

Recurrent aphthous ulcerative disease: presentation and management

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Abstract

Recurrent aphthous ulceration (RAU) is the second most common type of ulceration seen in the oral cavity. Notwithstanding an extensive literature and numerous proposed aetiologies, the cause of the disease remains obscure. In addition to the current conservative management of RAU lesions with corticosteroids, new treatment options are available and some have proven successful in open trials. This paper reviews patient work-up and management.

Key words: Recurrent aphthous ulceration, mouth ulcers.

Abbreviations and acronyms: FBE = full blood examination; HAU = herpetiform aphthous ulceration; MaAU = major aphthous ulceration; MiAU = minor aphthous ulceration; RAU = recurrent aphthous ulceration.

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INTRODUCTION

Recurrent aphthous ulceration (RAU) represents the second most common type of oral ulceration after traumatic ulceration. It is, however, the most common type of recurrent ulcerative disease in the mouth and possesses a number of specific features that place it alongside recurrent dermatoses and mucocutaneous conditions. This concept is not appreciated by many clinicians and hence the condition is dismissed as a "mouth ulcer" that is self-limiting and requires no treatment other than antiseptic/anaesthetic proprietary preparations. Interestingly, if the degree of functional morbidity and restriction caused by an exacerbation of RAU were transferrable to another part of the body, it would receive early and specific treatment. The aim of the current paper, therefore, is to present the main features of RAU, place the disease in its correct position as an immunologically mediated mucosal disease and suggest a management plan.

Definitions

An ulcer is any breach of the oral mucosa causing exposure of the lamina propria. They may be classified on a number of bases and the most common are listed in Table 1. Aphthous ulceration is defined by the authors as a recurrent, non-infectious, non-vesicular and immunologically mediated oral mucosal disease.

Epidemiology

Approximately 20 per cent of the general population is affected by RAU with onset ranging from childhood to middle age. Some populations have a much higher incidence and, at least in some cases, this seems related to increased educational levels and the coincident rise in personal and work-related stressors. For example, at The University of Queensland Dental School approximately 50 per cent of students will suffer from RAU. The appearance of RAU in adulthood or a worsening of the condition may suggest an underlying systemic disease including haematological, immunological and connective tissue conditions and these require investigation and elimination.

At least 40 to 50 per cent of patients report a familial trait and, in many cases, this correlates with both earlier onset and more severe disease. It seems likely there is a genetic basis to the condition with both circumstantial and laboratory-based evidence but the mechanism(s) remain undetermined.¹ Of immediate clinical relevance is the 90 per cent expression in children whose parents both have active RAU.² This latter feature often suggests to parents that the ulcers represent an infectious disease. The authors believe it is important for patients to be aware of the strong possibility of genetic transmission. It places RAU in perspective as a genetic condition and explains why some generations do not express the disease but the trait continues. This level of understanding by a patient should also limit the search for an elusive cause to the condition as opposed to possible triggers for recurrences.

Aetiology

The trigger of an episode of RAU is unknown, but extensive investigations in large patient series have

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Table 1. Common causes and examples of ulceration of the oral mucosa

Aetiology	Examples
Trauma	acute or chronic
Apthous ulcerative disease	minor, major, herpetic
Viral	herpetic gingivostomatitis, herpangina
Mucocutaneous/immunological	RAU, lichen, pemphigus, pemphigoid
Neoplasia	squamous cell carcinoma
Ischaemia	necrotizing sialometaplasia

identified a range of local, haematological, gastrointestinal, immunologic, genetic, nutritional, allergic, psychological, and medication reactions as probable triggers in some RAU patients.³⁻⁵ However, in the majority of patients there is no consistent event coincident with an exacerbation. In the small percentage of patients where a systemic association can be made, e.g., inflammatory bowel disease, then the activity of RAU tends to reflect the activity of the associated condition. These conditions are listed in Table 2.

