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Recurrent Aphthous Stomatitis in the Diagnosis of Behçet's Disease

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Recurrent aphthous stomatits (RAS) is also known as recurrent oral ulcers, recurrent aphthous ulcers, or simple or complex aphthosis. RAS is the most common inflammatory ulcerative condition of the oral mucosa in North American patients. RAS has been the subject of active investigation along multiple lines of research including epidemiology, immunology, clinical correlations and therapy. Clinical evaluation of the patient requires correct diagnosis of RAS and classification of the disease based on morphology (MiAU, MjAU, HU) and severity (simple versus complex). In order to properly diagnose and treat a patient with lesions of RAS, the clinician must exclude other causes of acute oral ulcers. Complex aphthosis and complex aphthosis variants associated with systemic disorders should be considered. The aphthous-like oral ulcerations of patients with HIV disease represent a challenging differential diagnosis. The association of lesions of RAS with hematinic deficiencies and gastrointestinal diseases provides an opportunity to identify a "correctable cause" which, with appropriate treatment, can result in a remission or substantial lessening of disease activity. Finally, when all of these factors are considered, the evaluation of the patient for Behçet's disease can be continued on firm grounds that one of the major criteria for the diagnosis of Behçet's disease has been met.

Key Words: Recurrent aphthous stomatitis, oral ulcers, simple aphthosis, complex aphthosis, Behçet's disease

Recurrent aphthous stomatitis (RAS) is also known as canker sores, recurrent oral ulcers, recurrent aphthous ulcers, or simple or complex aphthosis. Many patients confuse RAS with recurrent herpes simplex virus infections and believe that RAS is a "herpes infection." RAS is the most common inflammatory ulcerative condition of the oral mucosa in North American patients(Rogers, 1977; Hutton and Rogers, 1987; Rees and Binnie, 1996; Ship, 1996; Woo and Sonis, 1996) and has been recently reviewed by this author(Rogers, 1998). This work provides some of the information in this manuscript.

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The lesions of RAS are localized, painful, shallow, round to oval ulcers often covered by a grey to tan fibromembranous slough and surrounded by an erythematous halo (Fig. 1). Lesions of RAS typically afflict the non-masticatory, soft mucosa of the oral cavity, largely sparing the masticatory mucosa of the hard palate and maxillary and mandibular alveolar ridges. Sites of predilection include the undersurface of the tongue and the floor of the mouth as well as the buccal, labial, sulcular, soft palatal and oropharyngeal mucosal surfaces. The lesions of RAS are self-limited, persisting for one to two weeks, resolving with or without scarring, and recurring after periods of remission. Although some patients have infrequent recurrences, two to four times each year (simple aphthosis), other patients may have almost continuous disease activity with new lesions developing as older lesions heal

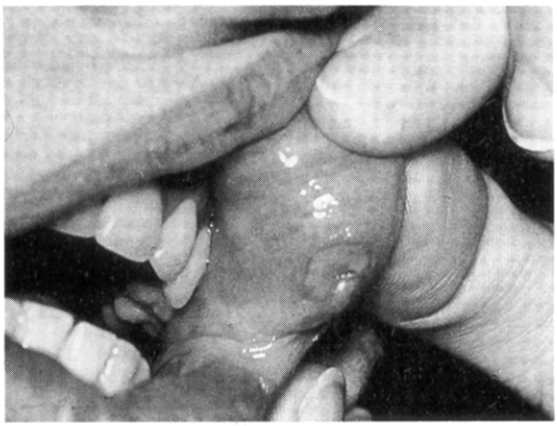

Fig. 1. Recurrent Aphthous Stomatitis. A large(major aphthous) ulcer is present on the left upper labial mucosa. The ulcer is covered by a tan fibromembranous slough and is surrounded by an erythematous halo.

(complex aphthosis).

The lesions of RAS usually are noted in childhood or adolescence and recur with decreasing frequency and severity with age. The prevalence of RAS varies with the population studied, ranging from 5 to 50%. It is estimated that 20% of the general population will have RAS during their childhood or early adult life. Some populations, such as dental and medical students, have a prevalence rate as high as 50%. Women are afflicted more commonly than men.

