Review article: oral ulceration – aetiopathogenesis, clinical diagnosis and management in the gastrointestinal clinic

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Accepted for publication 15 August 2003

SUMMARY
Oral ulceration is a common complaint of patients attending out-patient clinics. The aim of this review is to provide the gastroenterologist with a differential diagnosis of oral ulceration, and a practical guide for the management of recurrent aphthous stomatitis, including topical and systemic therapy. The association of recurrent aphthous stomatitis with Behçet’s disease and other systemic disorders, including coeliac disease, is discussed. Recent evidence concerning the immunopathogenesis of Behçet’s disease is reviewed, including renewed interest in the role of Streptococcus sanguis and possible infectious triggering of an inappropriate immunoinflammatory response, resulting in tissue damage. The efficacy and limitations of conventional treatment for this multisystem disorder are outlined together with the potential role of novel biological agents, such as anti-tumour necrosis factor-α therapy. Oral ulceration, as a manifestation of inflammatory bowel disease and a complication of drug therapy, is described. Guidance is given concerning indications for referral of patients with oral ulceration to an oral physician/surgeon for further investigations, including biopsy if appropriate.

THE DIFFERENTIAL DIAGNOSIS OF ORAL ULCERATION
The principal causes of oral ulceration are trauma, recurrent aphthous stomatitis, microbial infections, mucocutaneous disease, systemic disorders, squamous cell carcinoma and drug therapy (see Table 1 and Figures 1–6).

RECURRENT APHTHOUS STOMATITIS
Recurrent aphthous stomatitis (RAS) is characterized by recurrent bouts of one or several shallow, rounded or ovoid, painful ulcers, that recur at intervals of a few days or up to 2–3 months. RAS is a common oral mucosal condition and has been reported as affecting 20% of the general population at any time. The peak age of RAS onset is during childhood, with a tendency to decrease in severity and frequency with age.

Clinical features
Three clinical presentations of RAS are recognized: minor recurrent aphthous stomatitis (MiRAS), major recurrent aphthous stomatitis (MjRAS) and herpetiform ulceration. The clinical presentation of these types of RAS are shown in Table 2. Patients may sometimes present with a mixed pattern of RAS, but this is relatively uncommon.

Minor recurrent aphthous stomatitis (MiRAS)
This is the most common form of RAS and approximately 80% of patients have lesions of this type. In its most characteristic form, MiRAS presents the picture of a number of small ulcers (one to five) appearing on the
buccal mucosa, the labial mucosa, the floor of the mouth or the tongue. Moreover, the ulcers are usually concentrated in the anterior part of the mouth; the pharynx and tonsillar fauces are rarely implicated in this form of ulceration. The prodromal stage of ulceration is variable, but there is usually a sensation described as ‘burning’ or ‘prickling’ for a short period before the ulcers appear. Following this phase, ulceration occurs directly by loss of the epithelium. The ulcers are usually less than 1 cm in diameter and, in most instances, their size is approximately 4–5 mm in diameter. However, the classification of ‘minor’ RAS does not depend on the dimensions of the lesions alone, but on a number of clinical features. The appearance of the ulcer base is grey–yellow, often with a red and slightly raised margin, and, unless influenced by the site (as in the depth of the buccal sulcus where they appear elongated), they are usually oval in shape. The ulcers are painful, particularly if the tongue is involved, and may make eating or speaking difficult. The course of these ulcers varies from a few days to a little over 2 weeks, but usually their duration is of the order of 10 days. Minor aphthae heal without scar formation. Following healing of the ulcers, there is a variable ulcer-free interval; 3–4 weeks is most common. In a few patients the recurrence of the ulcers appears to be entirely random, and in some cases there may not be an ulcer-free period between attacks, with new aphthae developing before existing ones have healed.

**Major recurrent aphthous stomatitis (MjRAS)**

MjRAS (Figure 1) accounts for approximately 10–15% of cases, and it varies from the minor form in a number of important clinical features. The ulcers tend to be larger than those of MiRAS, and they are of greater duration, up to a period of months in some cases. As a result of the long periods of time involved, there is probably a tendency for the production of a heaped-up margin which, when a single ulcer is seen in isolation, may lead to the suspicion that the lesion is malignant. On eventual healing, the ulcers may leave a substantial scar and this, together with the tissue destruction which may occur during the active phase of ulceration, may lead to gross distortion of the involved tissues. MjRAS may produce lesions throughout the entire oral cavity, including the soft palate and tonsillar areas, and ulceration may extend to the oropharynx.

