Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Periodontology and Implantology

Journal homepage: https://www.ijpi.in/

Case Report

Management of major recurrent aphthous ulcers with 5% amlexanox oral paste and rebamipide tablets- A case report with a brief literature review

Shamimul Hasan[1]*, **Mohd. Faisal Siddique**[1]

[1] *Faculty of Dentistry Jamia Millia Islamia, Jamia Nagar, New Delhi, India*

ARTICLE INFO

Article history:
Received 11-10-2023
Accepted 20-11-2023
Available online 02-12-2023

Keywords:
Amlexanox
Rebamipide
Recurrent aphthous stomatitis
Major aphthaous
corticosteroids

ABSTRACT

Recurrent aphthous stomatitis (RAS) is a common chronic inflammatory oral mucosal disorder marked by the presence of painful, recurring ulcers, occurring either as solitary lesions or in multiple clusters. While the clinical features of this condition are easily recognizable, the precise etiology remains obscure. The disorder manifests in three forms, of which minor RAS are the commonest and heal within 10-14 days. Major RAS presents as larger, painful chronic ulcerations and heals with scarring in 6-8 weeks. A comprehensive medical history and a thorough systemic examination can aid the physician in determining whether the condition is idiopathic or linked to a underlying systemic disorder. The management of oral aphthous ulcers poses a significant challenge and there is no established and defined therapeutic regimen available for RAS.

We present a case of major RAS in a 37-year-old patient who was unresponsive to topical and systemic steroid therapy. 5% Amlexenox paste and rebamipide tablets were used in the present case. The patient showed favourable healing within a week therapy with no recurrences during the 6-month follow up.

1. Introduction

The term "aphtha" is derived from the Greek word "aphthi," signifying inflammation or a burning sensation. It was coined by Hippocrates, who initially used these terms to describe oral diseases.[1] The term "recurrent aphthous stomatitis" (RAS) is appropriate for individuals in whom an identifiable cause cannot be determined, requiring a diagnosis based on exclusion.[2]

RAS is one of the frequently encountered conditions affecting the oral mucosa that primarily affects individuals in the age range of 10-40 years, with an estimated prevalence ranging from 5 to 25%.[3] Painful, round ulcers with distinct red borders and a grayish-yellow pseudo membranous base seen in typically healthy individuals characterize RAS. A burning sensation may occur 2 to 48 hours before the ulcers develop.[4] RAS exhibit a site predilection for the non-keratinized mucosa, occurring primarily on the buccal & labial mucosa, lateral and ventral tongue surfaces, and the floor of the mouth.[5]

RAS may be categorized into three forms: Minor (accounting for over 70% of cases), major (occurring in 10-15% of cases), and herpetiform (present in 5-10% of cases). These types vary in terms of morphology, distribution, severity, and prognosis.[2] Despite its high prevalence, the precise etiology of RAS remains obscure.[6] The prevailing theory on the development of RAS suggests a local immune dysfunction in which T-lymphocytes play a crucial role.[7]

Currently, there is no established treatment protocol for RAS, and the management primarily relies on alleviating pain, minimizing inflammation, and facilitating wound healing. Topical steroids are considered the standard first-line pharmacotherapy for RAS, however, prolonged use of steroids can lead to various side effects.[2–6]

* *Corresponding author.*
E-mail address: shamim0571@gmail.com (S. Hasan).

https://doi.org/10.18231/j.ijpi.2023.043

Amlexanox (C16H14N2O4) is a topical anti-inflammatory drug authorized for the treatment of RAS. It acts by inhibiting the formation and release of histamine, tumor necrosis factor-α (TNF-α), and leukotrienes from mast cells, neutrophils, and mononuclear cells.[8] Currently, 5% Amlexanox oral paste is the only therapeutic product for RAS approved by the Food and Drug Administration (FDA) US.[9]

Topical therapy solely does not result in diminution of a new lesion development and may not be an adequate therapy for patients with major RAS or those experiencing frequent episodes of multiple minor RAS.[2,10]

Rebamipide is a commonly employed therapy for Behcet's disease patients, particularly those presenting oral aphthous as the primary symptom.[11] Furthermore, it may also be beneficial in the prevention and treatment of RAS.[12] The drug is easy to administer, exhibits patient compliance, and helps reduce both the count of aphthae and pain scores. It functions by reducing oxygen radicals, enhancing vascularity, and stimulating the production of protective prostaglandins in ulcerated mucosa, thereby expediting the healing process.[12,13]

