Mini Review

Oral Aphthosis: Management Gaps and Recent Advances

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Abstract

Introduction: Though oral aphthosis is common, it has a significant impact on the quality of life in the patients. It is the most common oral ulcerative condition encountered in clinical practice. This study describes the characteristics and patterns of oral aphthosis seen at a tertiary dermatological centre in Singapore, with emphasis in evaluating the management gaps and in identifying underlying systemic diseases and nutritional deficiencies. Materials and Methods: This is a retrospective review of medical records over a 10-year period between June 2000 and June 2010. Two hundred and thirteen patients were identified using the search terms 'oral ulcers', 'aphthous ulcers', 'oral aphthosis', and 'Behcet's disease'. Patients with Behcet's disease without oral ulcers and other diagnoses such as pemphigus vulgaris, lichen planus and herpes simplex were excluded. The remaining patients were evaluated with regard to demographic characteristics, characteristics of oral ulcers, associated connective tissue disorders and nutritional deficiencies, diagnostic tests results, treatment response as well as follow-up duration. Results: One hundred and seventy-five patients were included in this study. One hundred and one patients had recurrent oral aphthosis, with 77 having simple aphthosis and 24 having complex aphthosis. Fourteen patients (8%) fulfilled the International Study Criteria (ISG) for Behcet's disease, of which, 85.71% had complex aphthosis. The therapeutic ladder for such patients ranged from topical steroids and colchicine through to oral corticosteroids and/or dapsone therapy. Conclusion: Recurrent oral aphthosis is a niche condition in which dermatologists are well-poised to manage. This study demonstrates that a more definitive management and therapeutic algorithm for oral aphthosis are needed for better management patients in the future. In particular, complex aphthosis needs to be monitored for progression onto Behcet's disease.

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Key words: Behcet's disease, Oral ulcers, Recurrent aphthosis

Introduction

Oral aphthous ulcers are a common condition which has significant impact on the patients' quality of life, causing much pain and interference with mastication and speech. It is the most common oral ulcerative condition encountered in clinical practice. Recurrent aphthous ulceration or recurrent aphthous stomatitis (RAS) is often an "orphan" disease. Patients are often seen by a variety of medical specialties including dermatologists, dental physicians and otolaryngologists, with no definite medical speciality assuming particular interest in the management of these patients. Dermatologists are often faced with referrals for patients suffering from oral aphthosis, many of whose care has been transferred from one speciality to another. It is therefore important that we are able to treat such patients with the specialised care that they require. Given the fact that some oral aphthosis may present concomitantly with skin lesions or as manifestation of a systemic disease may require various systemic therapies that require monitoring, dermatologists are in a good position to offer care for these patients.

Confusion exists on how oral aphthosis are classified. The morphological classification characterises oral ulcers based on their clinical features. Table 1a shows how oral aphthae can be classified morphologically.

RAS is defined as recurrent episodes of oral aphthous ulceration where the ulcers heal spontaneously with subsequent recurrence. The individual ulcers may occur in any form: minor, major or herpetiform aphthae. RAS can be further subcategorised as simple or complex aphthosis based on the disease severity aphthosis as reflected in Table 1b.

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Table 1. Classification of Oral Aphthae by Morphology and Severity

Table 1a. Classification of Oral Aphthae by Morphology[1]	Table 1b. Classification of RAS by Severity[2,3]
Minor aphthae (80%) (Fig. 1) - Single to few ulcers - Ulcers < 1 cm in diameter - Spontaneously healing in 7 to 10 days - No scarring	**Simple aphthosis** A) Diagnosis: - Recurrent attacks of aphthae of any morphology with distinct ulcer free periods B) Majority of RAS cases
Major aphthae (10%) (Fig. 2) - Single to few ulcers - Deeper ulcers > 1 cm in diameter - Prolonged healing longer than 2 weeks - Often scarring	**Complex aphthosis** A) Diagnosis: - Almost constant presence of ≥3 oral ulcers OR - Recurrent oro-genital aphthosis
Herpetiform aphthae (10%) - 10 to 100 ulcers - Very small (1 to 3 mm) ulcers, often grouped - Spontaneous healing in days to weeks - Sometimes scarring	B) Forms of complex aphthosis i. Primary, idiopathic complex aphthosis ii. Secondary complex aphthosis a. Human immuno-deficiency virus (HIV) b. Cyclic neutropenia c. Inflammatory bowel disease or celiac disease d. Haematinic, vitamin or mineral deficiencies e. Specific syndromes eg. Behcet's syndrome, *PFAPA syndrome or †MAGIC syndrome