**Table 1. Principal causes of oral ulceration**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary ulcer*</td>
<td>Trauma, Squamous cell carcinoma, Infections (e.g. syphilis, tuberculosis)</td>
</tr>
<tr>
<td>Recurrent bouts of one or more ulcers healing spontaneously</td>
<td>Recurrent aphthous stomatitis (RAS), Behçet’s disease</td>
</tr>
<tr>
<td>‘Aphthous-like’ ulcers due to systemic disease or drug therapy.</td>
<td></td>
</tr>
<tr>
<td>Single bout of ulceration, preceded by vesicles and affecting multiple oral sites</td>
<td>Viral infections (e.g. herpangina and primary herpetic stomatitis)</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td></td>
</tr>
<tr>
<td>Persistent oral ulceration affecting different sites†</td>
<td>Mucocutaneous disease (e.g. oral lichen planus, Fig. 2)</td>
</tr>
<tr>
<td>Immunobullous disease (e.g. oral pemphigus)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease (e.g. Crohn’s disease)</td>
<td></td>
</tr>
<tr>
<td>Haematological (e.g. leukaemia)</td>
<td></td>
</tr>
<tr>
<td>Drug therapy (e.g. nicorandil)</td>
<td></td>
</tr>
</tbody>
</table>

* If a single persistent oral ulcer shows no sign of healing 10–14 days after any putative trauma is removed, then it must be considered as malignant, unless proven otherwise.
† Patients may report intermittent oral ulceration if these conditions undergo periods of remission.

**Table 2. Clinical features of recurrent aphthous stomatitis (RAS)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Minor (MiRAS)</th>
<th>Major (MjRAS)</th>
<th>Herpetiform ulceration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age of onset</td>
<td>2nd decade</td>
<td>1st and 2nd decades</td>
<td>3rd decade</td>
</tr>
<tr>
<td>Number of ulcers/bout</td>
<td>1–5</td>
<td>1–3</td>
<td>5–20 (100)</td>
</tr>
<tr>
<td>Size of ulcers (mm)</td>
<td>≤ 10</td>
<td>&gt; 10</td>
<td>1–2</td>
</tr>
<tr>
<td>Duration</td>
<td>7–14 days</td>
<td>2 weeks – 3 months</td>
<td>7–14 days</td>
</tr>
<tr>
<td>Heal with scarring</td>
<td>No</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>Site</td>
<td>Non-keratinized mucosa, especially labial/buccal mucosa, Dorsum and lateral borders of tongue.</td>
<td>Keratinized plus nonkeratinized mucosa particularly soft palate.</td>
<td>Non-keratinized mucosa but particularly floor of mouth and ventral surface of tongue.</td>
</tr>
</tbody>
</table>

* Unless a number of ulcers coalesce.
The number of ulcers present at one time varies from one to 10 in MjRAS. Frequently, a single ulcer will persist for a long period, while other (usually smaller) ulcers fade. Unlike MiRAS, there does not appear to be a cyclical pattern in MjRAS, and the ulcers are usually unpredictable in their onset. Long periods of remission may be followed by intervals of intense ulcer activity, without any obvious precipitating factor. The prolonged and painful ulceration may present significant problems to the patient; difficulty eating, speaking and swallowing can severely affect a patient’s quality of life.

Herpetiform ulceration

This distinctive form of RAS differs in many ways from both MiRAS and MjRAS, and is less common, affecting 5–10% of cases. In herpetiform ulceration the ulcers are small (1–2 mm) and multiple (as many as a hundred ulcers may be present at the same time). Although any nonkeratinized oral mucosa may be involved, characteristically the affected sites are the lateral margins of the tongue and the floor of the mouth. Individual ulcers are grey and without a delineating erythematous border, making them quite difficult to visualize: they resemble ulcers of primary Herpes simplex virus (HSV) infection. In spite of their small size, these ulcers are very painful and may make eating and speaking difficult. A single crop of ulcers may last for approximately 7–14 days, and the period of remission between attacks is variable. Where many ulcers are present they may coalesce to form larger confluent areas of ulceration, usually with marked erythema. Healing with scar formation has been described in herpetiform ulceration, but this is probably a result of coalescence.

Aetiopathogenesis of RAS

Genetic factors are likely to predispose patients to RAS, and more than 40% of affected individuals have first-degree relatives with RAS. The aetiology of RAS is unknown, but a number of predisposing factors have been implicated and include trauma, stress, smoking cessation, hormonal imbalance and food hypersensitivity. Although some patients report that stressful life events (e.g. taking examinations in the case of students) can provoke an outbreak of ulcers, there is little substantive evidence to link stress to RAS. There appears to be a negative association between smoking and RAS, and some patients report the onset of oral ulcers after smoking cessation. Interestingly, nicotine-containing tablets appear to control the frequency of RAS. Some patients report being free from aphthae whilst taking oral contraceptives or when pregnant, and a minority of women with RAS have cyclical oral ulceration related to the luteal phase of the menstrual cycle. There is no convincing evidence linking
hypersensitivity to foods and RAS other than in coeliac disease, but some patients recognize that foods such as chocolate, cheese and tomatoes can precipitate attacks of RAS.