The evolving treatment strategy for RAS involves the topical application of 5% Amlexanox oral paste and the systemic ingestion of Rebamipide tablets. Published literature has demonstrated that 5% Amlexanox oral paste and Rebamipide tablets play a crucial role in the pharmacotherapy of RAS.[8,11,13]

2. Case Presentation

A 37-year-old male was referred by a private practitioner to our Outpatient Department for the evaluation of non-healing oral ulcers for the last 20 days. History revealed that he has been experiencing multiple episodes of oral ulcerations for the past one year. However, the frequency of ulcer episodes had increased in the past 3 months. His medical and family history was non-contributory, and the patient denied the intake of any systemic medications. There was no history of any fever, weight loss, hemoptysis, anemia, abdominal pain, or diarrhoea. The patient had sought advice from various private practitioners and had been prescribed medications. Past prescriptions included the topical application of Metrohex gel (0.25% chlorhexidine gluconate and 1% metronidazole), Turbocort oromucosal paste (triamcinolone acetonide 0.1%), and systemic intake of tablet Betnesol (Betamethasone, 0.5 mg twice daily) for 10 days. Nevertheless, the ulcers showed no improvement with the prescribed therapy. The general physical examination was non-contributory, with no systemic and nodal involvement.

On intraoral examination, an ovoid shallow ulcer on the left labial mucosa measuring 1.5 cm × 1.2 cm was seen. Similar presenting ulcers were also seen on the right lateral border of tongue and floor of the mouth, roughly measuring 1.2 cm x 1 cm in diameter and 2 cm x 1.5 cm respectively. The ulcers were surrounded by perilesional erythema and covered with a yellowish pseudomembrane. Mild tenderness (VAS score of 7) and induration on palpation was also elicited [Figure 1 (A-C)].

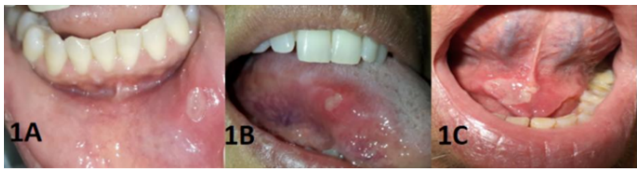

Figure 1: (A) Ulcer on the left labial mucosa **(B)** Ulcer at the right lateral of tongue **(C)** Ulcer on the floor of mouth

Figure 2: (A)-(C) Healed lesions

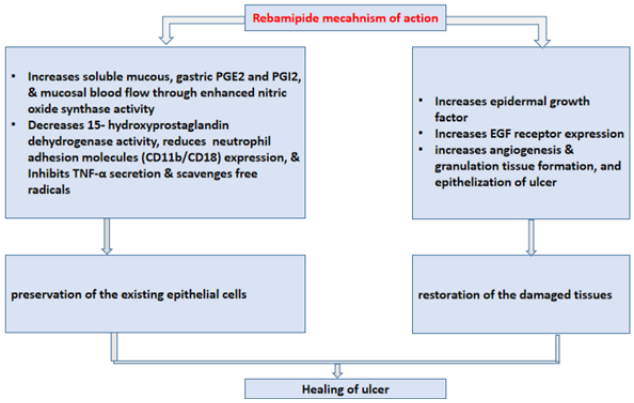

Figure 3: Flowchart depicting mechanism of action of Rebamipide

A diagnosis of major RAU was given based on the history, symptoms, and clinical examination. The patient reported hematological, biochemical, and radiographic investigations that had been done a week prior, following the private practitioner's recommendation. Hematologic investigations including complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum levels of iron, and ferritin were in the normal range. The Mantoux test showed a non-reactive result, and a chest radiograph (PA) view revealed normal lung fields and bronchovascular markings bilaterally. The colonoscopy reports, which were normal and showed no signs of inflammatory bowel disease. The patient was prescribed topical application of 5% Amlexenox oral paste (lexenox oral paste) three times daily and Rebamipide (tablet Rebagen) 100mg TDS for 10 days. The patient was reviewed after 10 days and the ulcers showed complete