*PFAPA syndrome: periodic fever, aphthous stomatitis, pharyngitis and adenopathy; †MAGIC syndrome: mouth and genital ulcers with inflamed cartilage

In the majority of cases, complex aphthosis is idiopathic (primary) but can also be secondary to a variety of underlying systemic diseases including nutritional deficiencies and inflammatory conditions.[2,4] It is important to exclude systemic diseases like Behcet's disease before making a diagnosis of idiopathic complex aphthosis.

In this study, we sought to characterise the spectrum of oral aphthosis that we encounter in a tertiary dermatological centre and their association with underlying disease states. We aim to identify the practice gaps in the management of such patients so that the care of these patients can be enhanced.

Materials and Methods

A retrospective medical records review was performed

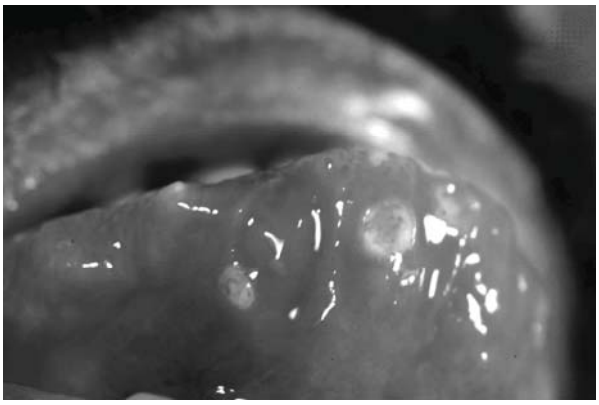

Fig. 1. Minor aphthae (several small ulcers <1 cm without scarring).

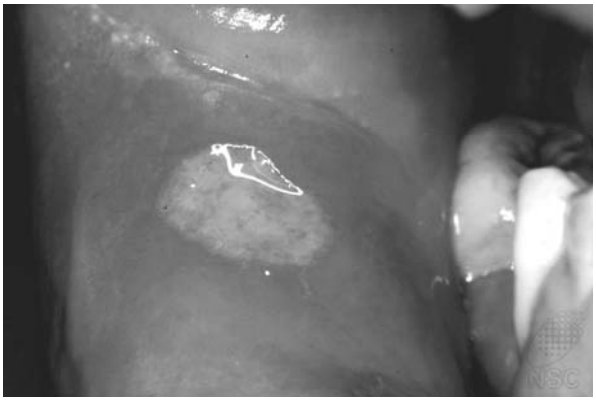

Fig. 2. Major aphthous ulcer (large ulcer >1 cm).

for patients seen over the 10-year period from June 2000 and June 2010 at the National Skin Centre, a tertiary dermatological centre in Singapore. A total of 213 patients were identified using the following search terms 'oral ulcers', 'aphthous ulcers', 'oral aphthosis', and 'Behcet's disease'.

The medical records of patients were retrospectively reviewed and patients with other diagnoses such as pemphigus vulgaris, lichen planus and herpes simplex were excluded from the analysis. Patients with a diagnosis of Behcet's disease without any oral ulcers were also excluded.

After excluding the above, a total of 175 patients were included in the study and were evaluated with regard to demographic characteristics, morphology and characteristics of oral aphthous ulcers, associated connective tissue disorders and nutritional deficiencies, diagnostic tests results, treatment administered and treatment response as well as follow-up duration.

Results

One hundred and seventy-five patients were included in this study and their characteristics were as follow: the age

range of patients presenting with oral ulcers was from 2 to 83 years, with a mean age of presentation of 39.1 years. The racial distribution of patients paralleled the ethnic distribution in Singapore, with the majority of patients being Chinese (76.57%, n = 134), and smaller proportion of Malays (8%, n = 14), Indians (6.86%, n = 12) and other ethnicities (8.57%, n = 15). There was slightly more males (52.57%, n = 92) compared to females (47.43%, n = 83).

