Recurrent Aphthous Stomatitis in Children: A Practical Guideline for Paediatric Practitioners

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is the most common chronic oral mucosal lesion affecting up to 25% of the population. The diagnosis is based on well-defined clinical characteristics, but the precise aetiology and pathogenesis remain unclear. The treatment of RAS should be based on the identification and control of possible predisposing factors. A wide range of topical medicaments is available as antiseptics, anti-inflammatory drugs and corticosteroids. The systemic treatment is indicated in patients with continuous and aggressive manifestation, which is extremely rare in children. The present article provides a review of the current concept and knowledge of the aetiology, pathogenesis, and management of RAS in the paediatric population.

KEYWORDS

recurrent aphthous stomatitis; children; pathogenesis; treatment

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INTRODUCTION

Aphthae (cancer sores) is one of the most commonly recorded painful lesions in the oral cavity and were first mentioned by Hippocrates (460–370 BC) who utilized the term "aphthai" (1). Recurrent aphthous stomatitis (RAS) is characterized by multiple recurrent small, round, or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors. They typically present in children and adolescents (2). Up to 25% of the population can be affected by aphthae. It is a disease with high recurrence rate (50% at 3 months). Aphthae are more common in females (3). Many predisposing factors have been identified. These include especially local trauma, genetic factors, nutritional deficiencies, viral and bacterial infections or immune and endocrine disease (4). All forms of aphthous ulcers have a significant impact on the quality of life and interfere with the child's well-being.

PATHOGENESIS

Several theories have described the pathogenesis of RAS. Significant interactions between the immune system, genetics and environmental factors play a significant role. DNA damage secondary to oxidative stress is thought to play a role in RAS (5). Evidence suggests an immunological basis for chronic inflammation. T cell-mediated immunity plays a significant role in RAS development. The imbalance between CD4+ and CD8+ T lymphocytes (decreased ratio) is very frequent observation. In patients with RAS. T cells are responsible for epithelial destruction via generated TNF-α. TNF-α has been found to be significantly increased in the saliva of RAS patients. A recent study explored the significance of single nucleoid polymorphisms in the genes for pro-inflammatory cytokines IL-1 and IL-6. This suggests a genetic component to the immuno-pathogenesis of RAS (6). The results of the recent case-control study strongly indicated that RAS patients have a systemic imbalance in the oxidant-to antioxidant ratio favouring oxidative damage (7). It is currently thought that an unknown antigen stimulates keratinocytes, resulting in cytokine secretion and leukocyte chemotaxis. The RAS may also be associated with a specific HLA haplotype such as HLA-A2, A11, B12 and DR2 (8).

Tab. 1 Systemic disorders associated with RAS (25).

Behcet's syndrome
Celiac disease
Cyclic neutropenia
Nutritional deficiencies (iron, folate, zinc, B1, B2, B6, B12)
IgA deficiency
Immunocompromised conditions, including HIV disease
Inflammatory bowel disease
MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)
PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis)
Reactive arthritis
Sweet's syndrome
Ulcus vulvae acutum

PREDISPOSING AND ENVIRONMENTAL FACTORS

LOCAL FACTORS

Local trauma during mastication or tooth brushing is regarded as a possible cause of RAS (2, 9). Trauma predisposes to RAS by inducing oedema, early cellular inflammation associated with increased viscosity of the oral submucosal extracellular matrix (10). Some changes in salivary composition, such as pH, and stress-induced salivary cortisol have been correlated with RAS (11).

DRUGS

Boulinguez et al. reported the association between some drugs as non-steroid anti-inflammatory drugs (NSAID) or b-blockers and RAS (12).

FOOD HYPERSENSITIVITY

Some foods such as chocolate, coffee, peanuts, cereals, almonds, strawberries, tomatoes, and wheat flour (containing gluten) are considered as predisposing factors (13). Besu et al. published the study reporting the strong association between high levels of serum anti cow's milk proteins and clinical manifestations of RAS (14).

NUTRITIONAL DEFICIENCY

Nutritional deficiencies associated with anaemia (iron, serum ferritin) have been reported to be common in RAS paediatric patients (15). Deficiencies of vitamin B1, B2, and/or B6 are also common (16).

HEREDITARY PREDISPOSITION

At least 40% of RAS patients have a familiar history of RAS (17). Children with RAS positive parents have a 90% chance of developing RAS. When patients have a positive family history, they tend to develop recurrent aphthous ulcers at an early age. They aphthous lesions appear more frequently and demonstrate severe symptoms. Studies of identical twins have also shown the hereditary nature of this disorder (18, 19).