Table 1: Summarizing the various forms of aphthous stomatitis

Features	Minor RAS(canker sore or Mikuliz's aphthae)	Major RAS (peri-adenitis mucosa necrotica recurrens or Sutton's disease)	Herpetiform RAS
Frequency of Occurrence	70-80%	10-15%	5-10%
Size of ulcers	<10mm	>10mm	2-3mm
Number of ulcers	1–5	1–10	10-100
Morphology	Roundoroval lesions Gray-whitepseudo membranes Erythematous halo	Roundoroval lesions Gray-whitepseudo membranes Erythematous halo	Multiple, Small ulcers that commonlyconverge Irregular contour
Depth	Shallow	Deep	Shallow
Distribution	Non-keratinized oral mucosa. Often: lips, buccal regions, tongue margins	Keratinized and non-keratinized oral mucosa. Often: soft palate, faucial pillars, gingiva, and dorsum of the tongue	Non-keratinized oral mucosa. Often: floor of the mouth, ventral surface of the tongue
Gender predilection	Males & Females	Males & Females	Females
Peak age of onset	2^{nd} decade	1^{st} & 2^{nd} decade	3^{rd} decade
Duration	10–14 days	6-8 weeks	10–14 days
Healing	No scarring	Heal with Scarring	Scarring uncommon

healing [Figure 2 (A-C)]. There was no recurrences observed in the 6 month follow-up period.

3. Discussion

Recurrent aphthous stomatitis (RAS) is considered a chronic inflammatory oral mucosal disorder.[14] Stanley has classified RAS into three distinct clinical variants.[15] The different types of RAS are summarized in Table 1.[1,8,14,16,17]

The exact cause of RAS is unknown, necessitating careful clinical observation and offering various therapeutic options, albeit with limited relief.[8,18] Cell-mediated immunity plays a role in the immunopathogenesis of RAS. TNF-α, produced by T cells, macrophages, and mast cells triggers mucosal inflammation by promoting the endothelial cells adhesion and neutrophils chemotaxis.[18] Various recognized predisposing factors encompass genetic alterations, nutritional and hematinic deficiencies, chronic mucosal trauma, smoking cessation, endocrine and immune dysfunction, food and drug allergies, and psychosomatic diseases like stress, anxiety, stress, and depression. RAS-like lesions may also be seen in various systemic conditions like inflammatory Bowel Disease and cyclic neutropenia, and syndromes such as Behcet's syndrome, Reiter syndrome, PFAPA syndrome, MAGIC syndrome, and Sweet syndrome.[2,3,8]

The diagnosis of RAS relies on the patient's history and clinical features.[10] Herpetic ulcers, traumatic ulcers, malignant ulcers, oral tuberculous ulcers, syphilitic ulcers, and RAS-like ulcers are given a place in the differential diagnosis of aphthous ulcers.[19] Natah et al.[20] proposed the diagnostic criteria for minor RAS.

The primary therapeutic objectives are to alleviate pain, diminish the size and duration of ulcers, and restore normal oral function. Secondary goals involve decreasing the frequency and severity of ulcer recurrences. Various treatments have been explored, encompassing topical agents, systemic medications, physical approaches, as well as natural and home therapies.[17]

Topical treatment is deemed effective for managing minor recurrent aphthous ulcers (MiRAU) and is also considered as a supplementary approach for treating major recurrent aphthous ulcers (MaRAU). Currently, recognized effective topical treatments include topical medication, cryotherapy, laser therapy, and cautery.[21] However, systemic pharmacotherapy (systemic steroids, azathioprine, colchicine, cyclosporine, thalidomide, levamisole) is allocated for patients with multiple minor aphthae, major RAS, and cases refractory to topical therapies.[8,22]

Amlexanox exhibits anti-inflammatory, anti-allergic, and immunomodulatory properties.[21,23] It inhibits the formation and release of histamine and leukotrienes from mast cells, neutrophils, and mononuclear cells, possibly through an increase in intracellular cyclic AMP content in inflammatory cells and a membrane-stabilizing effect, or by inhibiting calcium influx.[17,23] 5% amlexanox is the most effective pharmacotherapy for minor RAS, demonstrating a triple effect in preventing recurrence, reducing healing time, and alleviating pain. It is particularly effective when applied from the prodromal phase until complete healing, four times a day, yielding statistically significant results.[20,22]

Amlexanox oral paste is specifically prepared to enhance mucosal adherence, thus, minimizing the risk of the drug being rubbed or rinsed away by saliva, as indicated by the manufacturer's instructions (Macleods Pharmaceuticals, Mumbai, India).[24] Topical application of 5% amlexanox has infrequently demonstrated adverse effects like mild and transient tingling sensations, a metallic taste, xerostomia, and bleeding at the application site.[8,25]

Rebamipide 2-(4-chlorobenzoyllamine)-3-[2-(1H)-quinolinon-4-yl) is a mucoprotective medication that preserves the vitality of epithelial cells and facilitates the restoration of damaged tissue through multi-modal actions.[8,11,26]

It enhances the preservation of existing epithelial cells by increasing the content of soluble mucus, increasing the gastric concentrations of PGE2 and PGI2, down regulation of 15- hydroxyprostaglandin dehydrogenase, increasing mucosal blood flow through enhanced nitric oxide synthase activity, decreasing the expression of neutrophil adhesion molecules (CD11b/CD18), inhibiting the secretion of TNF; α by inhibiting the synthesis of inflammatory E; selectin and has a free radical scavenging effect on reactive oxygen species. It also restores the damaged tissues by increasing the expression of epidermal growth factor and EGF receptors. This eventually leads to angiogenesis, increased production of granulation tissue, and epithelization of ulcer healing.[12,27]

The mechanism of action of Rebamipide is illustrated in a flowchart [Figure 3].