A large body of laboratory and clinical evidence supports the premise that RAU is an immunologically mediated condition. There is a defined temporal sequence of cellular changes within the ulcerative lesion as it progresses through the varying stages of ulceration and the systemic immune system shows a range of altered parameters that reflect disease activity and susceptibility.^{6,7} The significant feature is that RAU has an immunopathogenesis and this places it alongside

Table 2. Conditions related to the onset of RAU in some patients

Physical trauma	toothbrushing, orthodontic brackets
Chemical trauma	chemical burns
Medications	NSAIDs, cardioselective Beta ₁ -blockers
Psychological	personal/work-related stress
Nutritional	iron deficiency folate deficiency (related to GIT disease) vitamin B ₁ , B ₂ , B ₆ , B ₁₂
Gastrointestinal disease	mal-absorption syndromes regional enteropathy (Crohn's disease) gluten sensitive enteropathy (Coeliac disease) ulcerative colitis
Endocrinological	premenstrual
Haematological	cyclic neutropenia anaemias haematological malignancies
Immunological	immunodeficiency states, HIV infection
Allergy/hypersensitivity	foods (tomatoes, chocolates, nuts, dairy, wheat) metals (nickle-based oral appliances)
Microbiological	streptococci, herpes viruses, Epstein Barr virus
Syndromal associations	Behcets Disease (multi-organ involvement including oral, genital and eye lesions) PFAPA/Marshall's Syndrome (periodic fever, aphthae, pharyngitis, cervical adenitis) MAGIC Syndrome (mouth and genital ulcers with inflamed cartilage/relapsing polychondritis)

skin conditions similarly mediated by the immune system. The two characteristics of a genetic trait and an immunopathogenesis are important discussion points for the patient and enhance their understanding of the recurrent nature of the ulceration. It also allows an understanding by the patient of suggested treatment and preventive strategies. Table 2 outlines a number of conditions that have been related to both the predisposition to develop aphthae as well as the initiation of specific episodes. The group can be clustered, for the purpose of discussion, into four groups: local factors, systemic factors, infectious agents and syndromal associations.

Local factors are exemplified by trauma. The non-apthous patient will experience oral mucosal trauma and the resultant ulceration is irregular in outline, shows minimal and short duration evidence of the cardinal signs of inflammation (heat, redness, swelling, pain, loss of function) and resolves within a few days depending upon the severity of the initial soft tissue injury. The apthous patient will follow a different route. The lesion will change within one to two days from the irregular traumatic ulcer to the typical regular outline of an apthous lesion which will run the protracted course of an apthous ulcer. This variation has been typed in our laboratory and there is a very clear distinction in the tissue reaction involving the expression of the inflammatory response between the two patients. This strongly suggests there is a level of local tissue reactivity present in RAU patients that is not present in non-apthous sufferers and that the cascade of tissue and systemic events leading to the development of an apthous lesion can be triggered by a local tissue event, e.g., trauma. It also demonstrates that the tissue reaction in the non-apthous patient is designed to minimize the inflammatory reaction and activate the healing phase as soon as possible. This does not happen in the RAU patient.

Systemic factors include a range of predisposing conditions and factors including the genetic trait. They seem to act by initiating the ulcerative lesion through the reactivity of the immune system rather than immunoreactivity being a response to a local factor. This aspect is not clearly understood but there is a significant body of evidence implicating a systemic immunological dysfunction in the aetiology of RAU. A possible scenario might be the inappropriate expression of epithelial cell surface proteins as a result of very minor trauma. In RAU patients increased numbers of lymphocytes in the circulating blood may respond to this change in the epithelial cell surface and destroy the cell and hence the very early stages in the development of an RAU lesion. Fortunately, RAU lesions tend to be self-limiting and not progress to chronic muscosal disease such as occurs with lichen planus.⁸

Infectious agents have been a suspected cause over a very extended period. Our current knowledge suggests there is no bacterial component to RAU although *Streptococci*, in particular, received considerable

attention some 30 years ago. If there is an infectious aetiology then it remains unconfirmed at this stage although there is circumstantial evidence for a viral aetiology based on both laboratory evidence and the positive response of some patients to the use of antiviral medication.^{9,10} The current authors feel there is no infectious aetiology based firstly on current knowledge and secondly the successful use of topical corticosteroid agents that would otherwise cause a negative reaction in the presence of infectious agents.

Syndromal associations are rare but the general rule that should be applied to every patient with a disease condition is to canvass the possibility of a systemic contribution or a syndromal association.^{11,12}

Clinical presentation

The accepted classification of aphthae is based on the three parameters of lesion size, duration and the presence of residual scarring. However, each lesion tends to follow a set presentation and course, albeit with variation in the duration and size of lesions. Clinically, patients and clinicians are often able to map the sequence of presentation through to resolution into the following stages: (1) prodromal – symptoms but without any visible clinical sign; (2) pre-ulcerative – initial presentation, usually erythema and slight oedema; (3) ulcerative – formation of the epithelial defect; (4) healing – symptom abatement and progressive healing; (5) remission – no evidence of lesions.