The presence of lesions of RAS is critical to the diagnosis of Behçet's disease. The diagnosis is rare without the presence of oral ulcers. The oral ulcers are aphthous in nature and are limited to non-masticatory oral mucosa such as the buccal, labial, sulcular, glossal, or oropharyngeal mucosal surfaces.

Some patients are referred for the diagnosis of Behçet's disease who have oral and genital disease or oral, ocular, and genital disease but do not have aphthous ulcerations. These patients have eventually been diagnosed as lichen planus, pemphigus, mucous membrane pemphigoid, and erythema multiforme.

Patients with Behçet's disease (BD) have typical lesions of RAS. The clinician, therefore, must understand the clinical characteristics, causes, and associated systemic disorders of RAS as well as the differential diagnosis of RAS.

CLINICAL CHARACTERISTICS: CLASSIFICATION

Cooke classified the lesions of RAS into three groups, and Lehner characterized them from a study of 210 patients(Table 1, Lehner, 1968; Cooke, 1969). These are: 1) minor aphthous ulcers, 2) major aphthous ulcers, and 3) herpetiform ulcers (Table 1). The most common form of RAS is minor aphthous ulcers (MiAU) which afflict 75 to 85% of patients with RAS. MiAU are one or more, small (<1.0 cm), oval or round, shallow ulcers covered by a grey to tan fibromembranous slough and surrounded by a peripheral zone of erythema (Fig. 2). MiAU are moderately painful and usually heal without scarring in one to two weeks. Lesions may recur frequently, but most patients suffer two to four episodes a year.

Major aphthous ulcers (MjAU) represent a more severe form of RAS. These lesions afflict about 10 to 15% of the sufferers of RAS. MjAU are also known as Sutton's ulcers or periadentitis mucosa necrotica recurrens(Sutton, 1911). Like MiAU, MjAU usually begins in childhood and adolescence. These lesions are morphologically similar to MiAU but are larger, usually>1.0 cm, and deeper (Fig. 3). MjAU heal more slowly (10 to 30 days) and characteristically heal with a scar. Lesions of MjAU may cause considerable discomfort, oral pain, fever and malaise.

The third variant, herpetiform ulcers (HU), are the least common, afflicting 5 to 10% of patients with RAS(Rogers, 1998). The lesions of HU are grouped as the adjective "herpetiform" implies but are not the result of a herpes simplex virus infection as is often assumed because of the word herpetiform. Individual lesions may be quite numerous, ranging from 10 to 100. The elemental lesion is a discrete 1 to 2 mm papule which evolves to a papulovesicle then an ulcer. HU lesions are grouped and, with evolution, become confluent into larger plaqueform lesions (Fig. 4). Because of size and depth, HU lesions may heal with scarring in 7 to 30 days.

Another valuble classification of RAS is simple aphthosis versus complex aphthosis (Table 2).

Table 1. Classification of recurrent aphthous stomatitis

Type	%F	Age(onset)	Size(mm)	Number	Location	Prevalence(%)
MiAU	56	10-19	<10	few	anterior	80
MjAU	44	10-19	≥10	few	ant>posterior	10
HU	73	20-29	1-2	many	both	10

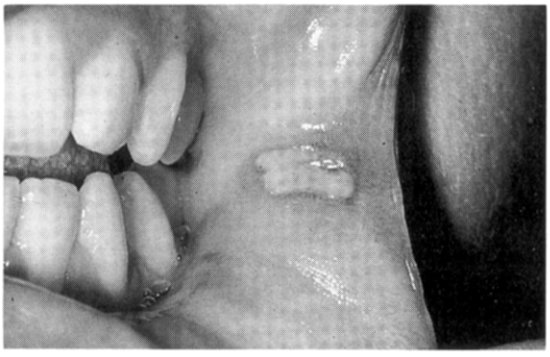

Fig. 2. Recurrent Aphthous Stomatitis, Minor Aphthous Ulcers. Two small aphthous ulcers are present on the left labial commissure where they have become confluent into a larger plaque. The ulcer is covered by a tan fibromembranous slough. Minor aphthous ulcers usually heal without scarring.

