

## Methotrexate-induced Oral Mucositis

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Methotrexate (MTX) is a chemotherapeutic agent that is used to treat a host of malignancies. But recently, MTX has also been used as a therapeutic agent for chronic inflammatory disorders such as rheumatoid arthritis, psoriasis, and systemic lupus erythematosus. However, MTX is an antimetabolite that affects rapidly dividing normal cells such as oral mucosal epithelial cells, gastrointestinal epithelial cells, and bone marrow cells—which explains why oral mucositis is often an initial manifestation of MTX toxicity. Because oral lesions are frequently initially presented in dental clinics, dentists should consider the possibility of adverse drug reactions in the differential diagnoses of oral lesions through a meticulous collection of patients' medical histories. In this report, we examine patients who suffered from oral ulcerative lesions upon diagnosis of MTX-induced oral mucositis. Then, we suggest approaches for the diagnosis and treatment of MTX-induced oral mucositis through a review of literature.

**Key Words:** Folic acid deficiency; Methotrexate; Oral mucositis; Rheumatoid arthritis

### INTRODUCTION

Since its introduction over 50 years ago as a treatment for childhood acute lymphocytic leukemia, methotrexate (MTX) has proved useful as a chemotherapeutic agent for various malignancies including hematological and trophoblastic malignancies, osteosarcomas, bladder cancer, head and neck cancer, lung cancer, and breast cancer.<sup>1)</sup> MTX is also widely used as a therapeutic agent for chronic inflammatory disorders such as rheumatoid arthritis (RA),<sup>2)</sup> psoriasis,<sup>3)</sup> systemic lupus erythematosus,<sup>4)</sup> granulomatosis with polyangiitis (Wegener's),<sup>5)</sup> Crohn disease<sup>6)</sup> and in the prevention of graft-versus-host disease.<sup>7)</sup>

MTX is a folic acid (FA) antagonist that interferes reversibly with the action of several key enzymes including dihydrofolate-reductase, thymidilate synthetase and aminoimidazolecarboxamide ribosyl-5-phosphate (AICAR) transformylase in the folate pathway.<sup>8)</sup> These enzymes are requisite for the synthesis of purines and pyrimidines. MTX's inhibition of the folate pathway interferences with nucleotide

synthesis and, consequently, inhibits the cell cycle.

The exact mechanism of MTX in immunological disorders has not been fully elucidated. However, it is known that intracellular accumulation of AICAR and homocysteine induces the release of adenosine, which has anti-inflammatory effects and immunosuppressive effects modulated by an increase in cyclic adenosine monophosphate.<sup>9,10)</sup> MTX can also modulate the function of immune cells and reduce the production of several cytokines (interleukins, tumor-necrosis factor, and interferon).<sup>2)</sup>

MTX is an antimetabolite that affects rapidly dividing normal cells, including oral mucosal epithelial cells, gastrointestinal epithelial cells, and bone marrow cells—which explains why oral mucositis is often an initial manifestation of MTX toxicity.<sup>11)</sup> Myelosuppression is another potential side effect of MTX that appears only after long-term administration. Myelosuppression is the most feared adverse effect of MTX toxicity as it can be fatal.

In this report, we examine patients who suffered from oral ulcerative lesions upon diagnosis of MTX-induced oral

mucositis. Through our report, we emphasize the importance of meticulous collection of patients' medical histories, clinical examinations (including laboratory tests), and medical consultations on differential diagnoses of oral ulcerative lesions. Then, we suggest approaches for the diagnosis and treatment of MTX-induced oral mucositis through a review of literature.

