Oral mucositis in patients receiving low-dose methotrexate therapy for rheumatoid arthritis: report of 2 cases and literature review

Matthias Troeltzsch, DMD, MD,[a] Gerhard von Blohn, MD,[b] Stefanie Kriegelstein, MD,[c] Timothy Woodlock, MD,[d,e] Volker Gassling, DMD, MD,[f] Ronald Berndt, MD,[g] and Markus Troeltzsch, DMD, MD[h]

Ansbach General Hospital, Ansbach; Schoen Clinic Medical Center Munich − Harlaching, Munich, Germany; University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; University of Schleswig − Holstein, Campus Kiel; Institute of Pathology, Ansbach; and University of Goettingen, Goettingen, Germany

Background. The differential diagnosis of ulcerative oral lesions is diverse. This report discusses the rare causes of oral mucosal ulceration and suggests approaches for diagnosis and treatment.

Methods. Two cases of methotrexate-induced stomatitis in patients receiving low dose methotrexate for rheumatoid arthritis are presented with a review of the current literature. In case 1, mucositis was caused by an unintended methotrexate overdose. In case 2, oral lesions were the result of chronic methotrexate toxicity. The treatment for methotrexate-induced mucositis required hospitalization in case 1, methotrexate discontinuation in both cases and oral folic acid supplementation in case 2.

Results. In both cases, the mucositis healed and no relapse was observed.

Conclusion. Mucositis may be an early sign of systemic conditions, and dental providers are often the first doctors involved in the assessment of oral mucosal diseases. Meticulous questioning of the patient's history and the physical examination is important for elucidating the underlying cause. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:e28-e33)

Methotrexate (MTX) is an established antimetabolic drug used to treat both benign conditions and malignancies.[1] As a folic acid analog, MTX interferes with the synthesis of DNA bases by inhibiting enzymes of the folate pathway, particularly dihydrofolate (DHF) reductase.[2] This effect can arrest the cell cycle, which is the main mechanism of the antineoplastic effect of MTX.[2] By blocking the replication of the immune stimulatory cells, MTX curbs the production of inflammatory mediators, which is beneficial in the management of rheumatoid arthritis (RA) and psoriasis.[2-6] The MTX regimens used in oncology are often the maximal tolerated dose, whereas a lower dose, 5-35 mg per week orally, is effective in antirheumatic therapy.[7]

[a]Resident, Department of Oral and Maxillofacial Surgery, Ansbach General Hospital, Ansbach, Germany.
[b]Department Chair, Department of Medicine/Gastroenterology, Ansbach General Hospital, Ansbach, Germany.
[c]Attending, Department of Foot and Ankle Surgery, Schoen Clinic Medical Center Munich − Harlaching, Munich, Germany.
[d]Medical Oncologist, Department of Medicine, Unity Health System, Rochester, NY, USA.
[e]Medical Oncologist, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA.
[f]Attending, Department of Oral and Maxillofacial Surgery, University of Schleswig − Holstein, Campus Kiel, Germany.
[g]Pathologist, Institute of Pathology, Ansbach, Germany.
[h]Resident, Department of Oral and Maxillofacial Surgery, University of Goettingen, Goettingen, Germany.
Received for publication Oct 8, 2012; returned for revision Dec 2, 2012; accepted for publication Dec 6, 2012.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2012.12.008

Clinicians are likely to commonly encounter this medication in that the prevalence of RA is approximately 1%,[8] and 50% of RA patients receive MTX treatment for at least 5 years.[5]

The frequency and severity of MTX toxicity is generally dose dependent,[2] although the individual tolerances of MTX vary. Toxicity is anticipated in cancer treatment protocols,[3,9] although case reports of toxic reactions at low doses of MTX emphasize the importance of considering this diagnostic possibility as well.[1,2,7,10-12] Renal and hepatic function, age, and concomitant medications influence the MTX metabolism and clinical tolerance.[5,13] MTX toxicity may include mucocutaneous ulcerations, nausea, vomiting, nephrotoxicity, hepatic toxicity, myelosuppression and reduced fertility.[10,14-17] Toxicity eventually leads to the discontinuation of MTX treatment in approximately 30% of patients.[11]

Ulcerative stomatitis can be an early sign of MTX toxicity, as high tissue turnover rates make gastrointestinal and mucosal cells especially sensitive to chemotherapeutic medication.[14,18,19] Therefore, oral medicine specialists and other providers must consider drug adverse effects in the differential diagnosis of ulcerative oral disease.[2,3,14] MTX toxicity can be treated and reversed by the substitution of folate or folinic acid (leucovorin).[2,3,9,20] 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.[3,20] A current market shortage of leucovorin may complicate MTX management and increase the incidence of patients suffering from MTX side effects.[21-24] The following case reports serve to increase the