There is strong evidence from histopathological and immunological studies that T-cell-mediated immune responses are implicated in RAS. Three stages are recognized in the development of an aphthous ulcer. Microscopic examination during the pre-ulcerative stage reveals a mononuclear (lymphocytic) cell infiltrate in the epithelium focal vacuolation and is followed by degeneration of the suprabasal epithelial cells accompanied by a mononuclear, mainly lymphocytic infiltrate in the lamina propria. As the ulcerative stage approaches there is increased infiltration of the tissues, particularly the epithelium, by mononuclear cells and accompanied by more extensive oedema and degeneration of the epithelium progressing to frank ulceration with a fibrinous membrane covering the ulcer. During the healing phase there is regeneration of the epithelium. The immunopathogenesis of RAS has yet to be fully elucidated, but the infiltration of the epithelium by T lymphocytes is likely to be in response to some, as yet unidentified, keratinocyte-associated antigen. Keratinocyte death is thought to be mediated by the differentiation of cytotoxic T cells and involves the production of tuour necrosis factor-α (TNFα) by these and other leucocytes. TNFα induces inflammation by its effect on endothelial cell adhesion and neutrophil chemotaxis. Other cytokines, e.g. interleukin and interleukin-2, may also play a role in the immunopathogenesis of RAS.

Oral streptococci were previously suggested as important in the pathogenesis of RAS and Behcet’s disease, either as direct pathogens or an antigenic stimulus, culminating in the genesis of antibodies that may conceivably cross-react with keratinocyte antigenic determinants. More recently a common antigen was demonstrated between oral mucosa and the 65 kDa heat shock protein (HSP). As there is a high degree of homology between the microbial 65 kDa and human 60 kDa HSP, the hypothesis was suggested that an autoimmune response to the endogenous HSP might be responsible for the pathological changes in Behcet’s disease. The role of the γδ T-cell subset in the immunopathology of RAS and Behcet’s disease and their participation in the immune response to bacteria-derived and autologous antigens in these conditions is currently under investigation (see section on Behcet’s disease). Although RAS and Behcet’s disease are likely to share some common immunopathogenic mechanisms the reasons why RAS lesions are confined to the oral cavity, and the oral lesions in Behcet’s disease are associated with multisystem disease remains unclear.

**Systemic conditions and ‘aphthous-like’ lesions**

Table 3 lists the principal systemic conditions associated with ‘aphthous-like’ ulcers. These frequently start in adulthood with no previous history of oral ulceration.

**Gastrointestinal disorders**

Crohn’s disease and ulcerative colitis may occasionally be associated with RAS but are more likely to manifest as other types of oral ulceration. The association of RAS with coeliac disease is well established. A number of studies have suggested up to 5% of out-patients who initially present with RAS have gluten-sensitive enteropathy (GSE). These RAS patients may not always have gastrointestinal symptoms or other clinical features of coeliac disease but usually have folate deficiency and sometimes reticulin antibodies, particularly immunoglobulin-A-class reticulin and/or gliadin antibodies. A recent study has demonstrated that the prevalence of RAS in a population with coeliac disease did not significantly differ from an unaffected matched population without coeliac disease. The authors conclude therefore that coeliac disease should be referred to as a ‘risk indicator’ not a ‘risk factor’ for RAS. A high prevalence of HLA-DRW10 and DQW1 has been associated with RAS. RAS in patients with coeliac disease appears to remit completely on a gluten-free diet; however, there is conflicting evidence concerning the remission of RAS in patients without GSE, who undergo dietary withdrawal of gluten. There may be a few RAS patients, with no detectable clinical or histological evidence on jejunal biopsy, who may...
respond to a gluten-free diet, but a study by Hunter et al. showed no significant benefit for RAS patients without evidence of coeliac disease.

Other systemic conditions and factors

Haematinic deficiencies (iron, folic acid or vitamin B₁₂) have been reported to be twice as common in RAS patients than in controls. One US study, however, did not report any iron or folic acid deficiency in RAS patients, and there is no convincing evidence of B₆ or zinc deficiency in individuals with RAS. Replacement therapy has not met with uniform success, although RAS may improve in some patients who are nutritionally deficient. HIV-associated ulcers tend to occur in crops of five or less on nonkeratinized mucosa, and may resemble minor or major aphthae. The ulcers are frequently very painful and last for several months; they can be extremely debilitating in these patients and can cause problems with eating. Care must be taken to exclude HSV or cytomegalovirus infection in HIV-infected patients presenting with oral ulceration. Large major-aphthous-type ulcers are likely to be seen in HIV patients with low CD4⁺ T lymphocyte counts. It has been postulated that the immune imbalance associated with HIV disease may amplify the local breakdown in immunoregulation in RAS and lead to more severe ulcers. A significant number of patients with cyclical neutropenia present with ‘aphthous-type’ ulceration which occurs at intervals (often monthly), reflecting their neutropenic status. Patients who are functionally neutropenic, for example those with chronic granulomatous disease or benign familial neutropenia, are also susceptible to ‘aphthous-type’ ulceration. Other systemic conditions associated with this type of ulcer include MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome, FAPA (periodic fever, aphthous ulcers, pharyngitis and cervical adenitis) syndrome, and Sweets’ syndrome.

Management of RAS

The diagnosis of RAS is not usually difficult and may be deduced, in most cases, from the history and characteristic clinical appearance. If there is any doubt about the diagnosis then appropriate diagnostic tests should be arranged to exclude other causes of oral ulceration.