The duration of symptoms before first consultation ranged from 2 days to 50 years and the ratio of patients presenting with chronic disease (e.g. >1 year) to those presenting less than one year of disease was 1:1.

A total of 101 patients had recurrent oral aphthosis of which 77 (76.2%) patients had simple aphthosis and 24 (23.7%) had complex aphthosis.

The most common sites of presentation of the oral ulcers were the labial mucosa and tongue, followed closely by the buccal mucosa. Less common sites included the gingivae, palate, and pharynx.

About a quarter of all patients (25.71%, n = 45) had associated symptoms of possible Behcet's disease such as genital ulcers; skin lesions such as erythema nodosum or acneiform papulopustules; or eye problems of uveitis or conjunctivitis. Out of 6 patients with a pathergy test performed, there was positive pathergy in 3 patients, all of whom were subsequently diagnosed with Behcet's disease.

After evaluation, a total of 14 patients (8%) fulfilled the International Study Criteria (ISG) for Behcet's disease (Table 2a). Of these 14 patients, the majority (85.71%, n = 12) had complex aphthosis, whilst only 2 patients (14.29%) had simple aphthosis. This is in contrast to the patients with RAS who do not fulfil criteria for Behcet's disease, where simple aphthosis remains the main diagnosis. However, by using O'Duffy criteria (Table 2b), an additional 19 patients would have been diagnosed with having incomplete Behcet's disease.

Amongst all patients, there were only 4 patients with associated connective tissue disease. Two patients had rheumatoid arthritis whilst 1 had seronegative spondyloarthropathy and 1 had systemic lupus erythematosus. Of these 4 patients, 2 had simple aphthosis whilst the remaining 2 had a single episode of aphthosis. None of them had complex aphthosis.

As this was a retrospective study, investigations done were physician dependent with a variety of investigations done to screen for infective, underlying connective tissue and autoimmune diseases, as well as for nutritional deficiencies. The results are tabulated below in Table 3.

Infective screening was largely negative except for a positive fungal smear in an immunocompromised patient with metastatic prostate cancer receiving chemotherapy.

Table 2. Criteria for Diagnosis of Behcet's Disease

Table 2a. International Study Group (ISG) Criteria for Diagnosis of Behcet's Disease[5]	**Table 2b. O'Duffy Criteria for Diagnosis of Behcet's Disease[6]**
(A) **Oral** • recurrent oral aphthae of any morphology at least 3 times within a 12 month period (B) **Genital** • recurrent genital aphthae OR • scarring (C) **Eye** • anterior or posterior uveitis OR • cells in vitreous on slit-lamp examination OR • retinal vasculitis (D) **Skin** • erythema-nodusum like lesions OR • papulopustular lesions consistent with Behcet's disease (E) **Pathergy** • positive pathergy test (neutrophilic vascular reaction of leukocytoclastic vasculitis) read by a physician at 24 or 28 hours, performed under sterile conditions with oblique insertion of a 20-guage or smaller needle	**Clinical criteria:** • Aphthous stomatitis • Aphthous genital ulceration • Uveitis • Cutaneous "pustular" vasculitis • Synovitis • Meningoencephalitis
Diagnosis of Behcet's disease: (A) in addition to ≥2 criteria of B, C, D or E being reliably reported by the patient or physician observed.	**Diagnosis of Behcet's disease:** ≥3 clinical criteria present, 1 being recurrent aphthous stomatitis. **Diagnosis of incomplete or forme fruste Behcet's disease:** ≥2 clinical criteria present, 1 being recurrent aphthous stomatitis. **Exclusion** Inflammatory bowel disease, systemic lupus erythematosus, Reiter's disease and herpetic infection.