## CASES REPORT

### 1. Case 1

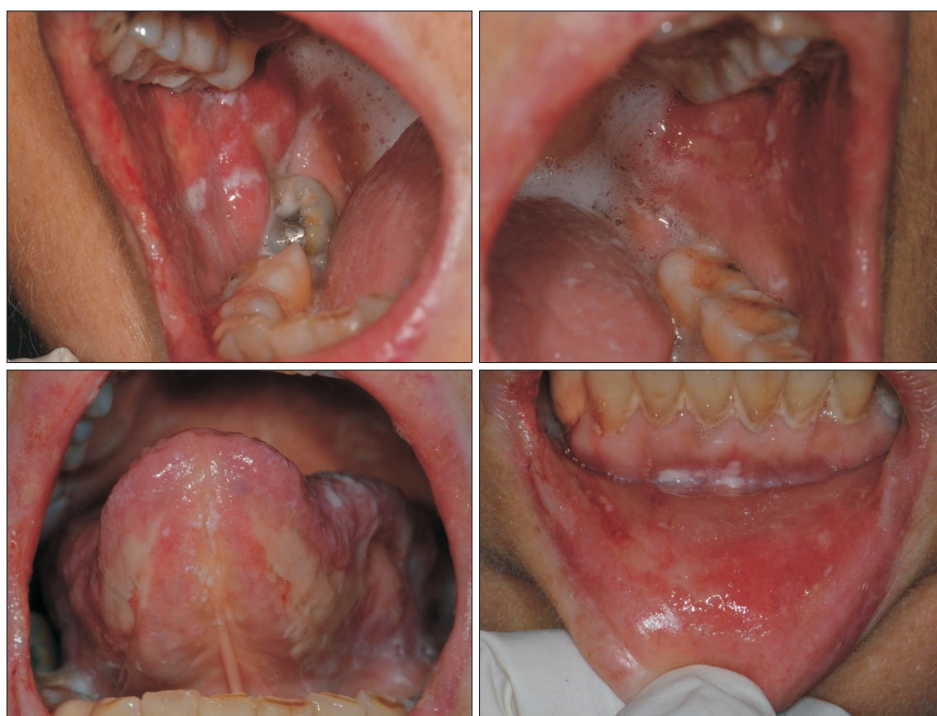
A 77-year-old female patient presented with oral ulcers that developed two months ago on both buccal mucosa. She has a habit of biting down on her buccal mucosa; therefore, she has been afflicted with oral ulcers before. She suffers from RA and consequently had undergone total knee arthroplasty two months ago. Her prescription list includes MTX, prednisolone (Solondo Tab.; Yuhanmedica, Cheongwon, Korea), leflunomide (Arava Tab.; Sanofi-Aventis Korea, Seoul, Korea), celecoxib (Celebrex Cap.; Pfizer, Seoul, Korea), rebamipide (Mucosta Tab.; Korea Otsuka Pharmaceuticals, Seoul, Korea), and rebepazole (Pariet Tab.; Janssen Korea, Seoul, Korea). She commenced a once-weekly dose of 17.5 mg of MTX two years ago.

Oral examination showed small erosive lesions on both buccal mucosa with tenderness to palpation. The clinical impression from the patient's first visit was traumatic ulcers due to clenching habits. The patient was prescribed topical steroid and sodium-lauryl-sulfate free toothpaste.

Yet in spite of continuous treatment, the patient's entire oral cavity soon exhibited widespread erythema and ulceration. Oral candidiasis was also suspected on the patient's second visit, which occurred two weeks after her first visit (Fig. 1). Upon her second visit, the patient was prescribed fluconazole (Diflucan Cap.; Pfizer) and the following laboratory tests were performed: complete blood count (CBC), routine chemistry, vitamin B12, folate, serum iron, ferritin, zinc.

The laboratory test results revealed that the patient's red blood cell (RBC) count and platelet count had decreased and that she was deficient in FA (RBC, 1.83; hemoglobin, 6.6; hematocrit [Hct], 20.7; platelet, 128; folate, 2.91). The remaining results were within the normal range.

The patient's symptoms were getting progressively worse, so she was referred to a rheumatologist for MTX toxicity. She was advised to not take any more MTX and was prescribed a once-daily dose of 1 mg of FA. The definitive diagnosis was oral mucositis due to MTX toxicity.



**Fig. 1.** Intraoral pictures at the second visit (two weeks after first visit). Widespread erythema and ulceration was shown on oral cavity.



**Fig. 2.** Intraoral pictures at the third visit (three weeks after first visit). Widespread erythema and ulceration recovered about two weeks after methotrexate cessation.



**Fig. 3.** Intraoral pictures at the first visit. Ulcerative and erythematous lesions were shown on labial and oral mucosa.