Patients with persistent and troublesome RAS should undergo screening to check for an underlying haematotic deficiency. This includes a full blood count and film, and measurement of inflammatory markers and haematinics (serum ferritin, serum B₁₂, serum and red cell folate). If there is any suspicion of coeliac disease, either due to the patient’s history or evidence of malabsorption on routine testing, then serological testing for anti-endomysial antibody and other appropriate investigations should be undertaken: is debatable whether all RAS patients should undergo screening for coeliac disease. Table 4 lists some of the therapeutic options available for the management of patients with RAS. The choice of therapy for RAS depends on the severity and frequency of ulceration, but the objectives of treatment are to relieve discomfort, reduce secondary infection, promote healing of existing ulceration and prevent new ulcers occurring.

Topical analgesic sprays or rinses such as benzylamine hydrochloride can be used to reduce discomfort; however, 2% lignocaine (lidocaine) gel, diluted as a rinse, is more effective for severe cases of RAS. Care must be taken if used in the posterior part of the mouth, as stronger analgesic preparations can affect the laryngeal reflexes: long-term use of topical lignocaine (lidocaine)

**Table 4. Therapeutic options for recurrent aphthous stomatitis (RAS)**

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical antiseptic</td>
<td>Chlorhexidine gluconate (mouthwash)</td>
</tr>
<tr>
<td>Topical analgesics</td>
<td>Benzydamine hydrochloride (mouthwash)</td>
</tr>
<tr>
<td></td>
<td>Lignocaine (lidocaine) rinse</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>Hydrocortisone hemisuccinate (pellets)</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide (in adhesive paste)</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate (mouthwash)</td>
</tr>
<tr>
<td></td>
<td>Beclometasone dipropionate (spray)</td>
</tr>
<tr>
<td></td>
<td>Budesonide (spray)</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone (with or without chlortetracycline) mouthwash</td>
</tr>
<tr>
<td>Topical antibiotic</td>
<td>Chlortetracycline mouthwash</td>
</tr>
<tr>
<td>Systemic immunomodulators</td>
<td>Prednisolone</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>Colchicine</td>
</tr>
<tr>
<td></td>
<td>Ciclosporin</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
</tr>
<tr>
<td>Other therapies that have been advocated</td>
<td>Low-energy laser</td>
</tr>
<tr>
<td></td>
<td>Levamisole</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
</tr>
<tr>
<td></td>
<td>Interferon-α</td>
</tr>
<tr>
<td></td>
<td>Pentoxifylline</td>
</tr>
<tr>
<td></td>
<td>Sucralfate</td>
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</tbody>
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is not advisable, as it may be absorbed. Several pastes and gels can be used to coat the surface of the ulcers and form a protective barrier against secondary infection and further mechanical irritation. Some difficulty may be experienced in applying some of these preparations, particularly to large ulcers and to those at the back of the mouth. Antiseptic mouthwashes containing chlorhexidine are widely used for the symptomatic treatment of RAS and are considered helpful by many patients, particularly if oral hygiene is difficult to maintain because of oral ulceration. Extrinsic staining of teeth associated with long-term use of chlorhexidine may be a problem. A more effective measure in the relief of symptoms caused by secondary infection is the application of topical antibiotics. A mouthwash containing tetracycline (dissolve soluble tetracycline capsule 250 mg in 5–10 mL water and rinse) or chlortetracycline is often highly effective in reducing the pain caused by severe ulceration, and as a result of the much less heavily colonized environment the ulcers often heal more rapidly than otherwise. The treatment of herpetic ulceration depends largely on this therapy, and response to the antibiotic mouthwash is often rapid and complete. There are obvious disadvantages, however, in the use of broad-spectrum antibiotics for this purpose, the risk of hypersensitivity reactions and the encouragement of growth of resistant organisms being the most important. Local secondary infection by opportunists such as Candida species may be a problem and limits long-term use.

Topical corticosteroids can be effective drugs in the treatment of RAS. Patient response is variable, and there are some individuals who gain little or no relief from their use. Corticosteroids used in this manner have two modes of action; their anti-inflammatory action modifies, in a minor way, the progress of the ulceration at all stages and to some extent reduces the discomfort experienced. The second effect of steroids, i.e. the specific blocking effect of the T lymphocyte – epithelial cell interaction, is much more important in the present context. Since the concentration of sensitized lymphocytes occurs before and during the early stages of oral ulceration, it follows that the drugs exert their maximum effect at this time. The drugs most commonly adopted for local oral application in RAS are hydrocortisone hemisuccinate (as pellets of 2.5 mg) and triamcinolone acetonide (in an adhesive paste containing 0.1% of the steroid). There is little risk of adrenal suppression provided that the recommended dose (four times daily) is adhered to. In severe MiRAS unresponsive to these preparations and in MjRAS it may be necessary to use a more potent steroid preparation such as a betamethasone sodium phosphate rinse (dissolve 0.5 mg in 5 mL of water and rinse for 2–3 min), steroid aerosol (e.g. beclometasone dipropionate, 100 µg/puff), or a high-potency topical corticosteroid, such as clobetasol 0.05% in orabase (1:1) or fluocinonide 0.05% in orabase (1:1). Prolonged use of potent topical corticosteroids carries a risk of systemic absorption and associated adverse effects; it may also predispose to oral candidosis.