Table 3. Investigation Results

Types of Investigation	Number of Patients	Results
Infective Screening		
Syphilis (RPR) and (TPPA)	14	All negative
HIV antibody	5	All negative
Tzanck smear	3	All negative
Herpes simplex virus (HSV) culture	27	All negative
Fungal smear	2	1 positive for yeast 1 negative
Connective Tissue Disease And Autoimmune Disease Screening		
Antinuclear antibody (ANA)	52	3 positive 49 negative
Anti-extractable nuclear antigen antibody (anti-ENA)	7	All negative
Anti-double stranded DNA antibody (anti-dsDNA)	10	All negative
HLA-B27	2	All negative
Nutritional Indices		
Haematinic indices (ferritin, iron, TIBC)	14	All normal
Folate	10	All normal
Vitamin B12	12	2 low 10 normal
Zinc	3	All normal
Magnesium	1	Normal
Inflammatory Markers		
Erythrocyte sedimentation rate (mm/hr)	47	
Range		2 to 114
Mean		31.8 mm/hr
Total white cell count ($x10^9$/L)		
Range		5.7 to 15.7
Mean		13 No cases of neutropenia

RPR: Rapid plasma reagin; TPPA: Treponema pallidum particle agglutination; HLA-B27: Human leukocyte antigen-B27; TIBC: Total iron binding capacity

Of the 3 patients with positive titres of ANA, both patients with low ANA titres of 1/100 and 1/160 were negative for more specific antibodies of anti-extractable nuclear antigen antibodies (anti-ENA) and anti-double stranded DNA antibodies (anti-dsDNA). The remaining patient with 1/400 ANA titre was lost to follow-up. None of these 3 patients with positive ANA titres had a history of connective tissue disease.

Nutritional indices were screened in a minority of patients with 2 patients found to have significantly low levels of vitamin B12 (147 pg/mL and 81 pg/mL respectively). None of the patients screened had iron, folate or mineral deficiency.

Inflammatory markers showed variable and non-specific results. Erythrocyte sedimentation rate (ESR) showed a wide range of results from 2 to 114 mm/hr, and a mean of 31.8 mm/hr. The mean total white cell count was $13x10^9$/L with a range from 5.7 to $15.7x10^9$/L. There were no cases of neutropenia detected. There was no correlation between ESR or total white cell count and response to treatment, relapse rate or with the diagnosis of Behcet's disease.

Biopsies were performed for 32 patients, with 16 patients having oral ulcer biopsies and 16 patients having skin biopsies. The results are tabulated in Table 4. After evaluation, only 5 patients with skin biopsies performed fulfilled ISG criteria for Behcet's disease; 2 patients had histology showing panniculitis and the rest either leukocytoclastic vasculitis or perivascular dermatitis.

Involvement of other relevant medical specialties was infrequent. Twenty percent (n = 35) of patients with recurrent oral ulcers were referred to other medical specialties of ophthalmology, rheumatology and dentistry, for assessment of associated symptoms. Two patients were co-managed with rheumatology for Behcet's disease. There were no abnormalities detected by the ophthalmology and dentistry subspecialities.

Table 4. Oral and Skin Biopsy Results

Site and Number of Biopsy	Histology Results	Number of Patients (%)
16 oral ulcers	Benign ulceration with inflammation or non specific changes	12 (75%)
	Actinic chelitis	1 (6.25%)
	Lichenoid dermatitis	1 (6.25%)
	Subcorneal pustule	1 (6.25%)
	External biopsy consistent with Behcet's disease (exact histology not available)	1 (6.25%)
16 skin lesions— 11 lower limb, 4 upper limb, 1 buttock	Septal panniculitis	7 (43.75%)
	- with concomitant leukocytoclastic vasculitis (LCV)	3
	- without vasculitis	4
	Perivascular dermatitis	3 (18.75%)
	Neutrophilic dermatitis	1 (6.25%)
	Granulomatous dermatitis due to ruptured cyst	1 (6.25%)
	Palisaded and neutrophilic granulomatous dermatitis	1 (6.25%)

Treatment prescribed was varied and physician dependent. A total of 156 patients received some treatment after consultation at the National Skin Centre. The majority (72.44%, n = 113) of patients were treated with topical steroids, either in isolation (27.56%, n = 43) or in combination with other topical or systemic treatment. Of those who did not receive topical steroids, colchicine was the preferred treatment, prescribed in 50% of patients (n = 78). Systemic steroids were used less frequently, being prescribed in 32 patients (20.51%).

With regard to the follow-up duration, the mean duration for all patients was short, ranging from 1 to 6 months. Of 98 patients with follow-up consultations, 56 (57.14%) patients experienced a relapsing course.