The prodromal stage is infrequent and transient and heralds the early ingress of lymphocytes from the peripheral blood (recirculating lymphocyte pool). This is the period when application of a topical corticosteroid may inhibit the further development of the lesion or at least minimize the severity and duration of any lesion that does progress to the ulcerative stage.

The pre-ulcerative stage is also transient and again is an ideal time to apply a topical corticosteroid. It represents the period when the local vascular response has allowed the clinical development of redness and swelling. Histologically, lymphocytes have now entered the basal epithelial layers and are initiating the cytotoxic process that will lead to epithelial cell death and progression to the ulcerative stage.

The ulcerative stage is the dominant stage and noted particularly by the patient due to local pain. Early epithelial destruction and breakthrough causes a small clinical ulcer which rapidly progresses to the full size determined for that particular lesion, most frequently 0.3–0.5cm in diameter. The lesion is umbilicated or crateriform with clear sharp raised margins and surrounding erythema and oedema. The lesion is generally round to oval and the depressed central zone carries a pseudomembrane that corresponds to a scab on a similar skin lesion. It is useful to think of aphthae as regular lesions that present a typical structure as opposed to traumatic lesions that tend to be irregular in outline and with a less clinically obvious acute

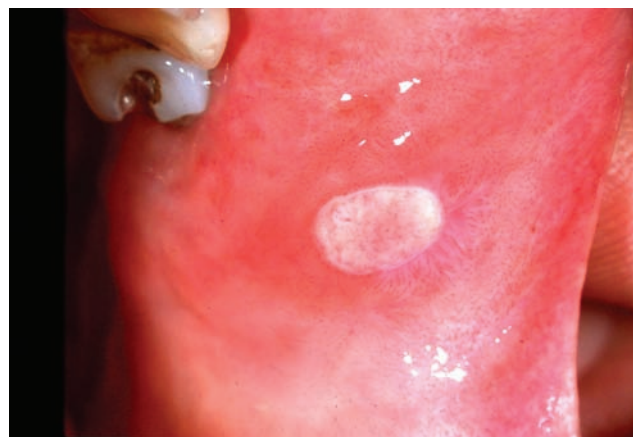


Fig 1. Minor recurrent aphthous ulceration. The lesion is discrete, crateriform, uniform in outline and less than 1cm in diameter.

inflammatory component. The ulcerative stage lasts for three to seven days.

The healing stage is identified by the abrupt cessation of pain and the appearance of granulations within the decreasing surface exudate. Healing progresses by secondary intention with ingrowth of marginal epithelium and gradual centripetal closure of the defect.

The remission stage identifies the ulcer-free periods. This may be prolonged or short, regular or irregular, apparently spontaneous in progression to a pre-ulcerative stage or triggered by an identifiable and sometimes predictable event, for example some dietary items and occasionally in the premenstrual phase.¹

Three clinical presentations within RAU are known: minor, major and herpetiform.¹³ Minor aphthous ulceration (MiAU), present in over 80 per cent of cases, shows lesions that are less than 1cm (2–6mm) in diameter and resolve spontaneously in 7–14 days without residual scarring in most sites. Prodromal symptoms may present as a hyperaesthesia or burning and reflects the initial hyperaemia at the presumptive ulcer site. They have a tendency to appear on the movable, lining and non-keratinized mucosae, predominately buccal and lip mucosa, ventral tongue, soft palate and in the vestibule. They may also occur on the dorsal tongue, palate and gingiva but this is uncommon. Lesions are non-vesicular and may be single or multiple (two to six) with several episodes a year. The submandibular, deep cervical and parotid lymph nodes may be palpable and sensitive depending upon the severity of individual lesions and the number present (Fig 1).

Major aphthous ulceration (MaAU) lesions are generally greater than 1cm in diameter, last four to six weeks without treatment and heal with scar formation. This level of ulcer involves the deep submucosa and subjacent tissues rather than being limited to the lamina propria and superficial submucosa as occurs with MiAU and hence the development of cicatrix. The duration, frequency of occurrence and associated level of morbidity reflects the overall severity of the condition compared with MiAU. Most commonly



Fig 2. Major recurrent aphthous ulceration. The lesion is greater than 1cm in diameter and involves deeper tissue layers.