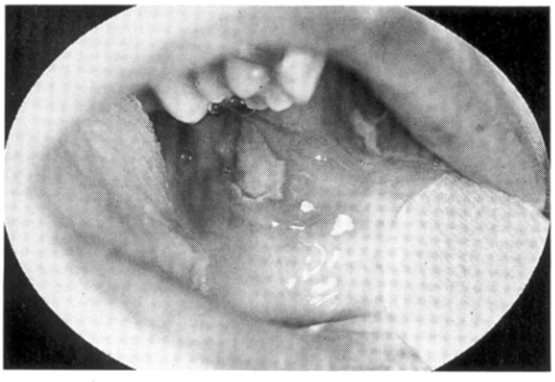

Fig. 3. Recurrent Aphthous Stomatitis, Major Aphthous Ulcer. One Large aphthous ulcer is present on the left buccal mucosa. A scar from a previous major aphthous ulcer is present on the upper left buccal mucosa. Major aphthous ulcers often heal with scarring due to the size and depth of the ulcer.

Table 2. Classification of recurrent aphthous stomatitis

Simple aphthosis	Complex aphthosis
Episodic	Episodic or continuous
Short-lived	Persistent
Few lesions	Few to many lesions
3-6 episodes/year	Continuous ulcers
Heal quickly	Slow healing
Minimal pain	Marked pain
Little disability	Disabling
Limited to oral cavity	May have genital lesions

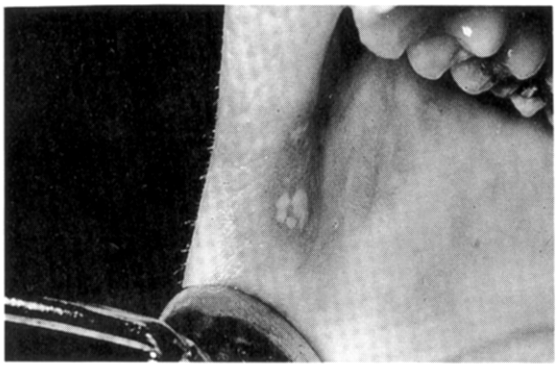

Fig. 4. Recurrent Aphthous Stomatitis, Herpetiform Ulcers. Grouped tiny aphthous ulcers are present on the right labial commissural mucosa. Some tiny elemental papulovesicles have become confluent while others are discrete. All are grouped, justifying the adjective herpetiform which means grouped, but does not imply causation by the herpes simplex virus.

Simple aphthosis represents the common presentation of a few lesions which heal in one to two weeks and recur infrequently. Complex aphthosis, on the other hand, represents a complicated clinical picture of severe disease, numerous, large, or deep lesions, new lesions developing as older lesions heal (continuous ulcerations), marked pain or disability, and, occasionally, associated genital or perianal lesions(Jorizzo *et al.* 1985). The presence of ano-

genital aphthae do not confirm the diagnosis of Behçet's disease, as some patients with complex aphthosis will have occasional genital aphthae but never develop Behçet's disease.

CLINICAL CHARACTERISTICS: NATURAL HISTORY

Stanley has divided the clinical features of RAS into four stages: premonitory, preulcerative, ulcerative and healing (Table 3, Stanley, 1972). The premonitory stage occurs during the first 24 hours of the development of a lesion of RAS. During this prodrome the patient may note a burning or tingling sensation at the site where a lesion will develop. Microscopically, mononuclear cells begin to infiltrate the epithelium, and edema begins to develop.

The pre-ulcerative stage occurs during the first 18 to 72 hours in the development of a lesion of RAS. In this stage, macules and papules develop with a surrounding reactive erythematous halo. Pain increases in intensity during the pre-ulcerative stage. The ulcerative stage persists for a few days to two weeks. At this time, the papule ulcerates and the wound is covered by a fibromembranous slough which is associated with a lessening of pain.

The healing stage occurs during days 4 to 35. The ulcer is covered by epithelium, and wound healing occurs, often leaving no scar or trace of the lesion of RAS.