THE SYSTEMIC DISORDERS

Several systemic disorders have been reported to be associated with RAS. The clinical and morphological findings are not distinguishable from those found in healthy individuals. The systemic disorders that are associated with lesions clinically similar to RAS are shown in Table 1. The celiac disease represents one of the frequent associations in children (20). Mucosal aphthosis is a feature of a systemic syndrome that includes recurrent fever with unknown source of infection (21). Such syndromes are referred to

Tab. 2 Clinical features of minor, major and herpetiform recurrent aphthous stomatitis (RAS) (36).

	Minor RAS	Major RAS	Herpetiform RAS
Gender predilection	Equal	Equal	Girls
Morphology	Round or oval lesions, covered by grey-white pseudomembranes, erythematous halo	Round or oval lesions, covered by grey-white pseudomembranes, erythematous halo	Small, deep ulcers. Irregular contour
Distribution	Lips, cheeks, tongue, mouth floor	Lips, soft palate, pharynx	Lips, cheeks, tongue, mouth floor, gingiva
Number of ulcers	1–5	1–10	10–100
Size of ulcers	<10 mm	<10 mm	2–3 mm
Prognosis	Lesions resolve in 4–14 days, no scaring	Lesions persist >6 weeks, high risk of scaring	Lesions resolve in <30 days, scarring uncommon

as auto-inflammatory diseases as PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) (22). The RAS can also be part of various neutrophilic dermatoses (23). The stress remains one of the significant factors affecting the immune system and is believed to predispose patients to RAS (24).

CLINICAL FEATURES

There are three clinical representations of RAS: minor (<70% of cases), major (10%), and herpetiform ulceration (10%) (Table 2). Recurrent aphthous stomatitis comprises recurrent bouts of one or more rounded, shallow, painful ulcers at intervals of a few months to a few days. Patients may have prodromal symptoms of tingling or burning before the appearance of the lesions. During this initial period, a localized area of erythema develops. Within hours, a small white papule forms, ulcerates, and gradually enlarges over the next 48–72 hours (26).

MINOR RAS

Minor RAS (also known as Mikulicz's aphthae) is the most prevalent form and typically occurs in children who are 5 to 18 years old (27). They affect only non-keratinized parts of mucosa. Superficial, round ulcerations are <10 mm, accompanied by a grey pseudomembrane and erythematous halo (Figure 1). They usually occur on non-keratinized mucosa of the labial and buccal mucosa, the floor of the mouth and ventral or lateral surface of the tongue. The ulcers heal within 10–14 days without scarring.

MAJOR RAS

Major RAS (or Sutton's disease or periadenitis mucosa necrotica recurrens) is less common; they are larger than 10 mm in diameter, more profound, often scared (Figure 2). These lesions have a predilection for lips, soft palate and tonsils. Lesions may appear on any mucosal surface. These lesions take up to 6 weeks to heal. The onset is usually after puberty and recurrence can last for decades.

HERPETIFORM ULCERATION

Herpetiform ulcerations (or Cooke's) constitute only 5–10% and are very rare in children (28). These lesions are small and multiple, typically affected lateral margins and ventral surface of the tongue and floor of the mouth. Individual ulcers are grey with an irregular contour. A single crop of ulcers may last for 7–14 days, making eating and speaking difficult (26).

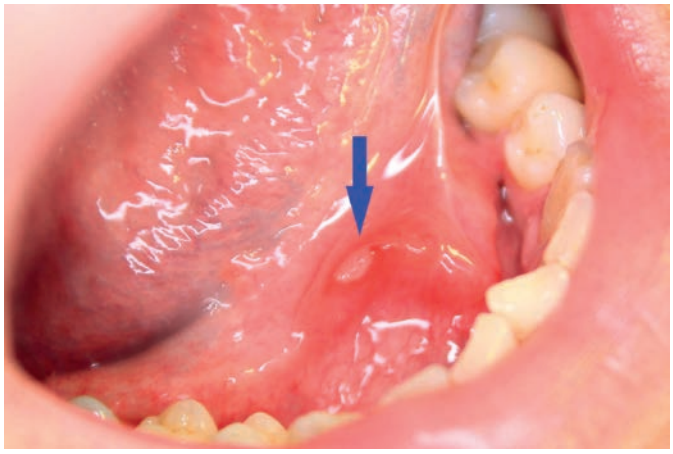

Fig. 1 Aphtha minor.

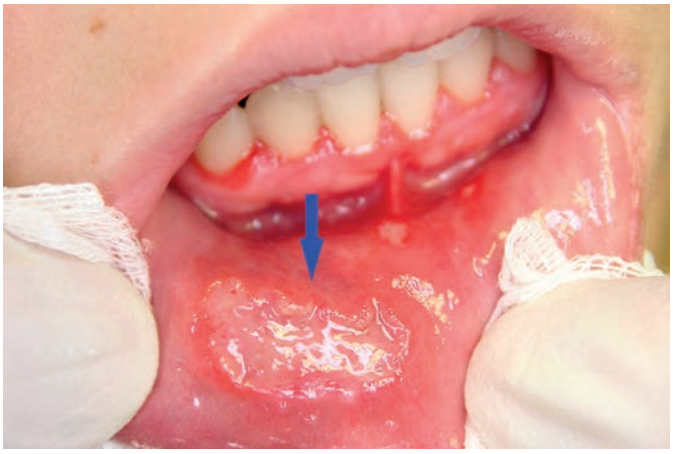

Fig. 2 Aphtha major.