MaAU are seen on the soft palate and fauces, tongue and buccal and labial mucosae. The ulcers are often multiple and asymmetrical. Like MiAU they have a crateriform profile but on a more exaggerated basis and with an irregular margin. Patients typically experience severe pain and associated lymphadenopathy (Fig 2).

Herpetiform aphthous ulceration (HAU) is a relatively rare form and presents as non-cluster pattern and non-vesicular lesions 1–3mm in diameter as distinct from viral ulcers. The number may reach 50–100 lesions with associated local pain. Characteristically, they involve the anterior part of the mouth, tip, lateral and ventral tongue and the floor of the mouth but rarely appear on the lips. The lesions will usually heal without scarring in 7–14 days. In contrast to herpes simplex virus primary infection, patients with HAU usually do not experience prodromal systemic symptoms (malaise, fever, pain) and do not have either vesicles or the extensive ulcerative gingival involvement (Fig 3).

Guidelines for management of patients with RAU

The successful management of RAU depends on a careful patient work-up and correct diagnosis including



Fig 3. Herpetiform recurrent aphthous ulceration. Lesions are non-vesicular and 2–3mm in diameter.

any features peculiar to a patient's presentation. It also requires patient understanding of the nature of the disease. A patient who leaves the consultation without an understanding of the nature of the condition and that it represents a specific disease like any other disease will not regard the condition as anything other than a mouth ulcer. This is a self-defeating position. The diagnosis and management of RAU requires consultation time and review time and preferably not slotted against "more important" issues such as a dental restoration.

A sequence for the diagnostic process used by the authors is:

1. General medical history
 - written pro-forma
 - include medications history
 - review with the patient
 - signed by both patient and clinician
2. History of the ulcerative disease
 - age at onset
 - duration of condition
 - frequency of recurrence
 - remission periods
 - exacerbating factors/events/medications
 - food intolerance (dairy, wheat, nuts, tomatoes, chocolate)
 - role of trauma
 - association with stress/anxiety
 - familial history
3. Clinical features of lesions – historical
 - single or multiple
 - average size
 - margins – irregular (traumatic), linear (Crohn's disease)
 - vesicular or non-vesicular
 - duration of individual lesions
 - tissue morbidity
 - level of functional morbidity and restriction
 - rate of onset (erythema multiforme)
4. Extra oral features
 - ocular or genital lesions (Behcets Disease, Reiter's Syndrome)
 - skin lesions (erythema multiforme)
 - GIT symptoms (inflammatory bowel disease)
 - haematological abnormality/deficiency
 - pyrexia
 - pharyngitis (PFAPA Syndrome)
 - chondritis (MAGIC Syndrome)
5. Previous assessments
 - medical
 - specialist
 - haematology, serology
 - histopathology
 - microbiology
6. Previous treatments
 - proprietary medications
 - prescription medications
 - clinical efficacy

7. Clinical examination

- general integrity of the oral mucosa
- cicatrix from previous lesions
- evidence of parafunctional habits
- current lesion(s)
- salivary function
- eyes and skin
- lymph nodes
- pyrexia

8. Laboratory investigations

- full blood examination (FBE)
- iron studies (serum iron, ferritin, TIBC, transferrin saturation)
- serum and red blood cell folate
- serum vitamin B₁₂
- other mucosal conditions, e.g., lichen planus, may require alternative blood screens

The authors employ a routine haematological screen covering full blood examination (FBE), iron studies, folate and vitamin B₁₂ for all patients presenting with RAU. Only a small number of patients show a specific anaemia or other haematological deficiency but their exclusion is an important part of the complete patient work-up. The authors have also noted that 10–20 per cent of patients with RAU show a tendency toward a sideropenia and this requires attention. The eyes, skin and other mucosal surfaces are also examined either directly or by questioning as a routine. This is a required part of the work-up of all mucosal disease patients and in many conditions can be surprisingly informative. Similarly, folate levels are an indicator of intestinal absorption function but patients are also questioned concerning any abdominal symptoms and particularly those without an identified cause.

