Recurrent aphthous stomatitis (RAS): guideline for differential diagnosis and management

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Abstract

Aim Recurrent aphthous stomatitis (RAS) is a painful and common ulcerative form that can pose a diagnostic challenge. In fact, similar oral ulcers can appear secondary to a variety of well-defined pathological conditions. Thus, the purpose of this work was to update the current knowledge about RAS

Methods A narrative review is presented aiming to clarify the extensive differential diagnosis of RAS and its management.

Results Clinically, RAS ulcers need to be differentiated from Behçet's disease, nutritional deficiencies, Crohn's disease and ulcerative colitis, PFAPA, MAGIC, HIV and xerostomia-related oral ulcers. A thorough medical history and review of symptoms, in addition to a careful evaluation of any oral feature, will help the clinician understand whether the ulcers are related to a systemic disorder or can be defined as idiopathic. The management of RAS is also challenging and currently there is not a defined treatment for controlling the symptoms.

Conclusion As a first aid in relieving the pain, topical applications of corticosteroids, antibiotics, and analgesics are highly recommended, while systemic therapy of RAS should be used in the case of multiple painful ulcerations compromising the quality of life of the patient. Also, natural anti-inflammatory substances from medicinal herbs, in the form of essential oils and extracts are promising agents in the management of RAS.

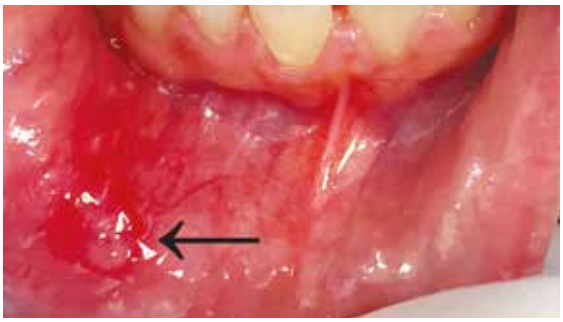
KEYWORDS Oral ulcers; Aphthae; Minor RAS; major RAS; Herpetiform ulceration; RAS treatment.

Introduction

Idiopathic recurrent aphthous stomatitis, also referred to as recurrent aphthous stomatitis (RAS), is a common ulcerative disease of the oral mucosa with a prevalence of 2–10% [Altengurg et al., 2014]. The cause of aphthous ulcers is still unknown, even if many factors are thought to be involved in the disease [Riera Matute and Alonso, 2011].

Ulcers occur in healthy individuals in childhood, adolescence, or in subjects under 30 years of age, and have the tendency to decrease in severity and frequency over time [Riera Matute and Alonso, 2011]. RAS starts with a typical burning sensation lasting from 2 to 48 hours until an ulcer is formed [Akintoye and Greenberg, 2014]. Typically, RAS is localised on the buccal and labial oral mucosa (Fig. 1, 2), and on the surface of the tongue. It is characterised by the development of painful round shallow ulcers [Edgard et al., 2017]. The necrotic centre of the ulceration is covered by a yellowish-grey pseudo-membrane and surrounded by a reddish edge (Fig. 3). Ulcers have a centrifugal growth and healing is achieved usually within 7–14 days by re-epithelialisation, which starts from the margins [Tarakji et al., 2015; Cui et al., 2016].

Since RAS can pose a diagnostic challenge, as similar oral ulcers can appear secondary to a variety of well-defined pathological conditions, the purpose of this narrative review was to update the current knowledge on its differential diagnosis.



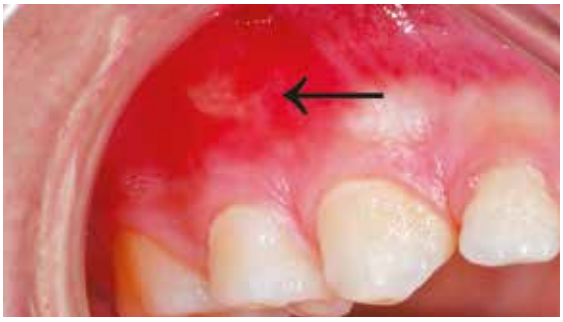


FIG. 1 The arrow points to Oral Minor RAS on the surface of the labial mucosa of a paediatric patient.

