Oral Ulceration Due to Methotrexate Treatment: A Report of 3 Cases and Literature Review

Introduction

Methotrexate (MTX) is an antimetabolite, acting as a DHP reductase inhibitor, resulting in blocking intracellular DNA synthesis\(^1,2\). It is used for the treatment of both benign conditions (rheumatoid arthritis\(^1,3,4,11\), psoriasis\(^1,2,3,5,6,12\), psoriatic arthritis\(^2,12\), collagen vascular disease\(^3\)) and malignancies (leukemia\(^3\), non-Hodgkin’s lymphoma\(^5,9\), cutaneous T cell lymphoma\(^2\), choriocarcinoma\(^3\)). MTX was approved as an antirheumatic drug in 1999\(^4,10\). The efficacy of MTX against rheumatic diseases was first noticed in the early 1950s, when aminopterine, a precursor of MTX, was used for rheumatoid arthritis (RA)\(^3,8\). The use of MTX in psoriasis was increased during the 1970s. In the 1980s, randomized clinical trials proved its efficacy against RA. Since then, rheumatologists have extensively used long-term low-dose methotrexate (LDMTX), especially in North America\(^3\).

LDMTX may also be administered to children; MTX is the only effective DMARD (disease-modifying antirheumatic medication) in juvenile RA. The long-term positive results, along with the fact that medication tolerance in children seems to be of a good level, have made MTX the most commonly used second-line agent after NSAIDs (non-steroidal anti-inflammatory drugs)\(^3\). In non-malignant conditions the weekly dosage is up to 25 mg (low dose)\(^3,5\).

Adverse effects to MTX include gastrointestinal toxicity\(^3,4,6,8,10\), hepatotoxicity\(^1,5,6,7,10\), myelosuppresion\(^1,5,10,12\) and oral manifestations (oral ulceration and oral mucositis)\(^5,10,12,13\). Severe oral manifestations are common in high-dose MTX therapy, especially for the treatment of malignancies.

The aim of this paper was to present 3 cases of oral ulcerations due to MTX treatment, along with a brief review of the literature.

Case Reports

The following cases were all presented and cured in Apostolos Matiakis (second author) private practice. All figures belong to his personal archive.

Case 1

A 38-year-old woman presented with ulcerative lesions at the labial mucosa (especially at the lower labial mucosa) and the floor of the mouth (Figs. 1 and 2). The above lesions were painful. She indicated that oral ulcerations developed for the first time and there was no history of recurrent apthae. Her medical history revealed that the patient suffered from psoriatic arthritis and was under MTX treatment.
A 78-year-old man, edentulous, was referred by his dentist, due to an insisting ulcer, (3mm x 7mm) at the left buccal mucosa (Fig. 3), causing a suspicion of malignancy. The patient reported severe topical pain, which increased during mastication.

Patients’ history revealed that he was under MTX treatment, due to RA. In cooperation with his rheumatologist, we decided to discontinue MTX treatment, which improved the clinical symptoms.

**Case 3**

A 52-year-old woman presented with aphthous-like ulcers, located on the left side of the tongue (Fig. 4). Due to the fact that she suffered from RA, the patient was under MTX treatment. Her rheumatologist accepted the interruption of the MTX administration, while methylprednisolone treatment was prescribed, leading to complete remission of the ulcerative lesions.

The previous information, as well as clinical examination, lead us to the conclusion that oral ulcers presented due to MTX administration. In cooperation with her rheumatologist, we decided to discontinue MTX treatment. In a few days, ulcers were significantly reduced.

**Case 2**

In our report, 3 cases of patients who presented oral ulcers due to MTX treatment are described. MTX is an effective antiproliferative, antineoplastic and anti-inflammatory medication. In a high dosage, it is used as a chemotherapeutic agent in treating malignant diseases, including leukemia, non-Hodgkin’s lymphoma and a number of solid tumors. Lower dosage of MTX, is used in controlling chronic inflammatory disorders, such as rheumatoid arthritis and psoriasis.

