CASE REPORT

Oral ulceration in rheumatoid arthritis: A case report

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Abstract

Various drugs have been implicated in producing adverse reactions. Over the past few years, newer drugs have been reported with oral presentations mimicking vesiculobullous lesions. These seemingly rare presentations have posed a diagnostic challenge to the clinician. This paper attempts to highlight one such commonly administered drug and also the diagnosis and management of its possible adverse effects that manifested in a patient with rheumatoid arthritis.

Introduction

Rheumatoid arthritis is a chronic, progressive multisystem disorder and its prevalence is approximately 0.5-1%.[1] Methotrexate (MTX), synthesized in 1948, is the preferred treatment for most of the patients of rheumatoid arthritis.[1] Although it was first used to treat arthritis in 1951 by Gubner, the drug was not used as a treatment for rheumatoid arthritis until late 1970s when Hoffmeister reported improvement in rheumatoid arthritis patients treated with MTX. When taken at lower doses, it helps in the control of chronic inflammatory disorders such as rheumatoid arthritis and psoriasis.[2] It is used as part of the disease modifying anti-rheumatic drug (DMARD) regimen.[3] MTX is usually administered weekly at a dose of 5-25 mg usually divided into 3 doses.[4] This drug is widely used. However, its oral complications receive little or no attention.

This article reveals a case of oral ulceration due to low-dose MTX and relevant literature to potential oral adverse effects is discussed. Dental practitioners should be aware of the possible oral effects that can occur in patients taking low-dose MTX.

Case Report

A 70-year-old man reported with a chief complaint of painful recurrent ulcers in his mouth for 3 months. He gave a history of ulcers appearing spontaneously 3 months ago with pain, bleeding and inability to eat properly. Medical history included diabetes and hypertension for 20 years and rheumatoid arthritis for 10 years. He was treated with prednisolone 20 mg daily, in two divided doses, for a period of 9 years orally. After stopping the prednisolone, he was on MTX (7.5 mg twice a week) and folic acid (5 mg once a week) for the past 1 year orally. For the past 20 years, he was on regular metformin 500 mg twice a day orally and atenolol 50 mg once daily orally for diabetes and hypertension respectively. The patient consulted a physician for the oral mucosal ulceration and was prescribed multivitamins and topical analgesic gel. The ulcers regressed only to recur full-blown within 10 days.

On intra-oral examination, multiple, shallow, erythematous ulcers measuring 4 cm × 3 cm were present with bleeding on the right and left buccal mucosa and upper and lower labial mucosa. They were irregular in shape and appeared as collapsed bullae [Figure 1]. On palpation, they were tender, non-indurated with desquamation and bleeding present. Nikolsky's sign was positive. Clinical provisional diagnosis was oral pemphigus vulgaris. The patient reported symptomatic relief with the administration of topical anesthetic gel, benzydamine hydrochloride 0.15% oral rinse and multivitamins. However, since the ulcers remained unchanged, a tzanck smear was performed.

The cytology smear showed plenty of mixed inflammatory cells containing predominantly neutrophils, eosinophils and

monocytes. There were no tzanck cells evident [Figure 2]. A biopsy was scheduled to be performed after 1 week. The patient's serum liver enzymes were found to be elevated. MTX (known to cause unexplained rise of liver enzymes), was suspected to be the cause. The patient's rheumatologist's was consulted, and the patient advised not to take MTX for a period of 1 week. In the meantime, the ulcers gradually reduced and slowly began to disappear. A section taken from the healing lesion showed dense chronic inflammatory cell infiltrate chiefly plasma cells and lymphocytes with area of basal cell degeneration and area of interface mucositis [Figure 3].

MTX was suspected as the responsible agent that caused the patient's oral ulceration, and his rheumatologist was contacted. When the dose of MTX was reduced to 7.5 mg once a week, resolution of oral ulceration was seen [Figure 4]. Thereby, the clinical impression was of oral ulceration secondary to MTX over dosage. Review after 2 weeks revealed that the patient was found to be with no oral ulceration. The patient's rheumatic arthritis remained to be well controlled on the once weekly MTX and folic acid dosing regimen. Six months later, when reviewed, the patient remained free of oral ulceration.

Discussion

MTX is anti-rheumatic agent that has been used in rheumatoid arthritis since its approval in the late 1980s.[4] It is known as a DMARD, because it not only decreases the pain and swelling of arthritis, but it also can decrease damage to joints and long-term disability. A few pioneering rheumatologists such as Hoffmeister and Scherbel treated patients who had rheumatoid arthritis with MTX during the 1960s and 1970s.[5] Severe oral ulceration is a