Thus, all lesions of RAS heal and new ones develop. One must understand the natural history of individual lesions of RAS in order to place treatment claims in perspective.

Table 3. Clinical features of recurrent aphthous stomatitis

Stage	Timing	Symptoms
Premonitory	First 24 hours	Beginning paresthesias
Pre-ulcerative	18-72 hours	Increasing pain
Ulcerative	Days to weeks	Diminishing pain
Healing	Days to weeks	Painless

CAUSES

The definitive cause of lesions of RAS remains obscure and is very likely multifactorial and colored by a host of predisposing factors. Thus, the etiology of RAS will not often be explained by a single factor. The clinician must seek to identify many predisposing factors and associated conditions (Table 4).

Trauma has been implicated by patients, clinicians and investigators as a predisposing factor for the development of lesions of RAS(Wray *et al.* 1981; Ross *et al.* 1985). Incidental oral trauma from tooth brushing, flossing, chewing gum, talking while chewing, sharp-surfaced foods, malocclusion, injections and dental treatments has been implicated or demonstrated in vivo. On the other hand, edentulous patients with dentures and many other patients do not develop lesions of RAS after acute or chronic trauma.

Smoking is a form of oral trauma, but in this instance, it may be protective against the development of lesions of RAS. The relationship of smoking with a lower prevalence of RAS has been recognized for years(Chellemi *et al.* 1970; Axell and Henricsson, 1985). Smokers suffer from RAS less often and with less severity than non-smokers(Axell and Henricsson, 1985). Indeed, some patients note the onset or recrudescence of RAS with smoking cessation and remission with reinstitution of smoking cigarettes. Increased keratinization secondary to the trauma of smoking is thought to explain these findings.

However, use of smokeless tobacco or nicotine chewing tablets may be associated with a lower prevalence or reduced disease severity, suggesting

Table 4. Predisposing factors for recurrent aphthous stomatitis

Trauma
Non-smoking
Emotional Stress
Hormonal Factors
Viruses
Bacteria
Genetics
Food Hypersensitivity
Immune Dysregulation

that nicotine may provide some protective role.

In 1957, Sircus *et al.* reported emotional or environmental stresses preceded the development of the initial episode of RAS in 60% and the development of recurrent episodes in 21% of patients(Sircus *et al.* 1957). Stress has been implicated in many studies since then, particularly among dental and medical students and other students with high expectations and demanding responsibilities(Crivelli *et al.* 1988).

McCartan and Sullivan have concluded that numerous studies have failed to support a convincing association between the lesions of RAS and the menstrual cycle(McCartan and Sullivan, 1992). There are, however, some patients whose disease remits with estrogen-dominated oral contraceptives or pregnancy.

Many authors have implicated microbiological agents as the cause for RAS over the years. These include viruses such as herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus and adenoviruses. Various bacteria have also been suspected. A large volume of literature regarding the L-form of a streptococcal bacteria and its relationship to the lesions of RAS exists. To date, there is little convincing data to implicate an infectious cause for the lesions of RAS.

Thirty years ago, Ship recognized a definite proclivity for patients with RAS to have parents and siblings with RAS(Ship, 1965). A high correlation has been reported in identical twins but not in nonidentical twins(Miller *et al.* 1977). Associations of certain HLA haplotypes with RAS have been reported but are geographically quite variable. Nevertheless, there is clearly a familial tendency to develop the lesions of RAS.

Many patients with lesions of RAS believe that foods are causative. Often the association represents irritating established ulcers rather than provoking their development. Numerous studies of small samples of patients with RAS have implicated a large number of foods, preservatives and dyes including gluten, cinnamaldehyde, benzoic acid, sorbic acid, and azo dyes.

Some studies have confirmed hypersensitivity by challenge and re-challenge or patch testing(Nolan *et al.* 1991), while other investigations such as double-blind studies with gluten-free and gluten-supplemented diets found that both groups of patients with RAS but without gluten-sensitive enteropathy showed improvement suggesting a prominent placebo response(Hunter *et al.* 1993). These data lend support to the multifactorial nature of RAS.