Nevertheless, MTX does not lack side effects. The frequency and severity of MTX toxicity depends on dosage, although tolerance in MTX may vary among patients. Renal and hepatic dysfunction may influence the MTX metabolism and clinical tolerance. Adverse effects of LDMTX have been classified in 3 major groups. The first group includes direct gastrointestinal and bone marrow toxicity. They are dose-dependent effects, though a clear correlation between plasma concentration and this effect
has not been established. These effects are mediated by folate antagonism and are the most common. The second group includes idiosyncratic or allergic reactions such as pneumonitis. The third one includes effects of long-term treatment in diseases such as liver or cardiovascular diseases, caused mainly by hyper-homocysteinaemia. General adverse effects include gastrointestinal toxicity3,4,8,10 (nausea1,7,9, vomiting1, abdominal discomfort, anorexia, dyspepsia, diarrheea), hepatotoxicity3,4,10 (hepatitis2, fibrosis6, cirrhosis3), myelosuppression1-5,8,10, (leukocy-topenia, thrombocytopenia, pancytopenia), hyperhomocysteinemia4,10, hypersensitivity causing pulmonary toxicity3,4,10, renal insufficiency2, central nervous system events (headaches, depression)3,4,9,10 and osteoporosis3,4,10. Oral lesions are less common, appearing as oral ulcers and mucocitis 1,3,4,6,7. The above is considered to be a dose-dependent effect 4,6. Oral ulcerations may be related to medication overdose5,6 or folate deficiency. Attention ought to be given when prescribing to patients who present with oral ulcerations whilst being under MTX5. Although oral manifestations are not life threatening, they have, however, a negative impact on patient’s quality of life5,9,13.

### Table 1. Case reports according to the referenced series

<table>
<thead>
<tr>
<th>Researchers</th>
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<th>Sex</th>
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Interacting drugs can also affect serum MTX levels, despite a correctly administered low-dose MTX. Drugs that interact with renal and hepatic function e.g. various NSAIDs (non-steroidal anti-inflammatory drugs, as aspirin and ibuprofen), antibiotics, sedatives and anticonvulsants should only be prescribed to patients on low-dose MTX treatment at limited doses and under meticulous supervision. MTX excretion is reduced by aspirin and other NSAIDs and penicillin, increasing the risk of toxicity. Nitrous oxide increases the antifolate effects of MTX and their concurrent use, such as in inhalational sedation, should be avoided.1,5

Further interest should be paid to the fact that some patients do not develop oral mucositis under a high-dose MTX regimen. Genetic polymorphism has been implicated as a predictive factor for MTX toxicity3,7.

The pharmacologic mechanism of MTX action involves inhibition of the synthesis of purines and pyrimidines by inhibiting the key enzymes dihydrofolate-reductase (DHFR)3,5,8,9, and thymidylate synthase1. Rapidly proliferating cells are susceptible to MTX because most cells are in the S-phase, where this medication exerts its effects. Gastrointestinal mucosa, hair and bone marrow are very susceptible to MTX, due to the high rate of cellular turnover2. Therefore, these tissues are among the first to be affected and disrupted by the side effects of cytotoxic medication, such as MTX.

Several mechanisms are considered for the development of erosions and ulcerations. One of them attributes ulcerations to shortening the time between doses of MTX. According to the weekly dosing schedule used by dermatologists and rheumatologists, medication is either taken as a single dose once per week or divided into 2 to 3 doses, usually taken in 12-hour intervals; patients are told to always take their medication on the same day(s) of the week. If a patient were to accidentally
take a MTX dose before the next scheduled time, the additional dose would theoretically stop proliferation of the small percentage of cells that escaped the initial MTX dose, thereby increasing the total number of cells affected by medication. Other mechanisms that may contribute to MTX-induced ulcerations include renal dysfunction, which leads to elevated MTX levels due to decreased renal clearance and concomitant administration of medication such as NSAIDs, sulfonamides, and salicylates, which increase soluble MTX levels by displacing the protein-bound fraction12.

