



Case Report

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# A Diagnostic Challenge of Methotrexate-Induced Mucositis: A Case Report



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**Citation** Katebi K, Taghavi Zenouz A, Ghavimi MA. A Diagnostic Challenge of Methotrexate-Induced Mucositis: A Case Report. Case Reports in Clinical Practice. 2022; 7(2): 82-85.

**Running Title** Methotrexate-Induced Mucositis



**Article info:**

**Received:** 07 April 2022

**Revised:** 25 April 2022

**Accepted:** 15 May 2022

**Keywords:**

Oral ulcer; Mucositis; Arthritis; Rheumatoid; Methotrexate

## ABSTRACT

Methotrexate is an anti metabolite drug that is used for treating several autoimmune diseases in low doses. It has been reported that oral ulcers occur in 11-17% of patients receiving low doses of Methotrexate. The purpose of this article is to report the Methotrexate-induced oral ulcers and their effects on patient's quality of life. The patient was a 69-year-old woman with a complaint of oral ulcers. She was taking alendronate, Methotrexate, and hydroxychloroquine for osteoporosis and rheumatoid arthritis diseases. The possibility of bisphosphonate-induced osteonecrosis was recognized due to necrotic ulcers with mandibular bone exposure in the first therapy session. Then, a new necrotizing ulcer on the hard palate appeared in the next session. Methotrexate consumption was discontinued and folic acid was initiated. The oral ulcers were fully recovered in three weeks. Methotrexate-induced mucositis should be considered in the differential diagnosis of patients with oral ulcers who receive low-dose Methotrexate.

## Introduction

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ethotrexate(MTX) is an immunomodulatory drug acting as a folic acid antagonist, which is usually administered in high doses for treating leukemia, lymphomas, and tumors as a chemotherapy agent. Methotrexate irreversibly binds to the dihydrofolate reductase and thus reduces cell proliferative activity

[1]. Moreover, low doses of MTX (maximum 25 mg MTX per week) is used in the treatment of some autoimmune diseases, such as rheumatoid arthritis, psoriasis, polymyositis, systemic lupus erythematosus, ..., due to and anti-inflammatory effects [2]. Although its application has been suggested in numerous guidelines for the treatment of the mentioned diseases for more than 50 years and considered safe in low doses, evidence regarding its efficacy and safety is very limited [3, 4]. Some studies have been suggested

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that several factors, including old age, concomitant use with other medications, and renal failure can intensify its toxicity [5]. Commonly, it affects tissues with high cell proliferation rates, such as bone marrow and the gastrointestinal tract. Oral ulcers were reported in 11-17% of patients treated with low doses of methotrexate [6]. Regarding the treatment of methotrexate-induced acute toxicities, Yelamos et al., stated that the supplementation of folic acid increased gastrointestinal tolerance, and inhibited hematologic toxicity [4]. They also argued that methotrexate administration must be discontinued in the case of pancytopenia, mucositis, and skin wounds since these complications may be lethal. Furthermore, they stated that patient hydration might be helpful in the renal elimination of methotrexate. After toxicity recovery, the methotrexate administration may be continued under the supervision of a physician.

In this report, a case of methotrexate-induced toxicity is presented, which posed a considerable diagnostic challenge due to the various medications the patient was receiving.

### Case presentation

A 69-year-old woman with a complaint of oral ulcers and severe pain in the buccal mucosa was referred to the Department of Oral Medicine, Faculty of Dentistry, Tabriz University of Medical Sciences, Iran, in December 2018. Her past medical history included rheumatoid arthritis, hypothyroidism, and osteoporosis, and she took medications including alendronate (70 mg weekly for the past two years), levothyroxine (100 µg daily), methotrexate (7.5 mg

weekly), hydroxychloroquine (200 mg daily), and naproxen (250 mg three times a day).

The oral clinical examinations showed a necrotic ulcer associated with mandibular bone exposure on the right mandibular ridge (Fig. 1). With the possibility of bisphosphonate-induced osteonecrosis, the ulcer was irrigated and ibuprofen 400 mg every 6 hours was administered. Then, the patient was referred to the oral and maxillofacial surgery department to remove sequestrates. Moreover, the patient's physician was consulted on the bisphosphonate discontinuation.

After two weeks, the patient returned while she had not visited oral surgeon nor her physician during this period. The second clinical examination indicated a new ulcer in the hard palate and maxillary edentulous ridge on the left side, and the patient had suffered extremely severe pain (Fig. 2). Therefore, an oral biopsy of the hard palate was taken and sent for histopathological examination due to the new manifestations and the possibility of viral, autoimmune diseases, and non-specific ulcers. The ulcers were then irrigated with a sterile serum to prevent secondary infections, and ibuprofen (800 mg every six hours) and acetaminophen codeine (350 mg every six hours) were prescribed to reduce the pain. Also, a complete blood count test was requested for the patient.