Rebamipide has demonstrated effective improvement in various mucosal conditions, including gastric ulceration and erosions.[28] Rebamipide also decreases both the number and pain of oral ulcers in patients with Behcet's disease.[13] Published studies have demonstrated the efficacy of Rebamipide in the pharmacotherapy of Behcet's disease and RAS,[8,12,13] supporting its recommendation as a long-term treatment for recurrent oral aphthous ulcers.[16]

Uncommon mild gastrointestinal side effects, such as nausea, vomiting, diarrhea, and constipation, have been observed with Rebamipide therapy.[8]

4. Conclusion

Extensive research has confirmed that RAS has a multifactorial etiology, and there is no established and precise treatment approach for the condition. Given that the primary concerns for most patients are pain and irritation resulting from aphthous stomatitis, the majority of treatments focus on relieving pain and addressing the patient's symptoms.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Compilato D, Carroccio A, Calvino F, Fede D, Campisi G. Hematological deficiencies in patients with recurrent aphthosis. *J Eur Acad Dermatol Venereol*. 2010;24(6):667–73.
2. Guallar IB, Soriano YJ, Lozano AC. Treatment of recurrent aphthous stomatitis. A literature review. *J Clin Exp Dent*. 2014;6(2):168–74.
3. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: a review. *J oral Pathol Med*. 2012;41(8):577–83.
4. Bernal JS, Conejero C, Conejero R. Recurrent Aphthous Stomatitis. *Actas Dermosifiliogr*. 2020;111(6):471–80.
5. Molania T, Shafaroudi M, Saeedi A, Moosazadeh M, Valipour M, Rostamkalaei F, et al. Evaluation of cinnamaldehyde mucoadhesive patches on minor recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled clinical trial. *BMC Oral Health*. 2022;22(1):235. doi:10.1186/s12903-022-02248-5.
6. Umpreecha C, Bhalang K, Charnvanich D, Luckanagul J. Efficacy and safety of topical 0.1% cannabidiol for managing recurrent aphthous ulcers: a randomized controlled trial. *BMC Complement Med Ther*. 2023;23(1):57.
7. Savadori P, Rai PM, Tadakamadla S, Khijmatgar S, Inchingolo F, Greco C. Minor Recurrent Aphthous Ulcer Management with Hyaluronic Acid Gel in an Italian Cohort: A Double-Blind Randomized Clinical Trial. *BioMed Res Int*. 2022;10:1–10. doi:10.1155/2022/7202831.
8. Hasan S, Perween N, Saeed S, Kaur M, Gombra V, Rai A. Evaluation of 5% Amlexenox Oral Paste and Rebamipide Tablets in Treatment of Recurrent Aphthous Stomatitis and Comparison with Dologel CT. *Indian J Otolaryngol Head Neck Surg*. 2022;74(3):5228–62.
9. Shrivastava K, Naidu G, Deshpande A, Handa H, Raghuvanshi V, Gupta M. Comparative evaluation of the efficacy of topical amlexanox 5% oral paste and triamcinolone acetonide 0.1% oral paste in the treatment of recurrent aphthous stomatitis (RAS). *J Indian Acad Oral Med Radiol*. 2018;30:235–75.
10. Sharma R, Pallagatti S, Aggarwal A, Sheikh S, Singh R, Gupta D. Double-Blind, Placebo-Controlled Trial on Clinical Efficacy of Topical Agents in Reducing Pain and Frequency of Recurrent Aphthous Ulcers. *Open Dent J*. 2018;12:700–13.
11. Matsuda T, Ohno S, Hirohata S. Efficacy of Rebamipide as adjunctive therapy in the treatment of recurrent aphthous ulcers in patients with Behcet's disease: A randomized, double-blind, placebo-controlled study. *Drugs R D*. 2003;4(1):19–28.
12. Kudur MH, Hulmani M. Rebamipide: A novel agent in the treatment of recurrent aphthous ulcer and Behcet's syndrome. *Indian J Dermatol*. 2013;58(5):352–4.
13. Khandwala A, Van Inwegen R, Alfano MC. 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;83(2):222–52.
14. Slebioda Z, Szponar E, Kowalska A. Etiopathogenesis of Recurrent Aphthous Stomatitis and the Role of Immunologic Aspects: Literature Review. *Arch Immunol Ther Exp*. 2014;62(3):205–20.
15. Stanley HR. Aphthous lesions. *Oral Surg Oral Med Oral Pathol*. 1972;33(3):407–23.
16. Parvathi DMK, Ramesh D, Koppal S, Byatnal AR, Rukmangada T, Byatnal AA, et al. Efficacy of rebamipide and levamisole in the treatment of patients with recurrent aphthous ulcer- A comparative study. *J Clin Diagn Res*. 2014;8(11):119–41.
17. Yousef NJ, Aljoujou AA, Mashlah AM, Hajeer MY. Assessment of the Effectiveness of Aloe vera Versus Amlexanox in the Treatment of Recurrent Aphthous Ulcers: A Three-Arm Placebo-Controlled Randomized Clinical Trial. *Cureus*. 2022;14(10):e30693. doi:10.7759/cureus.30693.
18. Hasan S, Saeed S, Rai A, Kumar A, Choudhary P, Panigrahi R. Thalidomide: clinical implications in oral mucosal lesions- An update. *Ann Med Health Sci Res*. 2018;8:21–8.
19. Sriram S, Hasan S, Saeed S, Ahmad SA, Panda S. Primary Tuberculosis of Buccal and Labial Mucosa: Literature Review and a Rare Case Report of a Public Health Menace. *Case Rep Dent*. 2023;2023:6543595.
20. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA. Häyrinen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. *Int J Oral Maxillofac Surg*. 2004;33:221–55.
21. Liu H, Tan L, Fu G, Chen L, Tan H. Efficacy of Topical Intervention for Recurrent Aphthous Stomatitis: A Network Meta-Analysis. *Medicina*. 2022;58(6):771.

