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Single Case

Primary Idiopathic Complex Aphthosis: Diagnosis and Successful Treatment with Montelukast in a 44-Year-Old Filipino Female

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Keywords
Complex aphthosis · Oral pathology · Inflammation

Abstract
Recurrent aphthous stomatitis (RAS) is an oral condition characterized by frequent attacks of painful oral ulcers. Complex aphthosis (CA) is a severe form of RAS described as the almost constant presence of ≥3 oral ulcers with or without genital aphthosis. Management of primary CA varies, but most patients warrant the use of systemic agents. Because of prolonged treatment, it is preferred to use systemic medications with the least side effects.
Herein, we present a case of a primary idiopathic CA. Workup and examination were done to exclude Adamantiades-Behçet's disease and other diseases. The patient was shifted to montelukast after poor tolerance to colchicine. Favorable control of CA was noted during the 5-month follow-up period while the patient was on montelukast.

Introduction

Recurrent aphthous stomatitis (RAS) is the most common mucosal disease accounting for 20–50% of the general population with a peak incidence during the second decade of life [1].

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RAS may result from immune dysregulation leading to a proinflammatory state, or it can be a secondary manifestation of underlying systemic conditions such as nutritional deficiencies, microbial infections, and autoimmune blistering diseases [2, 3]. Complex aphthosis (CA) is a severe form of RAS, defined as the almost always constant presence of ≥3 oral ulcers with or without genital aphthosis along with the exclusion of Adamantiades-Behçet's disease.

Despite having a high incidence worldwide, RAS continues to be a poorly understood condition [3]. Currently, the treatment of this disease remains to be a dilemma. The goals of management are focused on alleviating pain, decreasing the duration of ulcers, and minimizing recurrences [3]. Treatment of CA may even be more challenging due to its severity and intractability, often requiring the use of systemic therapies. Agents with fewer adverse effects are preferable due to protracted treatment.

Case Report

A 44-year-old female presented with an 8-year history of persistent and painful oral ulcers. The patient was well with no known aggravating factors except for emotional stress. She received several medical therapies, from topical antiseptic solutions to systemic antimicrobials. However, these did not provide any relief of aphthosis. The patient self-medicated with oral prednisone for several years, which controlled the disease activity. However, she developed incapacitating attacks of oral aphthosis a few months before consult. This was not associated with fever, weakness, joint pains, photosensitivity, and genital or ocular symptoms. Persistence of oral aphthosis prompted admission and subsequent referral to dermatology.

Physical examination revealed multiple oral ulcers on the right tonsil, tonsillar pillar, and posterior pharyngeal wall (Fig. 1). Palpable, tender lymphadenopathy was noted at her right level II neck, measuring approximately 1 × 1 cm with surrounding edema. The rest of the physical examination was unremarkable, including normal genitalia and ocular findings. She also tested negative in her pathergy test. Computed tomography scan of the head and neck showed soft tissue swelling on the right neck but otherwise she had no other unusual findings. Other laboratory tests (complete blood count, HIV screening, ELISA desmoglein 3 level, bacterial culture, mycology, and tzanck smear) were unremarkable as well. Herpes simplex virus IgG was positive, implying a previous infection. However, her clinical findings did not fit for an active herpes infection during the time of her admission. Although nutritional deficiency screening was ideal, this was eventually deferred due to the patient's limitation in resources. Nevertheless, no other manifestations of nutritional deficiency were noted in her review of systems.

Otorhinolaryngology opted to do bilateral tonsillectomy to definitively rule out malignancy due to the chronicity of the non-healing ulcers. Direct immunofluorescence was negative. Histopathology revealed hypertrophic tonsils with ulceration. Diffuse mixed infiltrates and granulation tissue reaction were seen, with no signs of atypia or viral cytopathic changes. It was also negative for fungal elements assessed using the Periodic Acid-Schiff stain (Fig. 2a–d). Diagnosis of CA was favored, based on history, clinical evaluation, and the exclusion of underlying diseases. During the postoperative period, the patient developed more aphthous ulcers around the buccal mucosa, gingiva, and tongue. Colchicine was started and gradually titrated up to 1.5 mg/day. This was combined with topical glucocorticoids and intralesional triamcinolone acetonide injection (10 mg/mL). Significant reduction of severity, duration, and frequency of aphthosis was observed while the patient was on treatment (Fig. 3a–b).

However, colchicine was discontinued after 3 months due to gastric intolerance. Recurrence of oral ulcers was then noted on follow-up 1 month after discontinuation of therapy.

A trial of montelukast (10 mg/day) combined with topical therapies were given based on the pilot study of Femiano et al. [2] During the 5-month period while the patient was on montelukast, a significant reduction in pain, duration, and attacks of oral aphthosis was noted. Specifically, the patient reported a 50% decrease (from 8/10 to 4/10) in her pain score using an 11-point visual analog scale, after the first week of treatment. In addition, the patient was noted to have an average of 3 or less small ulcers per month during the entire period of observation. Faster healing time of her ulcers was also reported, from approximately 4 weeks without medication to 1–2 weeks while on montelukast.