MTX toxicity can be treated and reversed by the substitution of folate or folic acid1,3,5-8 (leucovorin). Leucovorin, the reduced form of folate, bypasses the target of MTX, the enzyme dihydrofolate reductase, and can therefore restore the cell’s ability to produce DNA bases despite MTX treatment. A current market shortage of leucovorin may complicate MTX management and increase the incidence of patients suffering from MTX side effects1.

Other possible solutions to oral toxicity of LDMTX are3,4:
- topical treatment (analgesics, antiseptics, steroids) which only provide symptomatic relief;
- excision of lesions (it can be effective in some cases, especially when biopsy is required);
- cessation of LDMTX (relapse of the disease that MTX was prescribed);
- MTX dosage reduction (less effective than cessation);
- interruption of MTX for 2-3 weeks (may cause relapse of the disease, requiring higher doses subsequently);
- fortnightly (instead of weekly) MTX dosing (may be appropriate for well-controlled patients);
- switching to another drug (azathioprine, sulphasalazine) - less effective and more likely to cause adverse effects;
- combination of MTX and other medication (may allow dose reduction of all, and consequently reduce toxicity);
- combination or substitution with newer biological agents (leflunomide, etanercept, infliximab) - high cost and unproven long-term safety (further research required).

Gobbo et al9 (2013) reported the use of LLLT (low-level laser therapy) as an effective treatment of low-dose MTX related oral mucositis in patients affected by rheumatoid arthritis. The previous treatment is safe, atraumatic and rapid, whilst being free of side effects and easy to apply. Also, it does not interfere with other therapies and can help in avoiding a dangerous discontinuation of MTX therapy. As LLLT reduces pain, even if a fibrous scar remains visible after treatment, this new technique is believed to be useful in the management of such lesions. Nevertheless, further investigation is needed to evaluate this innovative technique.

If a medication is suspected to be the cause of an oral ulceration, cooperation is essential with the prescribing doctor in order to discuss the possibility of alternative medication or dosage reduction. After cessation, change, or dosage reduction, ulcerations may decrease in 1-2 weeks. In cancer patients, the combination of radiotherapy and chemotherapy can cause mouth ulcers, which are due to either MTX or to the radiation. Radiation may cause xerostomia, fact that leads to more painful ulcers13.

Ulcers are common symptoms observed in the oral cavity and some of the above are induced by medication (such MTX). Ulcers presenting with typical clinical findings, may be differentially diagnosed, but the final diagnosis is often difficult and histopathological examination may be needed10.

In the case of immunosuppression with agents such as MTX or by cytotoxic chemotherapy, Epstein-Barr virus can be the cause of mucocutaneous ulcers (EBV positive biopsy)4,14-18. In patients with various types of immunosuppression, EBV has long been associated with B-cell lymphoproliferative disorders15-18. In 2010 Dojcinov et al18 were the first to propose EBVMCU (Epstein-Barr virus-positive mucocutaneous ulcer) as a newly recognized clinical-pathological entity after describing a series of EBV-positive circumscribed, ulcerative lesions with Hodgkin-like histological features associated with various types of immunosuppression. Typically, these ulcers present as isolated, circumscribed, cutaneous and mucosal lesions with a benign and self-limited clinical course16.

Dental practitioners are very likely to encounter patients under MTX treatment and so ought to be aware of clinical and histopathological oral manifestations. Since it is a widely prescribed medication by rheumatologists, dermatologists and oncologists, cooperation is required between the previous and dental practitioners as well as oral pathologists.

In conclusion, MTX is a non-rare prescribed medication by many medical specialists. Oral ulcers stand among MTX’s main side effects. Dental practitioners should be well informed about MTX prescription, in order to be able to estimate the potential adverse effects in their patients.

References
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