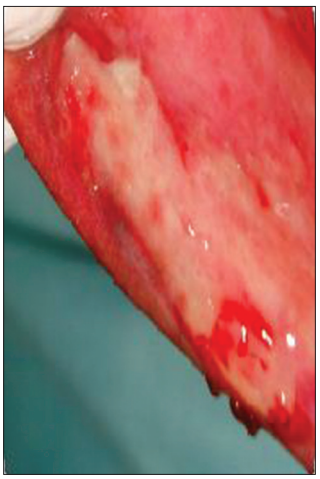

Figure 1: Ulceration of the lower labial mucosa on an erythematous background (4 cm × 3 cm) with bleeding

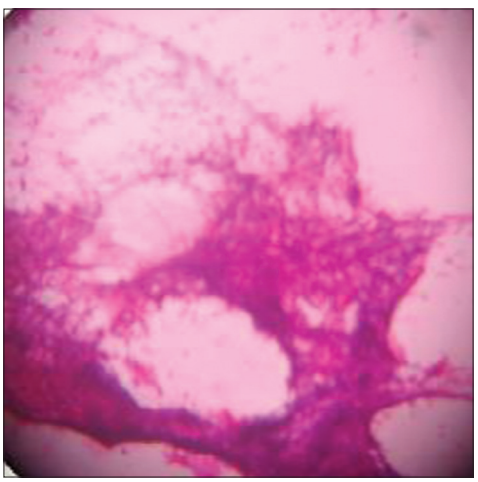

Figure 2: Cytology smear showing plenty of mixed inflammatory cells containing predominantly neutrophils, eosinophils and monocytes. There are no tzanck cells evident

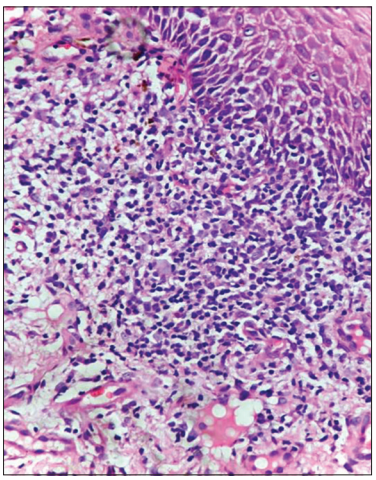

Figure 3: Histopathology of oral ulcer. Shows area of basal cell degeneration and area of interface mucositis with dense chronic inflammatory cell infiltrate chiefly plasma cells and lymphocytes (H & E, ×10)

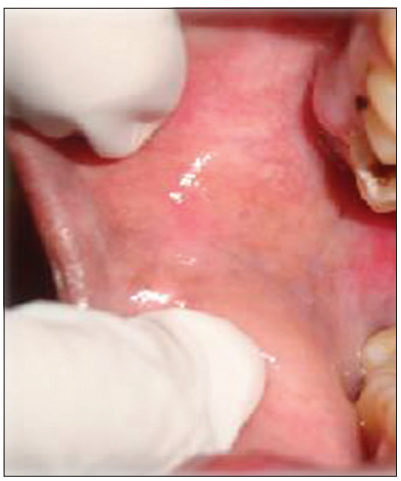

Figure 4: Completely healed oral mucosa on reduction of methotrexate dosage

common feature of the short-term, high dose MTX regimes used in the treatment of malignant disease.[6] Oral ulceration in the low dose MTX treatment regimens of rheumatoid arthritis is less common. Once a week, rather than daily dosing, helps reduce the risk of hepatotoxicity, but it can lead to over dosage if the drug is inadvertently taken daily.[7]

A study by Kremer et al in 1992 found up to 55% of patients reported episodes of mouth soreness over 90 months period while taking low dose MTX.[8] Allergic stomatitis is a known side effect of MTX with a mean frequency of 14%. It clinically presents as painful, erythematous, erosive or ulcerative lesion with a pseudomembranous necrotic surface. Widespread sloughing and ulceration may arise within days of commencement of drug therapy.[9] The mechanism of oral ulceration by MTX is that MTX competes with folinic acid for entry into the cell at the cell folate receptors whilst folic acid does not.[2] Folinic acid, as a reduced folate co-enzyme, can participate in DNA and RNA synthesis without the need for reduction by dihydrofolate reductase. However, folic acid is dependent on the reduction by this enzyme and folinic acid (or a synthetic equivalent leucovorin) can also displace MTX from dihydrofolate reductase thus creating a supply of fully reduced intracellular folate. Due to these mechanisms, folinic acid is suggested to be used as a "rescue therapy" to counteract severe MTX induced mucositis or myelosuppresion. The British National Formulary suggests 5 mg folic acid weekly for patients with mucosal or gastro-intestinal side effects of MTX.[10]

Interacting drugs affect serum MTX levels. Non-steroidal anti-inflammatory drugs (NSAIDs) have the ability to reduce MTX excretion by their effect on renal tubules. The British National Formulary also advises that the MTX dose should be carefully monitored if NSAIDs are given alongside and patients should also be advised to avoid self-medication with over-the-counter NSAIDs.[10]

Conclusion

Early diagnosis of adverse drug reactions is essential to avoid untoward oral complications. Treatment of these lesions is by identification and withdrawal of the offending drug.

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