CASE REPORT

A Case Report of Oral Ulcer in Rheumatoid Arthritis: A Diagnostic and Management Dilemma

Siti Asmat Md Arepen[1], Dinie Qistina Rajalie[2], Azreen Zaira Abu Bakar[2], Nor Azirah Salahuddin[1], Nour Hanan Daniah Mohd Bakhit[1], Ahmad Anwaar Muhammad Saifullah[1], Nor Eyzawiah Hassan[1]

[1] Otorhinolaryngology Head and Neck Surgery, Surgical-based Department, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia
[2] Department of Otorhinolaryngology, Hospital Kuala Lumpur, Malaysia

ABSTRACT

Chronic oral ulcer in patients with rheumatoid arthritis is a diagnostic challenge in primary health care. The possible causes include the disease itself, side effect of treatment, malignancy and infections. This is a case of a 63-year-old woman with underlying rheumatoid arthritis presented with chronic solitary oral ulcer. She was on oral methotrexate (MTX) and high dose folic acid for five years with good compliance. Tissue biopsy showed marked inflammatory cells infiltration and nuclear hyperchromatism with no evidence of malignancy nor infection. The ulcer was resolved after completing antifungal treatment for six weeks following failure of improvement after empirical antibiotic, elimination of possible trauma and discontinuation of MTX. The fungal staining was negative. There are possibilities of false negative results, thus broadened diagnosis with repeated and further investigations are recommended in cases who did not respond to conventional treatment.
Malaysian Journal of Medicine and Health Sciences (2023) 19(SUPP19):31-33. doi:10.47836/mjmhs.19.s19.9

Keywords: Oral ulcer, rheumatoid arthritis, methotrexate, autoimmune disease, immunocompromised patient

Corresponding Author:
Nor Eyzawiah Hassan, Doctor of Otorhinolaryngology, Head & Neck Surgeon
Email: eyzawiah@usim.edu.my
Tel: +606 7985002

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive multisystemic autoimmune disorder with a global prevalence of 0.24% (95% CI, 0.23-0.25%). The prevalence of RA in European countries ranges from 0.5% to 0.9%, while in Asian countries the range is from 0.26 to 0.75% (1). Typically, oral ulcers in RA patients are often attributed to the use of anti-rheumatic drugs for disease management. However, in view of the intricate clinical terrain of RA, infection due to the immunosuppressive state of the disease and malignancy associated RA such as lymphoma and oral cancer can closely mimic the presentation of oral ulcers. Therefore, a comprehensive assessment and multidisciplinary management are warranted to arrive at the diagnosis especially given that chronic oral ulcers are frequently encountered in primary healthcare settings. This case report explores the intricate diagnostic process and the challenges in managing chronic oral ulcers in an RA patient. What sets this case apart is the remarkable diagnostic dilemma it posed, urging us to consider fungal infections as a potential differential diagnosis for patients with similar clinical presentations in the future.

CASE REPORT

A 63-year-old woman with underlying rheumatoid arthritis presented with a painful ulcer on her tongue for one month. She has been taking oral methotrexate at a weekly dose of 20mg, along with daily oral folic acid for the past five years and she has remained compliant with her prescribed medications. She denied any history of trauma, frequent biting or betel nut chewing. Her other RA symptoms were well controlled, with no other systemic symptoms suggestive of oral methotrexate (MTX) toxicity such as shortness of breath, abdominal pain, diarrhoea and dehydration nor was there any constitutional symptoms. She is a non-smoker and does not drink alcohol.

Intraoral examination showed a 0.5 x 0.5cm superficial ulcer at the tip of the tongue, with a whitish bed and induration area surrounding it (Fig. 1). Apart from that, no discharge or bleeding was seen. Other ear, nose and throat (ENT) examinations including the neck, were unremarkable.