In severe cases of RAS, particularly MjRAS, it may be necessary to use some form of systemic therapy (Table 4); however, all drugs have side-effects and risks which must be weighed against their benefits for RAS. Apart from prednisolone, a number of systemic drug therapies has been advocated for the treatment of MjRAS and in some cases Behçet’s disease. Thalidomide has been used successfully for severe RAS which has failed to respond to other treatment modalities; it has also been advocated for use in HIV-associated oral ulceration. Thalidomide is a TNFα inhibitor that has anti-inflammatory effects; however, its use is limited because of teratogenic and other adverse effects (e.g. irreversible polyneuropathy). The potential use of anti-TNF therapy by novel biological agents (e.g. infliximab) for recurrent aphthae in Behçet’s disease is discussed in the next section. Colchicine inhibits cell-mediated immune responses and has been used in doses of 1.5–1.8 mg/day successfully in two small, open studies involving 23 patients with RAS.

**BEHÇET’S DISEASE**

Behçet’s disease is a multisystem, chronic relapsing inflammatory disease of unknown cause, which is characterized by recurrent oral (aphthous) ulcers, genital ulcers, uveitis and skin lesions. There may be a variety of other manifestations including joint, central nervous system, vascular and intestinal lesions of variable severity.

In 1990 the International Study Group for Behçet’s disease proposed criteria for the diagnosis of the disease (Table 5). According to these criteria, RAS must be present as well as at least two of the following: recurrent genital ulceration, eye lesions, skin lesions and a positive pathergy test. Behçet’s disease has diverse clinical manifestations and lacks any pathognomonic...
Oral ulceration in Behçet’s disease

RAS is seen in all patients with Behçet’s disease; it commonly precedes other systemic features and can be of major, minor or herpetiform types. However, it is difficult to predict with any certainty those patients initially presenting with RAS who will subsequently proceed to develop multisystem involvement as part of Behçet’s disease. Two studies have addressed this problem: in one, a clinical comparison between 38 patients with Behçet’s disease and RAS-only controls showed an increased number of concurrent ulcers and involvement of the soft palate and oropharynx in those diagnosed with Behçet’s disease. No differences were detected with respect to duration, frequency, age of onset or family history. Scrutiny of clinical photographs taken of Behçet’s disease patients in this study suggested that both ‘herpetiform-type’ and ‘aphthous-type’ ulcers appeared atypical. Clinical observations in oral medicine clinics suggest that aphthous ulcers in patients with Behçet’s disease appear to be associated with increased tissue oedema and appear to have an intensely erythematous border. The aphthae in Behçet’s disease often occur in the soft palate and oropharynx and have been observed on the hard palate, which is an unusual site for RAS in patients without Behçet’s disease. Patches of mucosal erythema may be observed in patients with the disease, indicating possible instability of the oral mucosa prior to ulceration. Patients may paradoxically report no painful symptoms during active disease, despite extensive oral ulceration being clinically evident. A Korean study examined the prognosis of the clinical relevance

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Prevalence (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent oral ulceration</td>
<td>100</td>
<td>Minor aphthous. Major aphthous or herpetiform ulceration observed by a physician or reliably reported by patient. Recurrent at least three times in one 12-month period.</td>
</tr>
<tr>
<td>Plus two of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent genital ulceration</td>
<td>80</td>
<td>Recurrent genital aphthous ulceration or scarring, especially in male patients, observed by physician or reliably reported by patient.</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>60–70</td>
<td>Anterior uveitis. Posterior uveitis. Cells in vitreous on slit lamp examination. Or Retinal vasculitis observed by qualified physician (ophthalmologist)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>60–80</td>
<td>Erythema nodosum-like lesions observed by physician or reliably reported by patient. Pseudofolliculitis. Papulopustular lesions. Or Acneiform nodules consistent with Behçet’s disease observed by physician and in post-adolescent patients not receiving corticosteroids</td>
</tr>
<tr>
<td>Positive pathergy test</td>
<td>Variable</td>
<td>An erythematous papule, &gt; 2 mm, at the prick 48 h after the application of sterile needle, 20–22 gauge, which obliquely penetrated avascular skin to a depth of 5 mm; read by a physician at 48 h.</td>
</tr>
</tbody>
</table>
of recurrent oral ulceration in Behçet’s disease, and investigators found that approximately half the patients who were initially diagnosed as RAS-only developed other manifestations of Behçet’s disease at an average of 7.7 years after onset. Highly recurrent RAS appeared to be a warning signal for Behçet’s disease in this study.