FIG. 2 The arrow points to Oral Minor RAS on the surface of the alveolar mucosa of a paediatric patient.

Clinical forms of RAS

According to the magnitude, number and duration of the outbreaks, RAS can be classified in three different types: Minor RAS (also known as Mikulicz's aphthae), Major RAS (or Sutton's aphthae), and Herpetiform RAS. All of these differ in morphology, distribution, severity, and prognosis [Field and Allan, 2003; Altengurg et al., 2014; Akintoye and Greenberg, 2014; Edgard et al., 2017] (Table 1).

Minor RAS

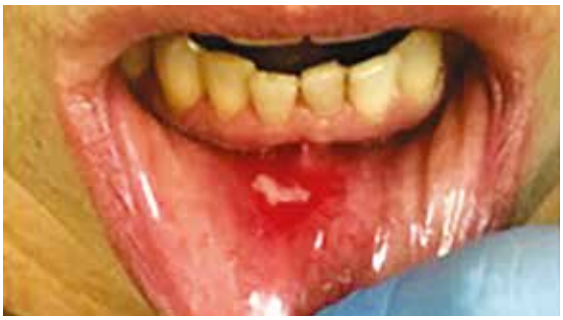
Minor RAS (MIRAS) is the most common form affecting about 85% of patients with RAS. The classification of MIRAS does not depend on the diameter of the lesion but on a number of clinical evidences [Edgard et al., 2017]. Aphthae are mostly concentrated in the anterior part of the non-keratinised mucosa of the oral cavity. Mainly, ulcers are located at the labial and buccal mucosa, the floor of the mouth and the ventral or lateral surface of the tongue. MIRAS can appear simultaneously in a number of 1–5 per time. The prodromal stage of ulceration is variable, and referred as a 'burning' or 'prickling' sensation before the ulcers appear directly by loss of the epithelium. Clinically, MIRAS is represented by shallow ulcers usually less than 1 cm in diameter deep and, in most of the cases, having a diameter of approximately 4–5 mm. Usually, their shape is round or oval with a grey-yellow base enveloped by red and quite raised margins. These lesions heal within 10 to 14 days without scarring [Porter and Scully, 2002]. Following, there will be a variable ulcer-free interval of 3–4 weeks. However, in some cases there is not an ulcer-free period between recurrences, with new aphthae developing before the previous healed [Field and Allan, 2003].

Major RAS

Major RAS (MJRAS) represents 10–15% of all RAS and shows more severe features with respect to MIRAS. Ulcers have greater diameter than those of MJRAS, and longer duration, up to months in some cases [Field and Allan, 2003]. Moreover, they often leave a significant scar with important distortion of the tissue. A heaped-up margin in a single ulcer should be considered suspicious of a malignant lesion [Field and Allan, 2003]. MJRAS does not have a cyclical pattern, and the ulcers are usually unpredictable in their onset. Also, the entire oral cavity can be affected by MJRAS, including the soft palate and tonsil areas causing significant pain and dysphagia and highly compromising the quality of life of the patient.

Herpetiform ulceration

Herpetiform ulceration makes up only 5–10% of all RAS cases. Generally, it affects women and has a later age onset than the other types of RAS. Despite the fact that any non-keratinised oral mucosa may be involved, ulcers manly affect the lateral margins and the ventral surface of the tongue, and the floor of the mouth. Ulcers are different from the other form of RAS: they are smaller (1–2 mm) in comparison to MIRAS and MJRAS and are multiple (5–100). They are grey without erythematous border and resemble ulcers of primary Herpes simplex virus (HSV) infection. The pain they provoke can impede eating and speaking, particularly when they coalesce. A single crop of ulcers may last for approximately 7–14 days, and the ulcer-free period is highly variable (Fig. 4).