Upon review two weeks post-MTX cessation, the patient's symptoms had abated and the ulceration was recovering normally (Fig. 2). Laboratory test results were as follows: RBC, 3.71; hemoglobin, 12.1; Hct, 36.9. The remaining results, including platelet count and folate levels, were within the normal range. It is clear that pre-existing folate deficiency increases MTX toxicity in the oral mucosa.

## 2. Case 2

A 71-year-old-female patient was referred from the department of rheumatology for evaluation and treatment of an oral ulceration that had developed a month ago. The patient's general health was complicated by RA, chronic

renal failure, hypertension and right hemiplegia due to left parietal intracerebral hemorrhage. She was diagnosed with RA 15 years ago, and her prescription list included MTX, FA (Folcid Tab.; Cho-A Pharm., Seoul, Korea), sulfasalazine (Salazopyrin-EN Tab.; Ilsung Pharmaceuticals, Seoul, Korea), methylprednisolone (Methylon Tab.; Kunwha Pharmaceutical, Seoul, Korea), bisoprolol fumarate (Concor Tab.; Merck Korea, Seoul, Korea), hydrochlorothiazide (Codiosartan; Yuhan, Seoul, Korea), esomeprazole magnesium (Nexium Tab.; AstraZeneca Korea, Seoul, Korea), amlodipine besylate+atorvastatin calcium (Caduet Tab.; Pfizer). She has taken 10 mg of MTX once weekly for two months—her medical history revealed that she had previously taken

MTX but was forced to discontinue five months ago due to pneumonia. Clinical examination revealed ulcerative and erythematous lesions involving the labial and oral mucosa (Fig. 3). Laboratory test results showed anemia and renal dysfunction. The results are as follows: RBC, 2.69; hemoglobin, 9.0; Hct, 27.6; blood urea nitrogen (BUN), 27.4; creatinine, 1.49; uric acid, 7.4. The patient was prescribed topical steroids and consulted for her anemia and renal dysfunction. However, her discomfort persisted, so her treatment was altered to control for drug side effects. Specifically, one week after her first visit, her prescription of MTX was reduced to a once-weekly dose of 5 mg. The patient's ulcerative lesion was resolved two weeks after the decrease in

MTX (Fig. 4).

### 3. Case 3

A 68-year-old female patient presented with severe stomatitis and the patient was unable to eat for three weeks due to her symptoms. The patient could not pinpoint any specific reason for her symptoms besides the fact that she took stomach ulcer medication three weeks ago. She was diagnosed with RA 15 years ago. Her prescription list included MTX 15 mg once weekly, FA (Folcid Tab.; Cho-A Pharm.), leflunomide (Leflunomide Tab.; Chong Kun Dang Pharm., Seoul, Korea), prednisolone (Solondo Tab.; Yuhanmedica), rebamipide (Mucosta Tab.; Korea Otsuka Pharmaceuticals),



**Fig. 4.** Intraoral pictures at the second visit (three weeks after first visit). The patient's ulcerative lesions were resolved two weeks after the decrease in methotrexate.



**Fig. 5.** Intraoral pictures at the first visit. Ulcerative and erythematous lesions with bleeding tendency were shown on entire oral mucosa.

alprozolam (Xanax Tab.; Pfizer), celecoxib (Celebrex Cap.; Pfizer), acetaminophen 325 mg+tramadol HCL 37.5 mg (Lapiset; Chong Kun Dang Pharm.), hydrochlorothiazide (Dichlozid Tab.; Yuhan) for RA and calcium carbonate 1,250 mg+cholecalciferol 1,000 IU (Dicamax Tab.; dalim BioTech, Seoul, Korea), atorvastatin calcium (Atorva Tab.; Yuhan), fimasartan potassium trihydrate (Kanarb Tab.; Boryung, Seoul, Korea), teriparatide (Forsteo Inj.; Eli Lilly, Seoul, Korea) for osteoporosis. Clinical examination revealed ulcerative and erythematous lesions involving lip, tongue, and oral mucosa with bleeding tendencies (Fig. 5). The clinical impression from the patient's first visit was erythema multiforme due to drug side effects. The patient was advised to abstain from new drugs for her stomach ulcer and was prescribed topical steroids. Three days after her initial visit, she received a periodic check for osteoporosis—the laboratory results revealed significant decreases in leukocyte, platelet, and erythrocyte counts. In addition, the patient's renal function was found to have decreased. The results were as follows: white blood cell, 1.39; RBC, 2.69; hemoglobin, 8.8; Hct, 26.8; platelet, 103; BUN, 29.1; creatinine, 1.16. Her folate and hepatic values were within the normal range. The patient was referred to the department of hematology for further hematologic evaluation due to the discovery of pancytopenia. She was hospitalized and subsequently ceased taking MTX. The ulcerative lesion resolved three weeks after the initial visit and her oral health remained satisfactory despite the patient's resumption of a once-weekly dose of 7.5 mg of MTX due to her deteriorating RA symptoms.