Aetiopathogenesis of Behçet’s disease

The aetiology of Behçet’s disease is poorly understood, but interactions between environmental and genetic factors are likely to influence the susceptibility and development of the disease, as well as being implicated in its pathogenesis. Susceptibility to Behçet’s disease is associated with the HLA-B51 MHC class 1 allele, and it has been reported that individuals in the appropriate geographical setting (i.e. living in areas along the Silk Route) who express this allele have an eight- to ten-fold greater risk of developing the disease. The relative risk of the disease among carriers of HLA-B51 is much less in Western countries, indicating that other genetic factors may be important in these individuals. The HLA-51 allele also affects the severity of Behçet’s disease, since it is more commonly detected in patients with posterior uveitis or progressive central nervous system disease than those with milder disease. Investigation of the aetiology of Behçet’s disease has focused predominantly on herpes simplex virus immunopathology, autoimmunity to oral mucosa or cross-reactive microbial antigens, and streptococcal infection. Its immunopathogenesis is likely to involve a T-cell-mediated response, and it has been demonstrated that lymphocyte function is abnormal in patients with the disease. There has been renewed interest in the role of Streptococcus sanguis as a causative agent, and recent advances have resurrected the theory of infectious triggering of the immune cascade in Behçet’s disease and have been strengthened by work with heat-shock protein and the concept of a ‘molecular mimicry’ mechanism. It has been suggested that bacterial products such as heat-shock proteins may incite an inappropriate immunoinflammatory response. Recent studies have investigated the role of the γδ T-cell subset in the immunopathology of Behçet’s disease. These T cells participate in the immune response to infections and in autoimmune by recognizing bacteria-derived and autologous antigens. γδ T Cells have also been reported as producing several cytokines, with the cytokine profile dependent on the nature of antigen, enabling the γδ T cells to influence the nature of the immune response. Levels of circulating TNFα, interleukin-1β and interleukin-8 have been reported as elevated in Behçet’s disease, and it has been postulated that these cytokines may be involved in the activation of neutrophils. Bank et al. have recently demonstrated and substantiated data from a number of other studies indicating that γδ T cells have increased in Behçet’s disease relative to healthy and disease controls, and in addition the γδ T-cell population increases with the active disease. This group also examined the proliferation of a subset of γδ T cells in response to bacterial products obtained from patients with the active mucocutaneous disease, and concluded that an exaggerated proliferative response to products released by micro-organisms present in oral (aphthous) ulcers may play a role in the expansion of γδ T cells in Behçet’s disease. This raises the possibility that therapeutic control of the oral environment, or manipulation of γδ T-cell-derived cytokines by drugs such as anti-TNFα, provides effective strategies against aphthous ulceration and thereby controls systemic manifestations of the disease.

Treatment of Behçet’s disease

Patients with Behçet’s disease usually have repeated exacerbations and remission of their clinical symptoms, and in these individuals treatment is essentially symptomatic. The choice of therapy depends on whether the clinical manifestations of the disease are local or systemic. Multidisciplinary involvement in the management of Behçet’s disease is essential, and patients should ideally be treated in centres with extensive experience of treating the disease.

Local treatment with corticosteroids often controls oral and genital ulcers, and immunosuppressive therapy is reserved for severe cases of mucocutaneous involvement. The oral lesions may respond well to topical corticosteroid preparations (Table 4), but it is important to monitor the patients for signs of oral candidosis and treat this with appropriate antifungal agents. Patients with painful oral ulceration also benefit from analgesic mouthwashes, e.g. benzylamine hydrochloride or lignocaine (lidocaine). The choice of systemic drug treatment for Behçet’s disease is dictated by the patient’s clinical
manifestations, but conventional therapy relies on anti-inflammatory and immunomodulatory agents. There is a paucity of controlled clinical trails relating to drug therapy, and prescribing for Behçet’s disease is, to a large extent, empirical. Ocular lesions in Behçet’s disease must be vigorously treated to prevent blindness, and therapy aims to reduce both the severity and frequency of ocular attacks. Despite therapeutic interventions, approximately 25% of all patients with ocular manifestations of Behçet’s disease will become blind. Systemic corticosteroids continue to be used extensively, and may be administered as intravenous pulse therapy. Ciclosporin is highly effective for ocular lesions, particularly in cases that have been refractory to other therapies, but its nephrotoxicity restricts usage of the drug. Azathioprine is a disease-modifying drug for Behçet’s disease and helps reduce recurrences; it is now considered to be the first-line drug for this condition. Thalidomide, despite its prescribing limitations and neurotoxic side-effects, has proved effective for the management of mucocutaneous lesions in Behçet’s disease but it is not disease-modifying, and withdrawal of the drug can lead to severe rebound of symptoms. After teratogenicity, polyneuropathy is the second most serious complication of thalidomide, and has been reported in up to 50% of patients taking the drug. Thalidomide-related polyneuropathy appears to be dose-related and can be irreversible if not diagnosed early. Mycophenolate mofetil does not appear to be effective for Behçet’s disease. Colchicine is frequently used, and recent trials have demonstrated its beneficial effects on mucocutaneous symptoms, presumably by inhibiting neutrophil function. Cyclophosphamide, with or without corticosteroids, may be indicated for central nervous system lesions.