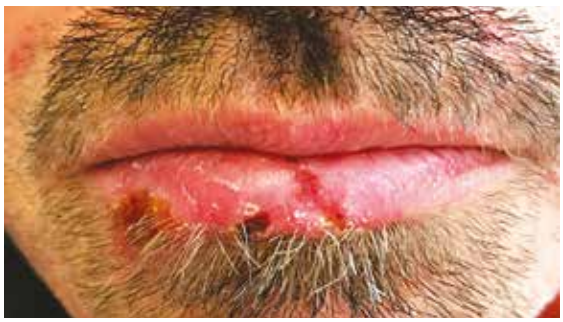


FIG. 3 Minor RAS affecting the vestibular oral mucosa.
FIG. 4 Multiple herpetiform ulcerations located at the labial mucosa surface of an adult patient. Herpetiform ulcerations can be present in 10% of patients with a history of RAS at young age.

Aetiopathogenesis of RAS

As described by Kastner et al. [2010], RAS can be classified as an auto-inflammatory condition caused by disregulation of innate immunity. Autoinflammatory diseases are defined as "clinical disorders in predisposed patients, which are characterised by abnormally increased inflammation mostly mediated by cells and molecules of the innate immune system" [Kastner et al., 2010]. In predisposed children, ulcers often occur in association to other autoimmune disorders. Among them, special emphasis has been given to Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, where ulcers are associated to periodic fever, pharyngitis and cervical adenitis [Wekell et al., 2016].

	Predisposing factors	Notes
1	Local mucosal injuries	Due to local anaesthetic injections, sharp tooth, dental treatments, and toothbrush injury
2	Genetic factors	A family history is found in up to 40% of patients
3	Foods	Chocolate, coffee, peanuts, cereals, almonds, strawberries, cheese, tomatoes
4	Stress	Stress induces immunoregulatory activity by increasing the number of leukocytes at sites of inflammation
5	Pharmacological treatments	Several classes of medications including antibiotics, chemotherapy drugs, antiepileptics, diuretics, anti-inflammatories, and antiretrovirals
6	Immune disorders	Oral manifestations are frequently the first sign of an autoimmune disease
7	Endocrine disturbances	Celiac disease, diabetes mellitus, autoimmune thyroid disease

TABLE 1 Main factors predisposing to the onset of RAS.

A strong correlation has been found between RAS and genetic factors with various triggers causing the evidence of ulcerations [Riera Matute and Alonso, 2011]. Among the triggering factors traumas, drug therapy, food hypersensitivity, nutritional deficiency, systemic disorders, stress, hormonal changes, and tobacco smoking cessation have been related to the onset of ulcerations [Porter and Leao, 2005] (Table 2).

Immunopathogenesis

It is reported that antigenic stimuli could be directed to the mucosal keratinocytes, where they act stimulating cytotoxic T-lymphocyte (CD4 and CD8), and activating cytokines and neutrophil chemotaxis. The cytokines tumor necrosis factor α (TNF-α), interleukin-1 (IL-1) β and interleukin-2 (IL-2) play a critical role in the development of the disease [Natah et al., 2000]. In the pre-ulcerative stage, mononuclear lymphocytic cells infiltrate the epithelium, leading to a localised papula of vacuolised keratinocytes surrounded by a reactive erythematous halo of vasculitis. Healing occurs with epithelial regeneration.

Clinically, TNF-α has been found significantly higher in RAS patients saliva than in that of the control group [Chaudhuri et al., 2018]. Also, changes in the serum levels of immunoglobulins have been reported and this is probably related to an alteration of the cell molecules adhesion. This may explain the changes in the structure of the oral epithelium with the evidence of ulcerative areas [Riera Matute and Alonso, 2011].

Concerning the oral microbiota, a lower level of Streptococcus sp. together with an increase of Acinetobacter johnsonii has been reported in RAS patients in comparison to the healthy group [Stehlikova et al., 2019]. Furthermore, an increase in fungal spp., particularly Malassezia and Candida albicans, was demonstrated during the active RAS ulceration compared to controls. These evidences are consistent with the hypothesis of a microbial shift in RAS in favour of opportunistic pathogens, which persists to some extent even after the ulcer has healed.