Immunological studies of lesions of RAS have attracted a great deal of attention. Several studies have implicated in vitro immune dysregulation ranging from lymphocyte cytotoxicity(Rogers *et al.* 1974) to antibody- dependent cellular cytotoxicity (Greenspan *et al.* 1981) to T lymphocyte directed damage(Pedersen *et al.* 1992). The presence of severe aphthosis in HIV-positive patients and the similarity of tissue lymphocyte subsets in lesions of HIV-negative patients with RAS suggest a cell-mediated immunity disturbance in which infiltrating T lymphocytes play an important role(Pedersen *et al.* 1992; Regezi *et al.* 1993). This complex topic has been reviewed by Eversole recently(Eversole, 1989). Thus, immunologically mediated damage to epithelial cells may be the final common pathway in the development of lesions of RAS but the antigen or antigens responsible for initiation of the pathway remain obscure.

ASSOCIATED SYSTEMIC DISORDERS

Successful management of patients with lesions of RAS is dependent on an accurate diagnosis, classification of the disease, recognition of possible causative factors and the identification of associated systemic disorders which contribute to the disability, treatment, and prognosis of RAS. These disorders are listed in Table 5.

Complex aphthosis occupies a position on the continuum from limited disease (simple aphthosis)

Table 5. Associated systemic disorders

Ulcus vulvae acutum
Behçet's disease
MAGIC syndrome
FAPA syndrome
Cyclic neutropenia
Aphthous-like ulcerations of HIV disease
Hematinic deficiencies
Celiac disease (sprue, gluten-sensitive enteropathy)
Inflammatory bowel disease

Table 6. International conference on Behçet's disease criteria (1990)

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient which occurred at least 3 times in one 12-month period.
Plus 2 of:	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by physician or patient.
Eye lesions	Anterior uveitis, posterior uveits, or cells in vitreous on slit lamp examination; or Retinal vasculitis observed by ophthalmologist.
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions; or Acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment.
Positive pathergy test	Read by physician at 24-48 hours.

to systemic disease. Several systemic diseases may be characterized by complex aphthosis including: ulcus vulvae acutum, Behçet's disease, MAGIC syndrome, FAPA syndrome, and cyclic neutropenia. Ulcus vulvae acutum represents an acute severe episode of oral and vulvar aphthae often associated with an infectious gastroenteritis such as tuberculous enterocolitis, typhoid fever or *Yersinia* enterocolitis. Upon recovery simple aphthosis may remain as the only remnant of the disease. Behçet's disease(BD) is a multisystem disorder affecting young patients of Mediterranean, Middle East, Eastern Pacific or Japanese descent. Classic BD is a tri-symptom complex of oral and genital aphthae and ocular inflammation such as uveitis or iritis. Several classifications of BD exist. At the 4th International Conference on Behçet's Disease in 1990, a consensus panel developed diagnostic criteria(Table 6, International Study Group for Behçet's Disease, 1990). The cutaneous lesions of erythema nodosum are straightforward, but confusion exists regarding the pathergic skin test, the papulopustular lesions, the lesions of pustular vasculitis, and acneiform lesions. Nevertheless, the diagnosis of BD should not be made prematurely and without adequate evaluation, as the prognosis of BD may be grave, and the treatment may be toxic.

Patients with rare and unusual combinations of signs and symptoms including lesions of RAS have been reported as the MAGIC syndrome (mouth and genital ulcers with inflamed cartilage), the FAPA syndrome(fever, aphthosis, pharyngitis, and adenitis) and cyclic neutropenia. Aphthous-like oral ulcerations have been reported in HIV-positive patients. Lesions tend to be large like MjAU lesions and disabling like complex aphthosis. These lesions of RAS tend to occur in individuals with CD4+ counts<100 cells/mL. The differential diagnosis in this profound immunosuppressive state includes infections or drug-induced oral ulcers. The diagnosis of HIV-associated aphthous-like oral ulcers is one of exclusion.