Our initial assessment led us to a diagnosis of an infected oral ulcer, for which we initiated a two-week course

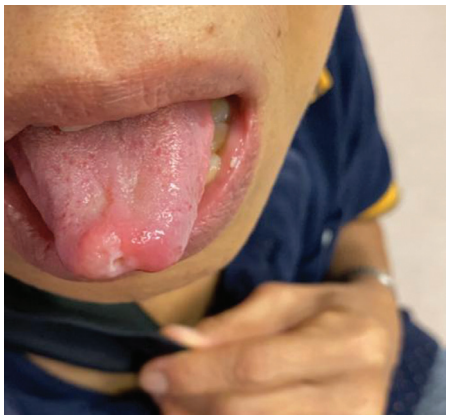

Figure 1: Oral ulcer over the tip of the tongue on initial presentation.

of empirical oral antibiotics. Unfortunately, the ulcer showed no signs of improvement during this treatment period, prompting a shift in our differential diagnosis to oral carcinoma. Consequently, a biopsy of the tip of tongue was performed, and the histopathological examination revealed it was consistent with ulcer with the presence of granulation tissue, marked infiltrate of neutrophil and lymphocytes, reactive change of squamous cell with moderate nuclear enlargement and nuclear hyperchromatic without dysplasia (Fig. 2). Grocott methenamine silver (GMS) staining for fungal was negative. All laboratory tests including renal and hepatic functions were normal. Based on these histopathological findings, we included chronic MTX toxicity as a possible differential diagnosis.

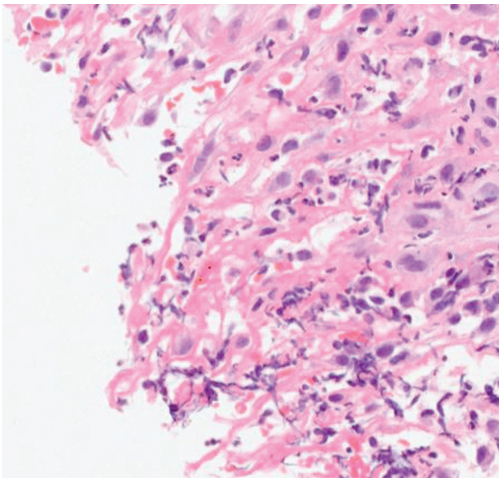

Figure 2: Histopathology findings (H&Ex20) showed the presence of granulation tissue, marked infiltrate of neutrophil and lymphocytes

The patient received consultations from both a rheumatologist and a dentist. The oral methotrexate was temporarily withheld for a period of three weeks, with a strong recommendation for strict adherence to folic acid supplementation. Simultaneously, she underwent dental intervention to address a sharp tooth in proximity to the ulcer. Regrettably, despite these measures, the ulcer showed no signs of regression (Fig. 3). Consequently, we broadened the scope of potential causes for the ulcer to include opportunistic infection. As there was no

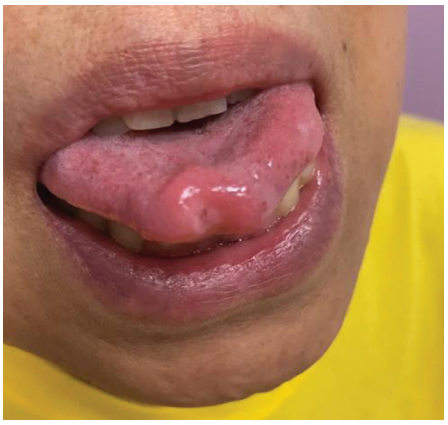

Figure 3: Poor healing oral ulcer three weeks after discontinuation of methotrexate

improvement of symptoms by the third week of watchful follow up, a consultation with the infectious diseases team was requested. Despite her initial negative fungal staining, we initiated a trial of oral antifungal fluconazole for six weeks with tapering up dosage (initial 100 mg daily for two weeks then 200 mg daily). Remarkably, the patient responded positively to the treatment with a notable alleviation of symptoms and substantial re-epithelialization of the ulcer after six weeks of antifungal therapy (Fig. 4). Therefore, no repeated tissue diagnosis nor fungal culture and sensitivity was performed. She remained free from the condition six months after completing the treatment, with no reports of recurrence.