Systemic conditions with RAS-like ulcers

A series of pathological conditions may mimic RAS (Table 3). These frequently start both in childhood and adulthood with no previous history of oral ulceration. Among them there are Behçet's disease, nutritional deficiencies, gastrointestinal diseases [Akintoye and Greenberg, 2014; Torreggiani et al., 2016; Soon and Laxer, 2017; Manthiram et al., 2020] and hematopoietic disorders [Defabianis et al., 2010; Condò et al., 2011; Garrocho-Rangel et al., 2018]. Furthermore, aphthous-like ulcerations can be associated to xerostomia where the alteration in quantity and/or quality of saliva causes tissue changes in the oral mucosa exposing the surfaces to ulcerative phenomena [Pinna et al., 2015; Pinna et al., 2019]. Conversely, neither common viral or bacterial infection of the mouth nor Helicobacter pylori infection have been correlated to the disease.

Behçet's disease

Oral aphthous ulcers in Behçet's disease have similar features to those of RAS: they are round or oval lesions surrounded by an erythematous halo and a white-yellow pseudomembrane. However, the simultaneous existence of more than six oral aphthae involving the soft palate and oropharynx, are of high significance for the diagnosis [Bulur and Onder, 2017]. Furthermore, according to the International Study Group, the ulcerations in Behçet's disease should occur more than three times within a 12-month period to be significant of the disease [International Study Group for Behçet's Disease, 1990]. Oral Streptococci were suggested as an important common factor in RAS and Behçet's disease, either acting as direct pathogens or

Disease	Types of oral lesion and location	Clinical features
Recurrent aphthous stomatitis (RAS)	Single or multiple ulcers; oral mucosa	Three different clinical types of aphthae: minor, major, herpetifom
Behçet's disease	Aphthous-like; oral and pharyngeal mucosa	Concomitant uveitis, genital and skin lesions
Nutritional deficiencies	Aphthous-like; oral mucosa	Concomitant iron, folic acid, and vitamin B12 deficiencies
Intestinal bowel disease (Crohn's disease and Ulcerative colitis)	Aphthous-like; oral mucosa	Concomitant intestinal involvement which often precedes the oral lesions
Periodic fever syndromes (PFAPA)	Aphthous-like; oral mucosa	Concomitant periodic fevers, pharyngitis, cervical adenitis
Mouth and genital ulcers with inflamed cartilage (MAGIC)	Aphthous-like; oral and pharyngeal mucosa	Concomitant genital ulcerations and cartilage inflammation
HIV-related oral ulcers	Aphthous-like; oral mucosa	Major aphthous ulcers and concomitant decrease in the absolute number of CD4+ cells
Xerostomia	Aphthous-like; oral mucosa	Concomitant sore throat, altered taste, burning sensation, mucositis, impaired chewing and swallowing

TABLE 2 Systemic conditions and aphthae-like ulcers.

	Minor RAS	Major RAS	Herpetiform RAS
Peak of age	2nd decade	1st and 2nd decades	3rd decade
Distribution	Non-keratinised mucosa, particularly labial/buccal mucosa, dorsum and lateral borders of the tongue	Keratinized plus nonkeratinised mucosa particularly soft palate	Non-keratinized mucosa, particularly floor of mouth and ventral surface of the tongue
Number of ulcerations	1–5	1–3	10–100
Size	< 10 mm	>10 mm	1–3 mm
Duration and prognosis	4–14 days with no scarring	2 weeks – 3 months with scarring	7–14 days with uncommon scarring

TABLE 3 Clinical features of minor, major and herpetiform RAS.

antigenic stimulus leading to antibodies against keratinocytes [Porter et al., 1988]. More recently, a common antigen was demonstrated against the oral mucosa and the microbial 65 kDa heat shock protein, which might be responsible for the pathological changes in Behçet's disease [Lehner et al., 1991]. However, even if RAS and Behçet's disease are characterised by some common immunopathogenic mechanisms, the reason why RAS lesions are limited to the oral cavity, and in Behçet's disease they are associated with genital ulcers, skin lesions and uveitis, is still unknown [Zeidan et al., 2016]