22. Maheswari TU, Shanmugasundaram P. Amlexanox in treatment of aphthous ulcers: a systematic review. *J Pharm Res*. 2013;6(1):214–7.
23. Meng W, Dong Y, Liu J, Wang Z, Zhong X, Chen R. A clinical evaluation of amlexanox oral adhesive pellicles in the treatment of recurrent aphthous stomatitis and comparison with amlexanox oral tablets: A randomized, placebo controlled, blinded, multicenter clinical trial. *Trials*. 2009;10:30–30.
24. Bhat S, Sujatha D. A clinical evaluation of 5% amlexanox oral paste in the treatment of minor recurrent aphthous ulcers and comparison with the placebo paste: a randomized, vehicle controlled, parallel, single center clinical trial. *Indian J Dent Res*. 2013;24(5):593–8.
25. Fu J, Zhu X, Dan H, Zhou Y, Liu C, Wang F. Amlexanox is as effective as dexamethasone in topical treatment of erosive oral lichen planus: A short-term pilot study. Oral Surg. Oral Med. Oral Pathol. *Oral Radiol*. 2012;113(5):638–81.
26. Kim HK, Kim JI, Kim JK, Han JY, Park SH, Choi KY, et al. Preventive effects of rebamipide on NSAID-induced gastric mucosal injury and reduction of gastric mucosal blood flow in healthy volunteers. *Dig Dis Sci*. 2007;52(8):1776–82.
27. Das SS, Sur J, Jain C, Jain TK, Swarnkar SS, Singh GB, et al. A brief review of muco-protective agent in the treatment of recurrent aphthous ulcer and Behcet's syndrome: Rebamipide EAS. *J Dent Oral Med*. 2019;1(3):39–41.
28. Akagi S, Fujiwara T, Nishida M, Okuda A, Nagao Y, Okuda T. The effectiveness of rebamipide mouthwash therapy for radiotherapy and chemoradiotherapy-induced oral mucositis in patients with head and neck cancer: a systematic review and meta-analysis. *J Pharm Health Care Sci*. 2019;5:16. doi:10.1186/s40780-019-0146-2.

Author biography

Shamimul Hasan, Professor https://orcid.org/0000-0001-6832-9150

Mohd. Faisal Siddique, Intern

Cite this article: Hasan S, Mohd. Faisal Siddique. Management of major recurrent aphthous ulcers with 5% amlexanox oral paste and rebamipide tablets- A case report with a brief literature review. *IP Int J Periodontol Implantol* 2023;8(4):225-229.