Case Discussion

There is no standardized algorithm for the diagnosis and treatment of CA. Workup and management are recommended to be tailored individually. Nevertheless, most cases of CA require systemic therapies, as topical agents alone have been reported to be inadequate for control of the disease [1, 3]. One of the more effective systemic agents commonly used in the treatment of CA is oral prednisone [3]. However, prolonged systemic steroid use is also known to be associated with severe adverse effects [1–3]. Another studied drug for CA is colchicine, reported to provide moderate control of disease in 28% of patients [1]. However, most patients develop gastrointestinal symptoms which hinders maximal dosing and long-term use [1].

Neutrophilic chemotaxis and activity are known to play essential roles in the pathogenesis of RAS. Thus, a leukotriene receptor inhibitor like montelukast may potentially reduce the symptoms of RAS [2]. The study of Femiano et al. [2] showed that montelukast (10 mg/day then every other day after 1 month) was as effective as prednisone (25 mg/day tapered after every 15 days) in pain relief and healing of ulcers in patients with RAS. Two-month use of montelukast in that study showed a reduction of oral ulcers and prevented recurrences during their follow-up period. Despite faster pain relief and healing with prednisone, they concluded that montelukast may be the safer choice as it was not associated with the adverse effects commonly seen with systemic steroid use. A series by Mertz et al. [4] also supports the effectivity of montelukast in periodic fever, aphthous stomatitis, pharyngitis, and adenitis.

Our case supports the report of Femiano et al. [2] that montelukast may be an effective drug in the management of RAS. It also suggests efficacy of montelukast even in CA, the severe form of RAS. Despite not achieving total pain relief, our patient reported a 50% decrease in pain score after just 1 week of treatment. This was similar to the results of Femiano et al. [2] which reported an average time to pain relief of 6.9 days in patients with RAS. Montelukast also provided efficacy in limiting the number of ulcers in our patient (maximum of 3 small ulcers monthly). This was in line with their results, which reported a significant decrease in the number of lesions per month compared to placebo. Healing time of the ulcers while on montelukast was also similar in our patient (1–2 weeks) and in their cohort (10–12 days).

Conclusion

Our case suggests that montelukast may be an effective treatment strategy in the management of CA. Its safety profile may also be preferable compared to other systemic agents

commonly used for this disease. Larger prospective studies with longer follow-up are warranted.

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Statement of Ethics

I testify on behalf of my co-author that our article submitted to *Case Reports in Dermatology* entitled "Primary idiopathic complex aphthosis: diagnosis and successful treatment with montelukast in a 44-year old Filipino female" fulfills the following:

1 This material has not been published in whole or in part elsewhere.

2 The manuscript is not currently being considered for publication in another journal.

3 All authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.

4 Consent was obtained from the patient to publish her case including photographs.

5 The patient, in this case, was not identified and pictures included in the manuscript show no identifying marks that would pertain to the patient.

6 This study was conducted in adherence to the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Both authors are involved in the following: conception or design of the work; acquisition, analysis, or interpretation of data for the work; drafting the work or revising it; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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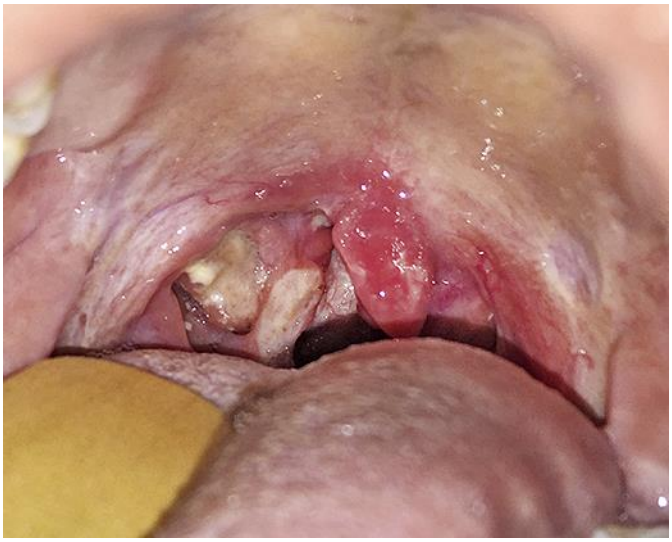

Fig. 1. Multiple well-defined ulcers with fibrinous base and surrounding erythema.