Nutritional deficiencies

Hematinic deficiencies (including iron, folic acid, and vitamin B12) have been proposed as potential aetiologic factors of RAS [Kozlak ST, 2010; Wang Z, 2021]. The mechanism relating hematinic deficiencies and RAS is not well understood [Al-Amad SH and Hasan H, 2020]. However, among the hypotheses there could be the essential role of vitamin B12 and folic acid in DNA synthesis and cell division. In deficiencies, an atrophy of oral epithelial cells with the consequent damage to the mucosal integrity in addition to an impairment of the epithelial barrier could be possible [Chiang et al., 2019; Sun et al., 2015]. Furthermore, iron, vitamin B12 and folic acid lead to microcytic and macrocytic anaemia, respectively [Morris et al., 2007; Sun et al., 2015]. RAS patients with anaemia or with high blood homocysteine levels may have a damage of the oral epithelial barrier with a consequent increase of RAS occurrence [Sun et al., 2015]. Also, some studies found a significant reduction of only serum vitamin B12 comparing RAS patients and healthy controls [Bao et al., 2018; Piskin et al., 2002; Koybasi et al., 2006]. Other investigations detected significantly decreased concentrations of iron and ferritin in RAS patients compared with the control group [Lopez-Jornet et al., 2014]. Some of these nutritional deficiencies may be secondary to other diseases, therefore haematologic screenings of RAS patients are appropriate particularly with regard to patients suffering from major RAS or minor RAS [Akintoye and Greenberg et al., 2014].

Gastrointestinal diseases (Crohn's disease and ulcerative colitis)

Superficial ulcers-like RAS may happen in gluten-sensitive enteropathy [Srinivasan et al., 1988]. However, any clinical, gastroenterological or serological features, which are characteristic of such disease can be included in RAS differential diagnosis.

In Crohn's disease (CD) oral manifestations occur in 20% to 50% of the cases [Litsas and Ari-Demirkaya, 2011; Katsanos et al., 2015; Favia et al., 2020]. They are more common in males than females and include specific and non-specific lesions. Aphthous stomatitis is ascribed to non-specific oral lesions group. Their presence lead to suspicion of inflammatory Bowel disease even if other intestinal symptoms may be absent [Muhvić-Urek et al., 2016]. The oral ulcers are described as round lesions surrounded by an erythematous halo with a central fibrin membrane [Lankarani et al., 2013]. Thus, under a clinical point of view, they are similar to those occurring in subjects not suffering from CD. Additionally, many non-specific oral lesions, having similar features to those of aphthous stomatitis, can occur in ulcerative colitis. Therapy and malnutrition are accounted as the main causes of aphthae in patients suffering from CD and ulcerative colitis. In this regard, it is supposed that the chemical therapy may have a direct toxic effect to the oral tissue or an indirect immunosuppressive activity leading to increased risk of infections, which in turn can cause oral ulcers [Muhvić-Urek et al., 2016].

Periodic fever syndromes

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterised by recurrent episodes of high fever associated with pharyngeal inflammation, aphthous stomatitis, and/or cervical lymphadenopathy [Marshall et al., 1987]. It is the most common periodic fever syndrome affecting children up to 5 years old. Generally, the fever will spontaneously resolve at the age of 7 years [Wurster et al., 2011]. PFAPA aphthae are of small diameter (<1 cm) and typically located on the non-masticatory surfaces of the mouth [Ali et al., 2016]. The lesions are round, shallow, and with well-defined margins [Batu, 2019]. The characteristic features are similar to those described in RAS, which however occur in subjects without any other systemic disorder [Long, 1999].

Mouth and genital ulcers with inflamed cartilage

Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome was first reported in 1985 in a series of five cases where Behçet's disease symptoms and relapsing polychondritis were manifested in the same individual, suggesting a common pathogenic mechanism [Firestein et al., 1985]. MAGIC syndrome is characterised by a wide variety of clinical manifestations, where the genital ulcerations in conjunction to oral aphthae and cartilage inflammation, involving the ears, nose, throat, and rib cage, are the most important features for the differential diagnosis [Onder and Gurer, 2001].