DISCUSSION

Oral lesions are notably prevalent in rheumatoid arthritis (RA), affecting approximately 59.1% of patients. In this particular case, the patient presented with chronic solitary tip of tongue ulcer that had been troubling her for a month. It is generally accepted in most literature that ulcers are considered chronic if it lasts for more than two weeks. While the nature and frequency of oral mucosal pathology in RA are less clearly described, the oral conditions might be due to hyposalivation (2). Furthermore, this lesion is believed to have multiple aetiologies which includes the manifestation of RA

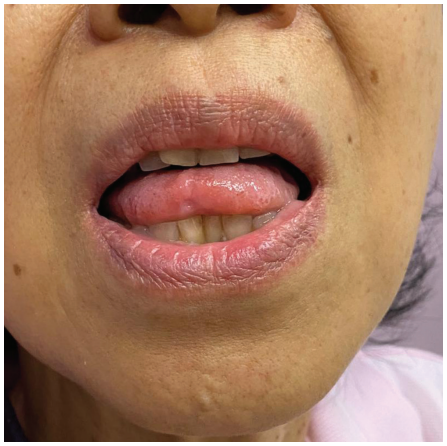

Figure 4: The oral ulcer is healed after six weeks of antifungal therapy

itself, effects of disease modifying anti-rheumatic drugs (DMARDs) like methotrexate (2-10%) and sulfasalazine (4%), opportunistic infections, malignancy and nutritional deficiency. Patients with RA have an increased risk of malignancy with standardized incidence ratios of 4.05 for Hodgkin lymphoma, followed by non-Hodgkin lymphoma (2.34) and squamous cell carcinoma (1.89) due to immunocompromised state of RA (3).

DMARDs including MTX are the mainstay treatment for RA. MTX inhibits the production of inflammatory mediators by blocking the replication of the immune cells. Oral ulcer is a known side effect of MTX as the oral mucosa has rapidly dividing cells which are sensitive to DNA base depletion. Most reported MTX-induced oral ulcers are due to unintended over dosage and chronic toxicity from low dose MTX, even if the correct dose is administered. MTX overdose is accompanied by systemic symptoms such as shortness of breath, abdominal pain, diarrhoea and dehydration. Diagnosis of chronic MTX toxicity is supported by histopathological features of biopsied tissue using Kalantzis criteria which includes hyperchromatic enlarged nuclei in scattered cells, mild dysplasia, and inflammatory connective tissue reactions (4). In addition, subclinical folate deficiency is common and should be ruled out prior to low dose MTX treatment but may recur during treatment. Pre-existing folate deficiency increases MTX toxicity toward the oral mucosa. The recommended treatment of MTX toxicity includes cessation of treatment, reducing its dose, folic acid or folinic acid supplementation, or a combination of these measures (4).

The immunosuppressed condition that results from treating RA can make patients more susceptible to opportunistic infections This etiology has often been overlooked when considering the possible cause of an oral ulcers. Mycoses of the oral cavity can cause chronic oral ulcer in immunocompromised patients. Although the histopathological examination of the present case did not reveal any bacterial or fungal colonization, the symptoms and signs did resolve following antifungal treatment. This may suggest of a possible false negative result for the GMS staining which has been reported in another study (5). Antigen and PCR-based diagnostic tests are valuable tools alongside microscopic inspection and culture methods to enhance the sensitive detection of fungal infections. Failed antibiotic therapy should not only prompt the commencement of antifungal treatment but also the thorough utilization of all accessible diagnostic resources. This includes repeating investigations as necessary without prolonged interval when initial findings yield negative results. Empirical antifungal therapy is usually initiated when an occult infection cannot be excluded and concurrently, the diagnosis should be pursued continuously.

Moreover, the patient's immunocompromised status can contribute to delayed healing. In this instance, distinguishing between healing attributed to antifungal treatment and slow healing resulting from immunosuppression is challenging. This limitation in our case makes it difficult to conclusively establish that the healing is solely attributable to the antifungal treatment rather than natural healing processes. This could be the limitation of our case to prove that the healing is due to the antifungal despite self-healing. Future case series or well-designed clinical studies may provide a more comprehensive understanding of antifungal responses, particularly in cases where cultures or stains yield negative results.

CONCLUSION

Chronic oral ulcer in rheumatoid arthritis patients continues to present a formidable challenge. Proper evaluation of the oral ulcer demands meticulous history taking, including a comprehensive assessment of the patient's medication list to identify possible drug interactions. Even though MTX toxicity is a common concern, opportunistic infections such as fungal infections should be considered if other measures are proven futile. Thus, a seemingly simple presentation of a chronic oral ulcer actually necessitates a thorough assessment with multidisciplinary approach and management.

ACKNOWLEDGEMENTS

We thank the Director General of Health Malaysia for his permission to publish this article (NIH.800-4/4/1 Jld. 98(50). Patient's verbal consent was obtained.

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