The therapeutic ladder for patients with a relapsing course ranged from topical steroids and colchicine through to oral corticosteroids and/or dapsone therapy. Colchicine was the preferred treatment for relapses and used in 44 patients (78.57%) with good response as monotherapy in 36 patients. A total of 8 patients required combination therapy of colchicines with either dapsone (n = 6), azathioprine (n = 1) or pentoxyphylline (n = 1) to achieve control of disease.

Discussion

Recurrent oral aphthosis which is very common and affects 0.5% to 25% of the population worldwide[7] with the majority of population based studies being carried out in Western populations. There has only been one large Asian study done in Malaysia with a point prevelance of 0.5%.[8] Although mostly benign and self limiting, it can cause significant impairment in the quality of life due to the pain and interference with eating and speech. RAS can be associated with a variety of clinical features, and systemic associations.

Through this retrospective review, we have identified some certain practice gaps in the management of patients with RAS which can be improved.

The pathogenesis of RAS remains poorly defined and likely involves a predominantly cell-mediated inflammation involving T-cells and TNF-α production. Several reports suggest a genetic predisposition with more than one third of patients having a first-degree relative with RAS 9 and an increased frequency of patients having human leukocyte antigen types A2, A11, B12, B51 and RD2.[9] Other predisposing factors for RAS include haematinic deficiencies 10, deficiencies of vitamin B12, folate and zinc, oral trauma, smoking, stress and hormonal changes related to the menstrual cycle. In particular, patients with RAS were found to have variable prevalence of haematinic deficiencies of 10 to 56%,[10,11] and folate or B12 deficiencies of 15% to 28%[12] as compared to 8% to 10% in the normal healthy population.

Haematinic and nutritional screening was deficient in our cohort of patients and as found in previous studies mentioned, the actual prevalence of vitamin B12 or other vitamin or haematinic deficiencies is like to be potentially higher.

Systemic diseases such as celiac disease, inflammatory bowel disease, human immunodeficiency disease (HIV) and neutropenia, also predispose to RAS.[13,14]

It is essential that all patients with RAS have a thorough systemic review and physical examination in order to exclude these secondary causes of aphthosis. Key points in the evaluation are highlighted in Table 5.

Table 5. Key Points for Physicians in the Evaluation of RAS

History:
1. Racial origin
2. Family history of RAS or secondary diseases
3. Thorough systemic review (genital ulcerations, gastrointestinal complaints, cutaneous, ocular or rheumatological complaints, relapsing fever, weight loss)
4. Risk factors for nutritional deficiencies (dietary history, menstrual or gastrointestinal blood loss, prior gastroinstestinal surgery or disease)
5. Risk factors for HIV or immunosuppression
6. History of aphthosis (frequency of relapses, duration of healing)
Physical examination:
1. Oral ulcer(s) (size, site, presence of scarring)
2. Genital ulcer(s) or scarring
3. Concomitant cutaneous, ocular or rheumatological signs suggestive of Behcet's disease General nutritional status, conjunctival or nailbed pallour, glossitis

The threshold for screening investigations should be low and performed in a more standardised manner. We recommend that RAS mandates a full blood count including differentials, haematinic, folate and vitamin B12 screening. If there are risk factors present, HIV testing should also be offered.

A major concern of physicians managing oral ulcers is whether these ulcers are a harbinger of Behcet's disease. This is especially so because oral ulceration is the most common manifestation of Behcet's disease and can occur in up to 99% to 100% of patients with the disease.[15] The incidence of Behcet's disease was originally a disease of countries bordering the Silk Road with a high prevalence in Japan, Korea, China, Iran and Turkey, and the highest prevalence being in the eastern part of the Silk Road in Japan and China (13.4 and 14 per 100,000 people respectively).[16] Currently, Behcet's disease can be found globally due to migration, however, racial origins still influence the

prevalence of disease and should be borne in mind when assessing patients.

The diagnosis of Behcet's disease can be difficult as there is no pathognomonic laboratory test to confirm the disease. In actual fact, the distinction between complex aphthosis and forme fruste form of Behcet's disease may well be arbitrary as some authors have proposed that aphthosis actually encompasses a spectrum of diseases ranging from simple recurrent aphthosis at one end, complex aphthosis in the middle and Behcet's disease at the other end.[2]

Various clinical diagnostic criteria for Behcet's disease exists, of which the International Study Group (ISG) criteria (Table 2a) is most widely used and has been validated by several groups as a diagnostic tool.[17] However, the various clinical signs may manifest dysynchronously or as an incomplete or forme fruste form. The ISG diagnostic criteria for Behcet's disease may be too restrictive and risks under diagnosis of forme fruste Behcet's disease. Other criteria like O'Duffy (Table 2b) which are less restrictive should be more widely used.