Recognition of the possible pathogenetic role of TNFα in Behçet’s disease has resulted in the use of anti-TNFα therapy. Recent trials with novel anti-TNFα agents (infliximab and etanercept) have indicated effective short-term remission. Infliximab (a chimeric anti-TNFα monoclonal antibody) has been used successfully for the treatment of recalcitrant orogenital ulceration in Behçet’s disease. These novel biological agents are, however, expensive compared with conventional treatment, and their long-term efficacy is yet to be proven in clinical trials. Overall, the goal of management in Behçet’s disease is to treat early to improve morbidity, to avoid recurrences and irreversible damage to organs, and to provide symptomatic relief for patients.

**ORAL ULCERATION AND INFLAMMATORY BOWEL DISEASE**

Oral involvement has for some time been recognized in patients suffering from both Crohn’s disease and, to a lesser extent, ulcerative colitis. Oral lesions may precede or accompany gastrointestinal disease and can be the only site of involvement.

*Oral Crohn’s disease and orofacial granulomatosis (OFG)*

Over the last decade there has been increasing attention paid to noninfectious granulomatous disorders of the orofacial region, which include oral Crohn’s disease and oral sarcoid, as well as clinical entities, known as the ‘Melkersson–Rosenthal syndrome’, and ‘Mieschener’s cheilitis granulomatosa’ (granulomatous cheilitis). The term ‘orofacial granulomatosis’ (OFG) was introduced to encompass these disorders and to describe a clinical syndrome presenting with swelling of the face, lips or oral tissues in association with histological evidence of noncaseating granulomatous inflammation within these tissues. Recent studies have investigated the association of OFG with ‘intolerance’ to specific foods, food additives, flavouring and the constituents of toothpastes. Cinnamon-aldehyde and sodium benzoates have been particularly implicated in this respect, and in some series there was a clinical response to specific elimination diets. It remains unknown whether sensitivity to food additives is the primary factor for some patients with OFG or a secondary aggravating factor to some underlying process.

The prevalence of OFG has not been determined but there does seem to be a geographical variation, for example the west of Scotland, UK, appears to have a higher number of cases. Oral medicine centres throughout the UK are reporting an increased number of cases of OFG, but this may be a result of increasing awareness and/or reporting of this condition. One study of 60 patients has reported that the median age of OFG at presentation was 20 years, but clinical experience indicates that many patients are older children or teenagers. The association of OFG with Crohn’s disease elsewhere in the gut has been the subject of debate, and this inter-relationship has been fully explored in a number of studies. The prevalence of symptomless intestinal disease of Crohn’s in patients with OFG has been reported as between 10% and 48% in various studies. The clinical features of OFG are shown in Table 6.
Oral ulceration and orofacial granulomatosis. Oral ulceration can be a particularly troublesome feature of OFG, and persistent linear ulcers (non-RAS) tend to occur at the base of hyperplastic tissue folds, particularly in the buccal and labial sulci, and can be painful, particularly when eating (Figure 3). A thickened buccal mucosa can also become traumatized along the occlusal ridge, resulting in ulceration; this can be quite deep and may become secondarily infected. Patients may also present with RAS, but this is not specific to OFG.

Management of orofacial granulomatosis. Patients with OFG must be appropriately investigated, not only to confirm the diagnosis but to identify any provoking factors and signs and symptoms suggestive of an underlying systemic condition, such as Crohn’s disease or sarcoidosis. Biopsy of an affected site (usually the labial or buccal mucosa and occasionally the gingivae) should be carried out by an experienced operator. Histologically, noncaseating and epithelioid granulomas, with or without multinucleated giant cells, are seen in about 90% of cases. Granulomas are not always present, and their absence does not exclude the clinical diagnosis of OFG. Granulomata may only be present in the underlying muscle, and it is therefore advisable to extend the biopsy deeper beyond the superficial tissue. Whether or not all patients with OFG should be patch-tested to identify possible allergies to foods, or food additives, is debatable. To date there is no totally convincing evidence of a clinical response to elimination diets, but there may be a therapeutic role for dietary manipulation in some patients. If OFG presents as a manifestation of underlying Crohn’s disease or sarcoidosis then this must be appropriately managed. Symptomatic therapy for associated oral ulceration and RAS includes the use of topical steroids (Table 4) together with antiseptic and analgesic mouthwashes. A large number of systemic drugs have been used for OFG. Short reducing courses of prednisolone may be helpful for severe oral ulceration, but long-term steroids are contra-indicated, particularly as many affected individuals are children or teenagers. Azathioprine has proved to be effective in some cases of OFG; other drugs advocated for this condition include clofazimine, hydroxychloroquine, danazol, cyclosporin, sulazosulfapyridine,
thalidomide, tacrolimus and antimicrobials, such as metronidazole and cotrimoxazole. Overall, results of drug therapy for OFG and its associated oral ulceration are disappointing and unpredictable.