Clinical management

Successful management of RAU is variable but, in most cases, a useful strategy can be tailored to the individual patient. It does require both patient compliance with instructions and an understanding and acceptance of the recurrent nature of this disease. Prior to commencing any treatment, the patient requires both an accurate diagnosis and an assessment of the level of morbidity. Those with extensive ulceration and particularly MaAU are generally not suitable for general practice management and require referral. Specific treatment for this heterogeneous group focuses on rapid symptom relief and lesion resolution and may involve systemic corticosteroids or other immunomodulatory agents. The current discussion will focus on MiAU as the most common and most readily treated.

Management of MiAU may be usefully divided into three phases: (1) symptomatic and supportive treatment; (2) specific treatment; (3) preventive treatment.

Symptomatic and supportive treatment is self-explanatory and focuses on the current level of patient morbidity. This phase is defined by the prescription of

generally proprietary preparations that address the obvious and major concerns of the patient: (a) antiseptic/anaesthetic preparations; (b) adequate analgesia; (c) maintenance of fluid balance; (d) adequate dietary intake.

It addresses the impact that RAU has both locally in the mouth as well as systemic morbidity and interference with systemic functions if present. This approach is somewhat traditional but, in combination with patient understanding of the specific disease of RAU, it reinforces the overall treatment strategy being proposed for an individual and, significantly, addresses the patients pain.

Specific treatment of MiAU requires a recognition and acceptance of the immunopathogenesis of RAU, irrespective of the exacerbating factor(s) of a specific episode. The temporal sequence of lymphocyte migration to the lesion site and subsequent cell-mediated cytotoxic destruction of epithelial cells is being addressed in this stage. The aim is to prevent epithelial destruction and the most effective general strategy to date is the appropriate use of topical corticosteroids.¹⁴ These have a broad based dampening effect on all immunocompetent cells as well as reducing tissue inflammation and oedema. The specific agent employed will depend upon the number, size and duration of lesions but, for most patients, a betamethasone preparation will be effective. The use of corticosteroids intra-orally is a separate topic and readers are referred to the article published previously in this journal.¹⁵ The essential issue with corticosteroids is early application, precise instructions and progress review. A haphazard try-it-and-see approach will not be successful and hence the emphasis in this article on patient understanding of RAU and a positive approach identical to that taken for any specific dermatosis. In many cases it also requires a significant update of clinicians knowledge and acceptance that RAU is a treatable condition and not “just a mouth ulcer”.¹⁵

Preventive treatment is a consideration for RAU patients who report regular exacerbations of their condition. It focuses on the earliest stage, the prodromal stage, and attempts to intercept ulcer development again by the use of topical immunosuppressants and particularly corticosteroids. Clinical experience shows that many RAU patients will enter a phase of complete clinical remission following the medium term use of a corticosteroid mouthrinse on a daily basis initially and then on a minimal maintenance dose over one to two months. Those patients who still develop aphthae will usually report a marked decrease in both the frequency and severity, both lesion size and associated morbidity, with this regime. This method of delivery is less readily controlled by both the clinician and patient and hence the opportunity for both oral and systemic adverse reactions is increased. A careful patient work-up is required along with close monitoring of patient compliance. It is generally inappropriate for paediatric

patients and those with general medical conditions likely to be steroid sensitive, e.g., diabetes and hypertension. Any suggestion of an infectious condition either locally in the mouth or systemic is an absolute contra-indication. Clinicians may benefit from specific advice from an oral medicine specialist prior to considering this treatment.

Other treatments

A range of immunomodulatory agents have been used against RAU over a very extended time. Most have achieved less success than the strategies proposed, other than in the small percentage of patients with refractory disease and particularly those with RAU that is related to a systemic condition. These medications, which include thalidomide, pentoxifylline, colchicine and etanercept, are not appropriate for general practice but practitioners should be aware that they are available and that newer agents are being trialled, some very successfully.¹⁶⁻¹⁹

CONCLUSION

The authors' experience with the majority of treatment failures is inadequate attention to the basic protocol as proposed here. Dental practitioners have great expertise in the arena of preventive dentistry and a compliant patient will receive every promised benefit from a detailed work-up, individual preventive plan, early support, monitoring compliance and regular review. If these same parameters are transposed to RAU then the frequency of success increases considerably. In many ways RAU management is similar to preventive dentistry as it manages a disease that often cannot be eradicated but can be controlled with careful attention to detail.

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