Dermatologists should be well-informed of these alternative criteria and be watchful for possible underlying Behcet's disease especially if the patient is of racial descent of populations with a higher prevalence of the disease. Furthermore, these patients often present first to dermatologists since skin and joint lesions are the second most common manifestation of the condition after recurrent oro-genital aphthosis.[18,19] It is vital that patients with RAS especially complex aphthosis be monitored for the development of any skin lesions typical of Behcet's disease such as erythema nodosum (Fig. 3). Patients with eye complaints or joint pains should be referred early to an ophthalmologist or rheumatologist respectively, to evaluate for extra-cutaneous manifestations of Behcet's disease.

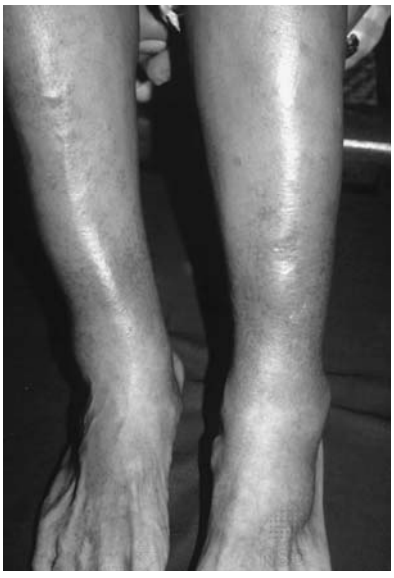

Fig. 3. Erythema nodosum (Erythematous tender nodules located symmetrically over both shins).

When evaluating complex RAS, dermatologists should also consider excluding other "pseudo-Behcet's" conditions such as mucocutaneous pemphigus (Fig. 4), oral lichen planus (Fig. 5) or oro-genital herpes simplex and perform the relevant investigations to exclude such potential mimickers.

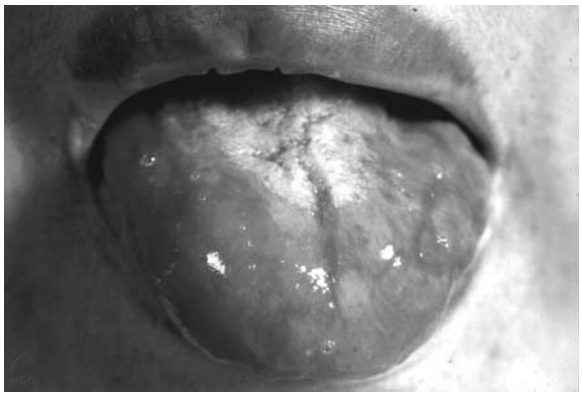

Fig. 4. Mucocutaneous pemphigus (Multiple shallow erosions over the tongue).

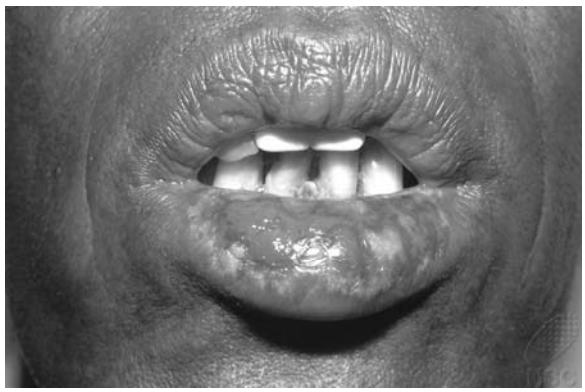

Fig. 5. Oral lichen planus (Erythematous erosions over the labial mucosa with violaceous rimming as well as Wickham's striae).

We propose that patients with complex RAS warrant a longer follow-up period and the following step-wise investigations.