Pyostomatitis and inflammatory bowel disease

Pyostomatitis vegetans is a rare oral disorder that is consistently associated with chronic inflammatory bowel disease and considered to be a highly specific marker for inflammatory bowel disease. The bowel symptoms often precede oral involvement by several months or years. Pyostomatitis vegetans has a distinct clinical appearance with miliary abscesses and pustular lesions affecting the oral mucosa and gingiva, which become thickened, erythematous and may exhibit vegetations or 'cobblestoning'. Pustular lesions often rupture, leading to erosions and ulceration, with fissuring, in a pattern described as 'snail-track' ulceration. The oral lesions predominantly affect the labial and buccal mucosa and the labial attached gingivae (Figure 5), although the hard and soft palate, vestibule and tonsillar region can also be affected. The histological features of pyostomatitis vegetans are often characteristic, although not pathognomonic, showing intraepithelial and subepithelial microabscesses containing large numbers of eosinophils. Topical steroid therapy has been successful for the treatment of pyostomatitis vegetans, but in many cases systemic treatment, with or without azathioprine or sulfamethoxypyridazine, is required. Management of the associated inflammatory bowel disease may result in improvement of the oral lesions.

Other types of oral ulceration have been described in patients with inflammatory bowel disease: pyostomatitis gangrenosum is rare but manifests as deep, foul-smelling ulceration (Figure 5) with an irregular outline and rolled margins.

Drug-induced oral ulceration

Oral ulceration is a well recognized but under-appreciated adverse drug reaction produced by or implicated in a number of prescribed and over-the-counter medications. The underlying mechanism in drug-induced oral ulceration is often unclear, but it can be due to local application of irritant preparations, such as aspirin and pancreatic supplements, or the effects of systemic drugs. Patients with learning disabilities or the elderly may have difficulty swallowing medication or may hold medication in the mouth, referred to as ‘pouching’, increasing the contact time of medication in localized areas.

A wide spectrum of systemic drugs has been implicated as causing oral ulceration, with clinical presentations ranging from superficial, nonspecific ulceration to aphthous-like lesions or widespread erosions of the mucosa. Aphthous-like and nonspecific oral ulceration may be caused by nicorandil (potassium channel activator), captopril and some nonsteroidal anti-inflammatory drugs, but the exact pathogenic mechanisms remain unclear. There are increasing reports of nicorandil-induced oral ulceration (Figure 6) and in one report of six cases from European centres, severe oral ulceration appeared within 1–10 months of starting nicorandil and mostly involved the tongue (Figure 6).
and buccal mucosa. Analysis of another six cases suggested that a threshold dosage of 30 mg/day of nicorandil might be necessary to induce the ‘aphthous-like’ lesions. Drugs used to suppress rheumatic diseases have been reported as causing oral ulceration, and include penicillamine, gold and methotrexate. A number of chemotherapeutic agents cause severe discomfort due to oral ulceration, and widespread mucosal involvement may necessitate opioid therapy or alteration to the therapeutic regimen. Opportunistic infections secondary to cytotoxic chemotherapy can also manifest as oral ulceration. Patients who develop lichenoid-drug eruptions affecting the mouth may report persistent or intermittent oral ulceration, and a wide range of systemic drugs have been implicated in this adverse reaction. A detailed list of current medications is critical to identify drug-induced oral ulceration, especially when the ulceration is resistant to therapy and of indeterminate cause. It is important to ascertain if the oral ulceration started, or became worse, at the commencement of drug therapy or after an increased dosage. Patients with drug-induced oral ulceration may show improvement with topical corticosteroid treatment, but definitive management is dependent on withdrawal of the putative drug; occasionally this is not an option. Older patients especially, but not exclusively, may be taking multiple medications, a number of which have been implicated as causing oral ulceration: this poses difficult and challenging management.

CONCLUSION

All patients with recurrent or persistent oral ulceration should be fully investigated to establish a definitive diagnosis and eliminate the possibility of an underlying systemic disorder or oral malignancy. The diagnosis of RAS is based on the patient’s history and clinical appearance of the ulcers. The majority of RAS cases respond to topical corticosteroid and/or topical antimicrobial therapy, but a few will require systemic immunomodulators. Patients with RAS may proceed to develop Behçet’s disease, which is diagnosed solely on the basis of clinical criteria. In spite of recent advances in systemic therapy for Behçet’s disease the functional prognosis of patients will remain poor until the underlying pathogenesis of the disease is elucidated. Clinical trials are currently being conducted to investigate the efficacy of anti-TNFα agents for Behçet’s disease. Patients with undiagnosed oral ulceration should be referred to an oral physician/surgeon for further investigations, including biopsy if appropriate.

ACKNOWLEDGEMENT

We acknowledge the expert advice of Professor Farida Fortune BDS, FDSRCS, MB BS, FRCP, Professor of Medicine in relation to Oral Health, Barts and the Royal London, Queen Mary’s School of Medicine and Dentistry, concerning Behçet’s disease.

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