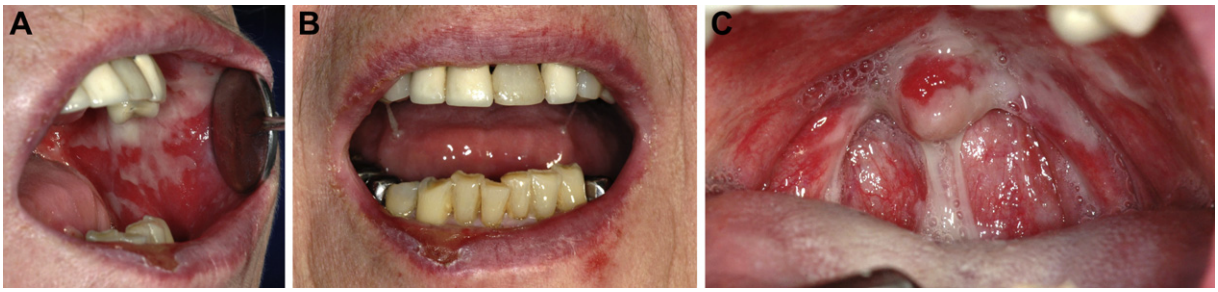

Fig. 1. **A,** Erythematous and ulcerative buccal mucosa. **B,** Dry lips with concomitant cheilitis. **C,** Rashes and ulcers of the uvula and pharynx.

awareness of dental providers and oral medicine specialists regarding oral adverse effects (i.e., acute or chronic stomatitis) of low-dose MTX treatment.

CASE 1

A 71-year-old woman was referred for the evaluation of a rapidly progressing necrotizing ulcerative gingivitis involving the lips and oral mucosa over the past week. She had dysphagia, abdominal pain, and diarrhea with no nutrition for 2 days. Clinical examination revealed inflamed, painful oral tissues with ulcers of the buccal mucosa, tongue and lip (Figure 1A and Figure 1B), consistent with WHO grade 4 oral mucositis.[25] The presence of uvular and pharyngeal rashes and ulcers were initial hints for the systemic nature of the disorder (Figure 1C). A shallow cutaneous ulcer of 1 cm in diameter in her right groin was detected during her physical examination (Figure 2). Her medical history included hypertension and active rheumatoid arthritis (RA), which had been treated with non-steroidal anti-inflammatory drugs. Her daily medications were valsartan 320 mg, aspirin 100 mg and omeprazole 20 mg. She did not report any allergies or malignant diseases. Further questioning revealed that MTX 15 mg oral once weekly had been recently prescribed to treat her RA. The patient was informed that her mucosal lesions were consistent with MTX toxicity, after which she admitted difficulty adhering to the recommended MTX dosing and schedule. After initially missing doses of the new medication, she had overcompensated for her non-compliance and had taken MTX 15 mg once daily for the last 10 days. Her history and diagnostic findings were consistent with a MTX overdose as a result of daily MTX intake, which had caused this acute reaction. Due to the patient's impaired general condition, dehydration and inability to tolerate oral nutrition and for the supervision of potentially lethal bone marrow suppression, she was hospitalized. Upon hospitalization, her vital signs included a blood pressure of 90/60 mm Hg, a respiratory rate of 26/min and a pulse of 110/min. Her initial laboratory blood testing confirmed dehydration, reduced renal function (low glomerular filtration rate,

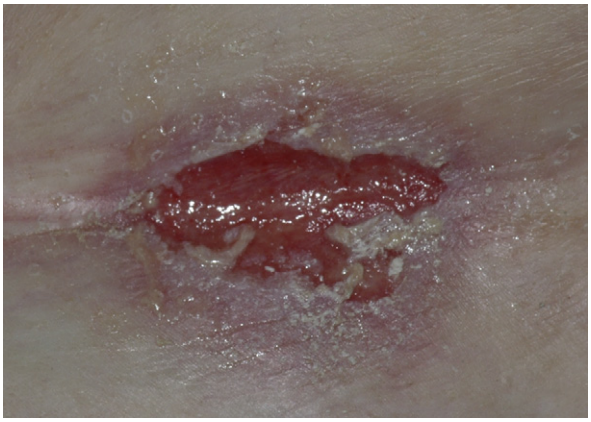

Fig. 2. Cutaneous ulcer of the patient's right groin.

hematocrit: 53%), early signs of bone marrow suppression (white blood count: 3.8 $\times$ 10^3/μL, platelets: 98 $\times$ 10^3/μL) and cellular destruction, as indicated by an increased lactic dehydrogenase (LDH; Table I). Her folate serum level was within the normal limits (folic acid: 3.9 ng/mL). Parenteral rehydration and nutrition was initiated, and MTX was discontinued. Analgesics (metamizole, IV [Novalgin; Aventis Pharma, Frankfurt, Germany] and acetaminophen, 1000 mg, IV [Perfalgan; Bristol-Myers Squibb, Munich, Germany]) were given for comfort, and antibiotics (cefuroxim 750 mg, IV [Cefuroxim-Ratiopharm, Ulm, Germany]) were administered intravenously to provide empiric coverage against the risk of invasive bacterial infection. Leucovorin was not administered. The patient remained hospitalized for 4 days. Oral nutrition was resumed after 2 days, and blood counts (platelets: 133 $\times$ 10^3/μL) and renal function (GFR $>$ 60 mL/min) recovered, as confirmed by laboratory tests on days 2 and 4 of hospitalization (Table I). The patient was discharged with improved general health, the absence of pain, and healing oral and cutaneous ulcerations, which were absent at a follow-up appointment 1 week later. MTX administration was resumed with the appropriate dosing regimen and folic acid supplementation after 1 month.