In addition to the blood tests proposed for all patients with RAS, these patients should also have a culture for herpes simplex taken from both oral and genital ulcers. If the culture is negative, a biopsy of the oral ulcer can be considered to exclude other conditions such as malignancy and mucocutaneous pemphigus, especially if the ulcer is chronic and poorly healed. Skin biopsy of concomitant skin lesions may also be helpful as it can support the diagnosis of Behcet's disease with a confirmation of panniculitis. More importantly, it can help to exclude other diagnoses such

Table 6. Proposed Investigations for Patients with Complex RAS

• Full blood count with differential counts
• Haematinic indices, folate and vitamin B12 levels
• Consider HIV test if there are risk factors present
• Culture to exclude herpes simplex virus infection (from both oral and genital ulcers if present)
• Consider biopsy of the following if herpes simplex culture is negative:
i. Oral ulcer(s) if the ulcers are poorly healing or chronic
ii. Any concomitant skin lesions such as erythema nodosum or acneiform papulopustules

as Sweet's syndrome. However, as shown in this review, the histological changes may be non-specific and clinical correlation is essential to reach a diagnosis of Behcet's disease. This systematic evaluation of patients with complex RAS will facilitate early diagnosis of underlying diseases and is summarised in Table 6.

Treatment objectives are pain control, expedition of ulcer healing and reduction of frequency of recurrences. Treatment should be individualised depending on the patient's symptoms, severity and frequency of relapse, presence or absence of extra-oral lesions and underlying medical problems.

The usual therapeutic ladder of RAS starts with topical treatment with analgesia, corticosteroids and antimicrobial preparations.[1,14] Of these, topical corticosteroids have remained the mainstay of therapy for RAS, and have shown a reduction in time to resolution of oral ulcers although there is no reduction in the rate of recurrences.[20] Although lacking randomised trials for use in RAS, intralesional injections of corticosteroids have also been used as they have shown efficacy in the treatment of oral lichen planus and HIV-associated aphthosis.

Additional topical therapies include other immunomodulators with anti-inflammatory effects such as calcineurin inhibitors, retinoids and tetracycline. Topical calcineurin inhibitors in particular are being more widely used to treat RAS as a steroid sparing agent. Although there are no established studies on the actual efficacy of these therapies in RAS, its efficacy has been extrapolated from its usefulness in oral lichen planus and oral pemphigus.[21,22]

If despite topical therapy, the ulcers remain difficult to control, systemic treatment may be required. Oral prednisolone is most commonly used, and has been shown to reduce the number of ulcerations while on treatment. However, recurrences often occur on withdrawing or stopping prednisolone. Several steroid-sparing immunomodulating agents such as colchicine and dapsone have also been widely used. Colchicine has been used successfully in recalcitrant cases, with equal efficacy to prednisolone,[23] however its use may be limited by gastrointestinal side effects. Dapsone has also been shown to be efficacious for the treatment of complex aphthosis either as monotherapy or in combination with colchicine.[3]

There has also been increasing interest in the use of thalidomide for severe, recalcitrant RAS. It has been shown to be rapidly effective in inducing remission, efficacious in low dose for maintaining remission, and overall well tolerated by patients.[24]

Promising new therapeutic options for difficult to treat RAS include systemic montelukast which has shown comparable results to prednisolone with fewer side effects;[25] clofazamine,[26] sublingual vitamin B12[27] and fumaric acid esters.[28] There has also been much interest in the efficacy of natural products like bee propolis and raw egg white. However, more trials on these emerging therapeutics need to be done before efficacy can be established.

With regard to the optimal follow up duration of patients with RAS, this is still very much physician dependent with no established therapeutic guidelines. Although there is no way of predicting whether a patient with RAS will develop Behcet's disease, a Korean study[15] found that approximately half the patients who were initially diagnosed as RAS eventually developed other manifestations of Behcet's disease over an average of 7.7 years after onset of RAS, with highly recurrent RAS appearing to be a warning signal for subsequent development of Behcet's disease.[15] Hence, we propose that all patients with complex aphthosis mandate a longer follow-up period to monitor for potential progression onto Behcet's disease.

Conclusion

In conclusion, although this study is limited by its retrospective nature, it has identified certain practice gaps in the management of oral aphthosis patients. A more standardised assessment of oral aphthosis involving proper characterisation of the ulcers together with a structured management algorithm and follow-up duration may improve patient outcomes and treatment results. It has also reinforced the importance of dermatologists having a good grasp of the condition in order to provide a specialised therapeutic plan tailored for each patient.

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