HIV-related oral ulcers

Oral lesions in HIV patients can be attributed to infections, neoplasms (i.e. Kaposi's sarcoma) or non-specific causes such as aphthous ulcerations [Tappuni and Flemming, 2001]. Morphologically, ulcers are similar to those of MIRAS and MJRAS. Infections related to cytomegalovirus or herpes simplex virus have to be excluded in such patients [Field and Allan, 2003]. Patients with low CD4T lymphocyte count generally have very painful, major aphthous ulcers. Even if ulcers appear as localised at first, they can quickly extend from the gingiva into the adjacent oral mucosa becoming ulcerative and necrotic, highly compromising the quality of life of the patients. These lesions may be related to an immune imbalance, which characterises the HIV disease and it is suggestive of a severe immune suppression [Muzyka and Glick, 1994].

Xerostomia

Xerostomia, or dry mouth syndrome, describes the subjective symptoms of a dry mouth deriving from a lack of saliva [Pinna et al., 2015]. However, it can be referred also to changes in saliva composition [Nederfors, 2000]. Xerostomia is caused by a large variety of causes including radiotherapy for head and neck cancers, chronic use of drugs, rheumatic and dysmetabolic diseases like diabetes, autoimmune conditions such as Sjögren's syndrome, and hepatitis C virus [Porter et al., 2004].

Objectively, patients affected by xerostomia have functional oral disorders such as sore throat, altered taste, recurrent dental caries and mucosal infections, burning sensation, changes in voice quality, and impaired chewing and swallowing function [Wolff et al., 2008]. Ulcerations may appear with characteristics similar to those of minor and major RAS. However, in the case of xerostomia ulcers generally

occur as isolated manifestation in patients who also refer the concomitant sensation of dry mouth [Pinna et al., 2015]. Furthermore, the clinical objective evidence of a reduced saliva flow is strongly indicative of xerostomia in such patients [Sreebny, 2000].

Management of RAS

Currently, there is no defined treatment in the relief of symptoms caused by RAS. The commonly accepted treatment strategy is to lessen the pain and duration of lesions (Li et al., 2016). Topical applications of corticosteroids, antibiotics, and analgesics are highly recommended in the therapy. However, longer and recurrent chemical treatments may cause fungal infections and drug resistance, which may further lead to more severe side effects and life-threatening complications. General recommendations concern to avoid hard, acidic, and salty foods along with alcohol and carbonated drinks. Furthermore, toothpastes containing sodium lauryl sulfate should not be used [Altengurg et al., 2014]. Chlorhexidine gluconate mouthwashes and topical corticosteroids have been evidenced to reduce the severity and duration of RAS ulcers [Tarakji et al., 2015]. However, chlorhexidine digluconate, largely used in commercial oral antiseptics, has shown high cytotoxicity against human fibroblasts and osteoblasts (Müller et al., 2017; Mummolo et al 2019). The use of systemic non-steroidal anti-inflammatory drugs (NSAIDs) or even steroids can have gastrointestinal and cardiac toxicity as well as nephrotoxic side effects (Coxib and Traditional NSAID Trialists' Collaboration 2013).

Conclusion

New pharmacological molecules differently acting from chemicals, able to reduce the inflammation process without side effects to the host, while promoting the wound healing processes are strongly needed. Natural anti-inflammatory substances from medicinal herbs, as in the form of essential oils as well as extracts, can be worthwhile in the management of RAS [Li et al., 2016]. The biological activity of essential oils and polyphenols from plants and herbs is related to the presence of different chemical classes. In this regard, terpenes and terpenoids in essential oils are promising agents in the prevention and treatment of inflammatory and autoimmunity disorders suggesting them as potential chemopreventive and therapeutic agents. Further interesting capabilities have been ascribed to polyphenols from extracts, which molecules include tannins, flavonoids and lignin-carbohydrate complexes strongly associated to anti-inflammatory, antioxidant and antimicrobial properties [Milia et al., 2020; Milia et al., 2021]. The hopeful use of nanotechnology should be a strategy to increase the activity of bioactive natural molecules in the releasing of beneficial and safe substances to threat RAS [Manconi et al., 2018; Pinna et al., 2019]. Although the large evidence of biocompatibility in oral cell lines, adequate clinical trials are still necessary to validate the use of medicinal herbs in humans [Porter and Scully, 2002].

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