5 mg once a week may be sufficient.<sup>[5]</sup> One issue with methotrexate use is the possibility of severe side effects. The toxicity of MTX can be increased by a number of variables, such as advanced age, concurrent usage with other drugs, and renal impairment.<sup>[6]</sup> It affects areas including bone marrow and the gastrointestinal tract that have high rates of cell growth. Between 11 - 17 % of patients receiving low doses of methotrexate reported developing oral ulcers.<sup>[7]</sup> Due to the high rate of tissue turnover in the gastrointestinal tract and mucosa, which makes these tissues particularly vulnerable to chemotherapeutic drugs, mucositis may be an early indicator of MTX toxicity.<sup>[4][7]</sup> It is possible to cure and reverse MTX toxicity by substituting folinic acid (leucovorin) or folate.<sup>[8][9]</sup> Lack of folic acid supplementation or overdosage as a result of unclear once-weekly regimen could be the cause of mucositis.<sup>[9]</sup>

This case study describes a 71-year-old female patient who had MTX-induced mucositis and how her lesion completely resolved after treatment. In this case study, overdosage from unclear instructions on its once-weekly regimen may be the cause of mucositis.

## Case Presentation

A 71-year-old woman was referred for the evaluation of odynophagia and insidious, progressive ulcers in her mouth over the past week. She had complaints of dysuria and lower abdominal pain for 4 days. During the clinical examination, ulcerations were discovered in the lower lip and lateral area of the mouth. Her medical history included vertigo, orthopnea, and occasional chest pain. She also had a history of head trauma following a fall, after which she reported associated pain in her left hip. Her daily medications were Hydroxychloroquine 300 mg, and Levothyroxine 25 mcg. She was taking MTX 15mg once a week. She did not report any allergies. Because of newly onset cytopenia and mucositis, the possibility of MTX toxicity was suspected and further interrogation revealed that MTX was consumed daily instead of weekly. Due to the patient's impaired general condition and for the supervision of potential lethal bone marrow suppression, she was hospitalized. Upon hospitalization, her vital signs included a blood pressure of 120/70 mmHg, a respiratory rate of 22/min, and a pulse of 78/min. Her initial laboratory testing confirmed early signs of bone marrow suppression (white blood cell count: 3,400 cells/cumm, platelets: 55,000 cells/cumm, red blood cell count: 2.49 million/cumm) with haematocrit and haemoglobin falling way below the normal level (Haematocrit: 22.8 %, Hb: 7.9 gm/dL). Her ESR was recorded as 60 mm/hr. A high dose folic acid supplement in the form of Leucovorin Calcium 50 mg was given to

prevent harmful effect of MTX, along with that Benzylamine gargle was given to reduce the inflammation. Inj. Esomeprazole 40 mg, Analgesics (Paracetamol 1 g, IV; Diclofenac gel) were given for comfort, antibiotic (Ticarcillin 3.1 g, IV) was administered intravenously to provide empiric coverage against the risk of invasive bacterial infection and Corticosteroid (Hydrocortisone injection 100mg, IV) to alleviate MTX-related side effects. The patient remained hospitalized for 4 days. The patient was discharged with improved general health and healed oral ulcerations. Esomeprazole PO 40 mg, Syrup Sucralfate PO 10 mL, Folic Acid PO, Sodium Bicarbonate PO 500 mg, and Choline Salicylate Gel were given as discharged medications.

## 2. Discussion

MTX is usually prescribed to treat chronic inflammatory diseases at a weekly dosage of 5 to 25 mg.<sup>[10]</sup> The prescribed dose for this patient was 15 mg. Most commonly reported adverse responses to methotrexate include myelosuppression and mucositis.<sup>[9]</sup> This is due to the pharmacologic mechanism of the MTX by blocking the important enzymes dihydrofolate reductase and thymidylate synthase, thereby MTX inhibits the synthesis of purines and pyrimidines. High demand causes DNA base depletion to be especially sensitive to rapidly dividing cells, such as those found in the bone marrow and the gastrointestinal tract, particularly the oral mucosa.<sup>[9][11][12]</sup> Therefore, the side effects of MTX are going to have an impact on and disturb these tissues.<sup>[11]</sup> In this case, the patient had been suffering from odynophagia, gradually progressive ulcers, and abdominal pain. Due to these symptoms, the patient was unable to tolerate oral feeding, leading to dehydration and a decline in her overall health. The patient had pancytopenia, which indicates bone marrow suppression. Patients who received a prescription for low-dose MTX but eventually overdosed on it either because the prescription was written incorrectly or the patients failed to understand the once-weekly regimen were shown to have oral mucositis in a prior study.<sup>[8][11]</sup> The patient in this case study also took daily dose instead of weekly dose because the patient didn't comprehend the once-weekly schedule. The patient was prescribed to take folic acid 6 days a week, she didn't take the folic acid supplements, it appears that MTX toxicity was increased as a result of folic acid insufficiency. Low-dose folate supplementation was having protective effects by lowering the Gastrointestinal and hepatic side effects of MTX in RA patients. This aligns with the suggestions put forth by certain authors.<sup>[13][14]</sup>

## 3. Conclusion

Methotrexate (MTX), a folate antagonist initially developed for cancer treatment, is now a cornerstone in managing Rheumatoid Arthritis (RA) due to its immunosuppressive and anti-inflammatory properties. However, MTX use can lead to significant toxicity, as highlighted in a case study of a 71-year-old woman who developed mucositis, a severe MTX-induced side effect. Her condition, characterized by painful oral ulcers and general malaise, was exacerbated by potential overdosage and lack of clear instructions on weekly MTX regimen. Hospitalization revealed early signs of bone marrow suppression, necessitating an intensive treatment regime including folic acid supplementation, antibiotics, and corticosteroids. Her condition improved significantly after a four-day hospital stay, underscoring the importance of careful MTX administration and monitoring to mitigate adverse effects. More frequently unintentional overdoses happened due to taking a daily basis instead of a weekly dose. This case emphasizes the necessity of clear dosing instructions and the critical role of folic acid in preventing MTX toxicity.

## Abbreviations

MTX Methotrexate

RA Rheumatoid Arthritis  
 ILD Interstitial Lung Disease  
 DMARDs Disease-Modifying Anti-Rheumatic Drugs  
 ESR Erythrocyte Sedimentation Rate

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