DIAGNOSIS

No specific diagnostic test exists to diagnose RAS. The correct diagnosis of RAS is dependent on a detailed clinical history and examination of the ulcers. Usually, it does not cause difficulties because of the clinical appearance and recurrence of the lesions. It is necessary to point out the possible problems in the differential diagnosis when aphthous stomatitis is considered as changes typical for herpetic gingivostomatitis with systemic prodromal symptoms that are absent in RAS. Histological examination is characteristic but not specific for RAS. Central ulceration covered by fibro purulent membrane is a frequent finding in early stages (29). Mixed inflammatory infiltrate is present in adjacent connective tissues. The histopathological examination is sometimes necessary to differentiate aphthous ulcers from other mucocutaneous diseases that have ulcerative manifestations such as neoplastic lesions. To rule out potential viral causes such as varicella zoster virus infections, herpangina, hand-foot-and-mouth disease or Coxsackie virus-related oral ulcers it is sometimes necessary to do microbiological examination (either direct or indirect diagnostics). Underlying systemic conditions should be identified (celiac disease, IBD, hematologic disorders, nutritional deficiencies) (30).

TREATMENT

The current concept of the management of RAS is aimed at supportive care. It is necessary to point out that once the development of lesion starts, it is not possible to stop the pathogenetic process. No pharmacological treatment has been curative, although several modalities have been effective in decreasing pain and erythema and increasing the rate of re-epithelialization of the lesions. The comfort of the treatment procedures (application form, frequency, and discomfort in the oral cavity) should be taken into consideration, particularly in paediatric patients. The positive fact is that children suffer most from minor lesions, but the treatment modalities are limited by the age and cooperation of the child. It is reasonable to begin treatment with topical medication. Topical treatment is aimed at prevention of superinfection, protection of existing ulcers, analgesia, decreasing inflammation, and treating active ulcers. Systemic therapy is exceptional in children. The systemic treatment is considered only in children with immunity defects (26).

TOPICAL AGENTS

Local anaesthetics (lidocaine, benzocaine, polidocanol) have a benefit in pain relieve. It is particularly important in children when painful lesions may lead to eating difficulties and dehydration. Possible application forms are solutions, gels, and adhesive pastes. A notable fact is a cooperation of the child; therefore, adhesive pastes are preferred in small children.

Antiseptics (chlorhexidine gluconate, benzydamine hydrochloride, triclosan, cetylpyrimidiumchlorid) prevent the secondary infection and may relieve symptoms. The different application forms are available.

Based on the immunologic nature of RAS, topical steroids may often control RAS. Topical triamcinolone or stronger steroids such as betamethasone may be used. Steroids act on the lymphocytes and alter the response of effector cells to precipitants of immunopathogenesis (31).

SYSTEMIC MEDICATIONS

Systemic treatment is indicated for severe and recurring ulcerations where topical management is not sufficient. Options for systemic treatment include the use of immunomodulatory drugs such as corticosteroids, dapsone, colchicine, tetracycline, thalidomide or biologic agents (such as TNF-α inhibitors). The use of these compounds is significantly limited in children, whereas the use of most of them except steroids is usually contraindicated. Treatment with systemic steroids provides an only transient response of RAS (32). Long term steroid use in RAS is not indicated.

Treatment with vitamin B12 has been suggested. Duration of ulcers and pain has been reduced in the study by Volkov showing a benefit of vitamin B12 administration (33).

One of the possible drugs is pentoxifylline inhibiting TNF-α production and other pro-inflammatory cytokines (34). This drug is, however, not indicated in children up to 18 years of age. Most of other medications for the systemic application have a significant immunosuppressive effect, and their indication is hardly justifiable in childre (35).

OTHER THERAPEUTIC AND PROPHYLACTIC MEASURES

The parents and the child should be informed to minimize the local traumatization of the oral mucosa, modify the diet, eliminate possible allergic agents, and reduce the emergence of stressful situations. Proper oral hygiene in older children is essential.

CONCLUSION

RAS remains a common oral mucosal disorder in the paediatric population. Its aetiology remains unclear. No specific trigger has ever been demonstrated. There is no safe therapy to ensure no recurrence of RAS. In severe cases, the complex paediatric examination of the child is recommended to eliminate the similarly looking oral manifestation of systemic diseases as anaemias, idiopathic gastrointestinal disturbances (celiac disease) and hypersensitivity to various allergens.

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CONFLICTS OF INTEREST

None declared.

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