Hematinic deficiencies have been associated with lesions of RAS for many years. Several studies have confirmed the presence of a subset of patients who may be deficient in iron, folic acid, zinc, vitamins B1, B2, B6 and B12 and whose disease remits or improves dramatically with replacement of their deficiencies(Wray *et al.* 1978; Tyldesley, 1983; Rogers and Hutton, 1986; Nolan *et al.* 1991; Porter *et al.* 1992). Hematological screening should be considered for all patients with complex aphthosis, those patients with persistently troublesome signs and symptoms, and any patient with signs or symptoms of malabsorption or nutritional deficiency. Screening includes a complete blood count with red blood cell indices, serum levels of zinc and vitamin B12, red blood cell or serum folate, and anti- endomysial or anti-gliaden antibody studies.

Gastrointestinal diseases have been associated with lesions of RAS for many years also. Indeed, according to DuBois and van den Berghe(DuBois

and van den Berghe, 1948), the word "sprue," signifying the gastrointestinal disease, is derived from the Dutch word "spruw" which signifies aphthosis. The association of lesions of RAS with gluten-sensitive enteropathy(GSE, sprue) has been recognized for years(Ferguson *et al.* 1980). The malabsorption associated with GSE can lead to deficiencies of B vitamins and folate. Some authors report that both oral and gut lesions resolve with a gluten-free diet and that some patients with lesions of RAS may not have symptoms of GSE, but the oral lesions will improve with a gluten-free diet(Wray, 1981). Thus, patients with RAS may have symptomatic or asymptomatic GSE with gluten hypersensitivity and/or nutritional deficiencies, either or both of which may be related to the development of the lesions of RAS. However, Hunter and co-authors report that, in the absence of documented GSE, a double-blind controlled study of patients with RAS did not confirm that a gluten-free diet or a gluten-supplemented diet consistently yielded benefit or worsening for patients, but did show a large placebo effect(Hunter *et al.* 1993).

The lesions of RAS may be associated with inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease. Simple or complex aphthosis may antedate, coexist or may serve as a marker for increasing intestinal disease activity. Patients with IBD not only have lesions of RAS but may also have erythema nodosum, papulopustular lesions or lesions of pustular vasculitis, and inflammatory ocular disease, such as iritis and uveitis.

Table 7. Differential diagnosis of acute oral ulcers

Recurrent aphthous stomatitis
Cyclic neutropenia
Recurrent intra-oral herpes simplex stomatitis
Trauma
Acute necrotizing ulcerative gingivostomatitis
Syphilis-primary, secondary, tertiary
Viral Diseases-See Table 8

Table 8. Viral infectious of the oral cavity

Infection	Presentation	Site	Age	Comment
Herpes zoster	painful grouped vesicles	Unilateral	Adults>children	Skin lesions
Herpetic gingivostomatitis	Painful grouped vesicles	Diffuse, lips	Children>adults	Fever, malaise
Recurrent herpes	Painful grouped vesicles	Single group, lips	Adults>children	Rare intraoral
Herpangina	Scattered tiny vesicles, petechiae	Posterior mucosa	Children>adults	Fever, pharyngitis
Infectious mononucleosis	Scattered tiny vesicles	Posterior mucosa	Adults>children	Fever, pharyngitis
Hand, foot, and mouth disease	Scattered tiny vesicles	Posterior mucosa	Children>adults	Hand, foot lesions
Varicella	Scattered tiny vesicles	Posterior mucosa	Children	Skin lesions
Measles	Bluish macules with red halo	Buccal mucosa	Children	Skin lesions
Rubella	Petechiae	Posterior mucosa	Children	Skin lesions

Thus, the distinction between multisystem IBD and Behçet's disease may be difficult.

DIFFERENTIAL DIAGNOSIS

All oral ulcers are acute at the onset of the condition. Some ulcers become chronic. If we accept 6 weeks as the boundary between acute and chronic, as is the case with acute and chronic urticaria, then chronic oral erosive or ulcerative diseases such as lichen planus, lupus erythematosus, pemphigus, cicatricial pemphigoid, and oral cancer could be included. Oral erosive and ulcerative conditions which typically resolve within 6 weeks are considered as acute.