Fig. 1. The mandibular edentulous ridge of the patient



Fig. 2. Maxillary edentulous ridge and hard palate of the patient

**Table 1.** Results of the patient complete blood count

| Test       | Result | Unit           | Normal values |
|------------|--------|----------------|---------------|
| WBC        | 12.43  | 10e3/ $\mu$ l* | 4-11          |
| Neutrophil | 8.82   | 10e3/ $\mu$ l* | 1.9-8         |
| Folic acid | 4.65   | Ng/ml          | >5.36         |
| Creatinine | 1.5    | Mg/dl          | 0.7-1.4       |



Histopathological results reported non-specific ulcers and lymphocytic sialadenitis. At the next visit, the ulcers had spread in the mandibular jaw, and the left side of the edentulous ridge was involved. Accordingly, the patient's pain has significantly intensified. Abnormalities of the patient's complete blood count test are shown in [Table 1](#).

Methotrexate-induced mucositis was considered due to the spread of ulcers in both maxilla and mandible and the history of long-term use of low-dose methotrexate. Accordingly, methotrexate was discontinued by rheumatologist, and folic acid supplementation (1.0 mg daily) was prescribed. The oral ulcer recovery was started by administering folic acid, and the ulcers were fully recovered in three weeks, so the patient's pain resolved.

## Discussion

Methotrexate-induced severe toxicity was rarely reported for low doses, and toxicity and side effects are usually observed in high doses [7]. Although different treatments have been recommended for methotrexate-induced oral ulcers, the most common treatment included MTX discontinuation and folic acid administration (29.17%), and MTX discontinuation alone (25%) [8]. Numerous studies have reported the mean wound-healing period after MTX discontinuation to be three weeks [9]. Some studies have shown that folic acid supplementation reduced the mucosal and gastrointestinal side effects by 39% in patients who were being treated with different doses of methotrexate [10, 11]. Similarly, the presented patient suffered from folic acid deficiency.

The differential diagnosis of oral ulcers is extensive and includes autoimmune diseases, recurrent aphthous stomatitis (RAS), viral and bacterial infections, agranulocytosis, allergic reactions, and drug side effects. Obtaining an accurate medical history and complete clinical examination can play a vital role in the precise diagnosis of the diseases [12].

Osteonecrosis was the first diagnosis in this patient due to the initial manifestation of ulcers in the mandible and the long-term history of using bisphosphonate, though the patient had no recent history of tooth extraction. Maxillary involvement and bilateral lesions led to increasing clinical suspicion of systemic autoimmune or viral diseases. Laboratory tests showed that the patient suffered from folic acid deficiency and a slight increase in creatinine level.

Despite the correct administration of low doses of methotrexate, interfering drugs can affect serum methotrexate levels. Drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, sedatives, and anticonvulsants should be prescribed with extreme caution and at the lowest dose for these patients because they may interfere with renal and hepatic functions. Aspirin, penicillin, and other NSAIDs have been reported to reduce the excretion of methotrexate and increase the risk of methotrexate-induced toxicity [13]. Note that the presented patient was taking 250 mg of naproxen three times a day. Also, the oral ulcers healed after three weeks with the administration of folic acid following the discontinuation of methotrexate.

Side effects of low-dose methotrexate are classified into the following three groups. The first group includes direct gastrointestinal and bone marrow toxicity. These side effects are dose-dependent, and the most common. The second group includes idiosyncratic or allergic reactions, and the third group is the long-term drug side effects, including cardiovascular and hepatic diseases, which are mainly caused by hyperhomocysteinemia. General side effects include gastrointestinal, leukocytopenia [14], kidney failures, headache. Oral lesions are less common and occur mainly in the form of oral ulcers and mucositis in the case of folate deficiency [15]. Although oral lesions are not lethal, they remarkably affect patients' quality of life [14, 15]. It should be noted that despite the administration of several analgesics during the treatment period of the present patient, the pain never completely disappeared.

In patients with single or multiple oral ulcers in different sites who use methotrexate, drug-induced mucositis should be considered as one of the differential diagnoses, though it is not very common. If other differential diagnosis have been ruled out, MTX may be discontinued with consultation with the patient's physician and the patient should be followed up for wound healing and in this period supportive treatments should be provided.

## Conclusion

Due to rareness of methotrexate induces oral mucositis and according to the fact that patient was using multiple medications, the diagnosis of this case posed a great challenge and discontinuation of methotrexate and supplementantation with zinc resulted in recovery.

## Ethical Considerations

All ethical principles are considered in this article. The patient was informed about the purpose of the research and its implementation stages. She was also assured about the confidentiality of her information and was free to leave the study whenever she wished, and if desired, the research results would be available to her. An informed consent was obtained from the patient for publishing the present case and her clinical images.

## Funding

This research has been supported by Tabriz university of medical sciences.

## Authors' contributions

All authors equally contributed in preparing this article.

## Conflict of interest

Authors declare that there is no conflict of interest.

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