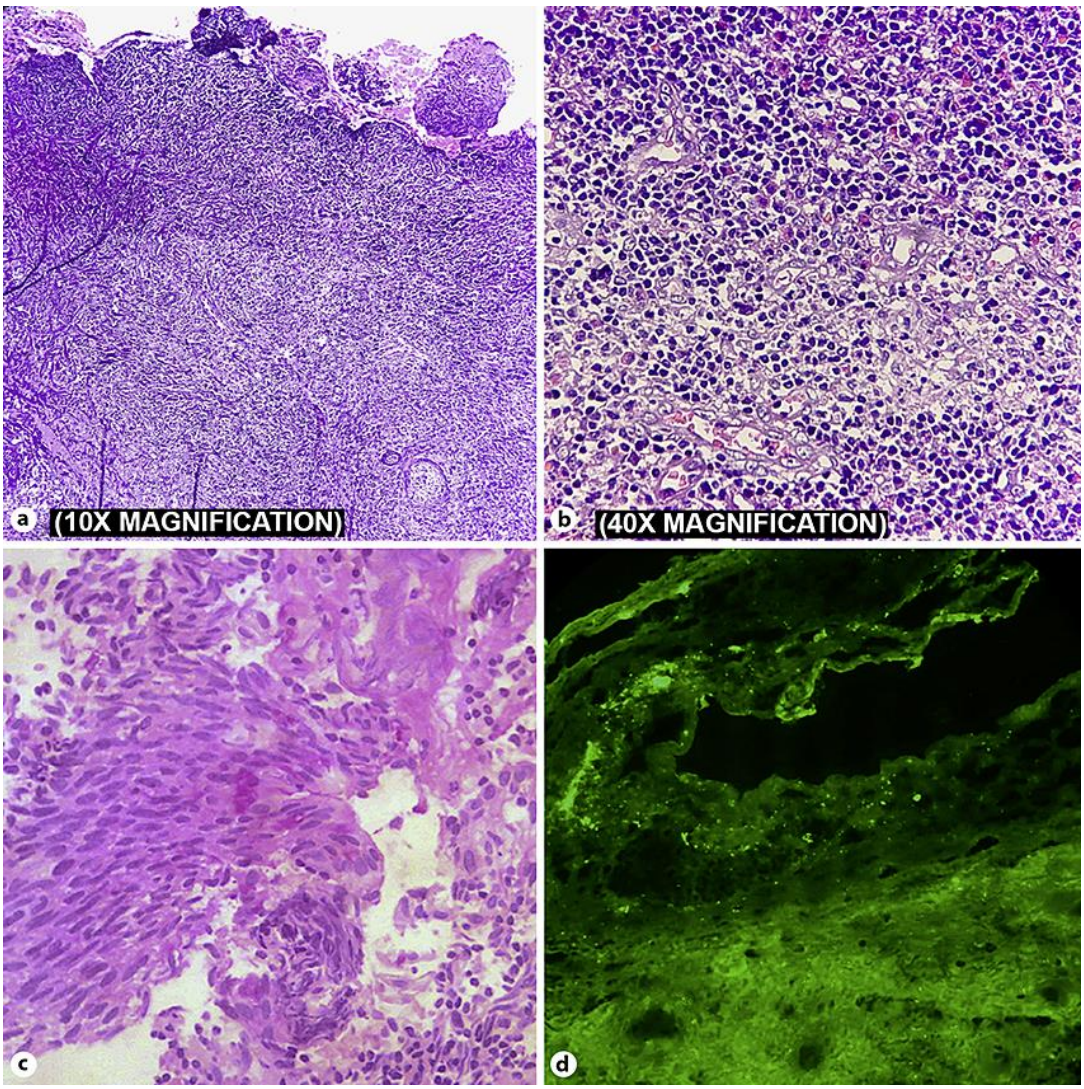

Fig. 2. **a**, **b** H&E shows hypertrophic tonsils with ulcerations, the dermis shows dense and diffuse mixed infiltrates; and proliferation of large dilated blood vessels with no signs of atypia or viral cytopathic changes. **c** Periodic Acid-Schiff stain for the assessment of fungal elements is negative. **d** Direct immunofluorescence is negative for immunoreactants.

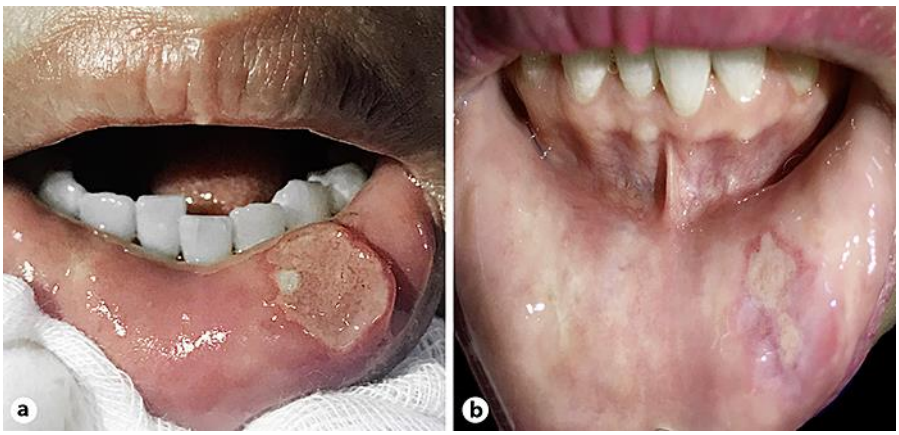

Fig. 3. **a** Postoperatively the patient developed multiple aphthous ulcers and was started on colchicine (up to 1.5 mg/day) with intralesional steroid injection as an adjunct. **b** Two weeks after treatment.