Some acute oral ulcers are aphthous in morphology and nature such as RAS while others differ in one or several characteristics. The differential diagnosis of acute oral ulcers is shown in Table 7. The differential diagnosis of acute oral ulcers of viral etiology is shown in Table 8.

The first differential diagnostic hallmark of RAS versus other acute oral ulcers is the recurrent nature of the condition. Recurrent oral ulcerations include trauma, RAS, cyclic neutropenia, and recurrent intra-oral herpes simplex virus(HSV) stomatitis.

The essentials of diagnosis for recurrent aphthous stomatitis are: recurrent ulcers of non-attached oral mucosa, three morphologic types (minor, major, herpetiform), few lesions at a time, intense pain early then lessening, complete healing between episodes, and affliction of young people. Both the oral ulcers and the neutropenia of cyclic neutropenia have a regular 3-week periodicity. Recurrent intra-oral HSV stomatitis typically afflicts the attached (masticatory) mucosa. These lesions are painful grouped papulovesicles.

Bacterial infection characterized by oral ulcers are acute necrotizing ulcerative gingivostomatitis (ANUG) and all stages of syphilis. ANUG (trench mouth, Vincent's infection) typically affects the interdental papillae but may involve the buccal or pharyngeal mucosa. The condition is quite painful. Oral lesions may be seen in all stages of syphilis including chancres, mucous patches, and gummas.

A clinical algorithm for acute oral ulcers is based on the recurrent nature, morphology, number, location, amount of pain, and presence of systemic symptoms. This algorithm is depicted in Table 9.

The lesions of RAS are shown in bold type.

Table 9. Clinical algorithm of acute oral ulcers

Recurrent	
recurrent	RAS, recurrent intra-oral HSV, cyclic neutropenia
Morphology	
discrete	minor & major RAS, syphilis, viral, trauma
grouped	herpetiform RAS, HSV, zoster
large	major RAS, syphilis
small	minor RAS, cyclic neutropenia
Number	
single	RAS, syphilis, trauma
multiple	RAS, viral, ANUG
Location	
interdental	ANUG, AHGS, recurrent intra-oral HSV
masticatory	cyclic neutropenia, HSV, zoster, trauma
non-attached	RAS, viral, syphilis, trauma
posterior	RAS, viral
diffuse	ANUG, AHGS
Pain	
mild	RAS, syphilis, trauma
moderate	RAS, viral, cyclic neutropenia
severe	RAS, ANUG, viral
Systemic symptoms	
present	ANUG, 2° syphilis, AHGS, herpangina

With the knowledge of clinical characteristics of RAS and of other acute oral ulcerations, the clinician can establish the aphthous nature of the lesions seen in patients with Behçet's disease and exclude other diseases in the differential diagnosis.

SUMMARY

Recurrent aphthous stomatitis has been the subject of active investigation along multiple lines of research including epidemiology, immunology, clinical correlations and therapy. Numerous review articles have been written since the 1960s(Lehner, 1968; Cooke, 1969; Rogers, 1977; Hutton and Rogers, 1987; Rees and Binnie, 1996; Ship, 1996; Woo and Sonis, 1996; Rogers, 1998) permitting the student to assess the large and actively growing literature regarding RAS.

Fortunately, most patients with lesions of RAS suffer from simple aphthosis which, while aggravating and frustrating as well as common (20% of young people), does not substantively interfere with the quality of life. We have learned more about patients suffering from complex aphthosis and have reason to be optimistic that we may find a "correctable cause" in as many as 15 to 20% of patients suffering from complex aphthosis.

The oral lesions of BD are aphthous in nature and are classified as complex aphthosis. While some patients with complex aphthosis will develop BD, some will remain as complex aphthosis sufferers for years until the disease undergoes spontaneous or treatment-induced remission.

In assessing oral ulcerations in the differential diagnosis of BD, the clinician must exclude all other causes of acute oral ulcerations such as bacterial or viral oral infectious diseases as well as the conditions associated with RAS. When the clinician is convinced of the aphthous nature of the oral ulcerations, the evaluation of the patient for BD can be continued on firm grounds that one of the major criteria for the diagnosis of BD has been met.

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