## DISCUSSION

In a previous study, oral mucositis was reported in patients who were prescribed low-dose MTX but ultimately overdosed either due to prescription error or patients' confusion regarding its once-weekly regime.<sup>11,12</sup> In this case study, however, MTX toxicity seems to have been elevated by several factors such as deficiency of FA,<sup>13</sup> reduced renal function,<sup>14</sup> and drug interaction,<sup>13</sup> even if the dosage of MTX does not change. In addition, while oral mucositis has commonly been known to appear as an initial sign of MTX toxicity, it actually develops relatively late after long-term MTX administration in our cases. MTX toxicity can

also prevent healing in previously existing lesions, such as traumatic ulcers.<sup>15</sup> The oral lesions that had lasted for more than a month were resolved within 2 to 3 weeks after discontinuation or dose reduction of MTX. Oral lesions that do not respond well to treatment require a differential diagnosis for toxicity of the drug through the careful collection of patient medical history and clinical examinations (including laboratory tests).

MTX is generally administered at a weekly dose of 5 to 25 mg for the management of chronic inflammatory disorders.<sup>16</sup> The toxicity of MTX is affected by administration of the dosage, the duration of the dosage, the age of the patient, and his/her renal and hepatic function. Potential risk factors for MTX toxicity include pre-existing folate deficiency, hypoalbuminemia, and interaction with other drugs.<sup>13</sup> For example, aspirin and other nonsteroidal antiinflammatory drugs displace MTX from protein and reduce renal clearance, increasing blood levels and toxicity.<sup>1</sup> Concurrent use of proton-pump-inhibitors can also be considered a potential risk factor, but is only reported in cancer patients receiving high doses of MTX.

Thirty percent to eighty percent of patients on low-dose MTX experienced adverse effects due to MTX toxicity,<sup>17</sup> and 5% to 35% of these patients stopped taking MTX as a result.<sup>18</sup> However, more severe adverse effects can be recovered relatively easily through administration of folate<sup>19</sup> and/or the dose reduction or cessation of MTX.<sup>18</sup> The toxicity of MTX can be reversible. It is entirely possible to interrupt MTX for 2 to 3 weeks or take MTX biweekly instead of weekly,<sup>15</sup> because cessation of MTX may aggravate existing diseases. Acute toxicity symptoms can be convalesced through the administration of an antidote called leucovorin, which is the reduced form of FA.<sup>19</sup> Topical treatment (i.e., analgesics, antiseptics, or steroids) can also help relieve symptoms.<sup>15</sup> But, if MTX toxicity persists thereafter, effective treatment seems difficult. Routine screening laboratory tests including CBC, serum folate levels, and a blood chemistry profile can be helpful in the prevention of these adverse effects in patients treated with low-dose MTX. In addition to laboratory tests, we recommend that drugs that interact with renal and hepatic function should only be prescribed to patients on low-dose MTX treatment at limited doses and under meticulous supervision.

Oral mucositis is a common concern for many patients, and dentists are often the first doctors to find out about the condition and treat it. Because oral mucositis may be an early sign of a more foreboding condition, early recognition may help in ensuring effective treatment. It is important to perform a thorough evaluation of the patient with oral mucositis and to thus determine the underlying cause of the patient's oral mucositis so that appropriate treatment can be implemented in a timely manner. Finding the underlying causes can be done through careful questioning of the patient's medical history and screenings/laboratory tests. Dentists should have the ability to determine these underlying causes and make a differential diagnosis with similar diseases. Dentists also must be aware that oral mucositis can be induced by drug toxicity. Furthermore, if systemic problems are suspected, referral of the patient to the appropriate department of medicine is highly important.

### CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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