Making sense of mouth ulceration: part seven

Crispian Scully[1]

The clinical appearance of an oral ulcer on its own is rarely diagnostic. In the light of multiple causes, some systematic way of dealing with ulceration is needed, such as my system of splitting causes into:

- Systemic
- Local
- Drugs.
- Malignancy
- Aphthae

This article discusses the last of the systemic causes – skin disorders.

Skin disorders

- Pemphigus
- Pemphigoid
- Dermatitis herpetiformis
- Linear IgA disease
- Epidermolysis bullosa
- Erythema multiforme.

Vesiculobullous diseases

Vesiculobullous diseases are potentially life changing; for example, pemphigus is life threatening. Any ulceration, especially multiple, lasting more than three weeks must therefore be regarded with suspicion.

This article covers the more important vesiculobullous diseases, which are characterised by the formation of blisters (vesicles/bullae) within (intraepithelial) or beneath (subepithelial) the epithelium.

Pemphigus

Pemphigus is the term for a group of rare autoimmune disorders; with antibodies directed mainly against epithelial intercellular 'cement' that helps keratinocytes adhere to each other (in desmosomes and termed desmoglein [DSG]).

Seen mainly in middle-aged and older people, and with a female predisposition, the common variant – pemphigus vulgaris (PV) – has a strong genetic background, and is prevalent in Ashkenazi Jews, Asians (India, Malays, Chinese, Japanese) and Mediterranean peoples.

HLA-DRB1*0402 or HLA-DQB1*0503 are found in more than 95% of PV patients. Pemphigus is usually idiopathic but sometimes implicated are:

- Pesticides (organophosphates)
- Malignancy
- Pharmaceuticals
- Hormones
- Infections/immunisations
- Gastronomy
- UV light
- Stress.

Triggers occasionally include:

- Drugs (thiols, phenols or non-thiol, non-phenols)
- Foods (black pepper, garlic, leek, onion, pepper, red chilli, red wine, tea)
- Radiation
- Surgery.

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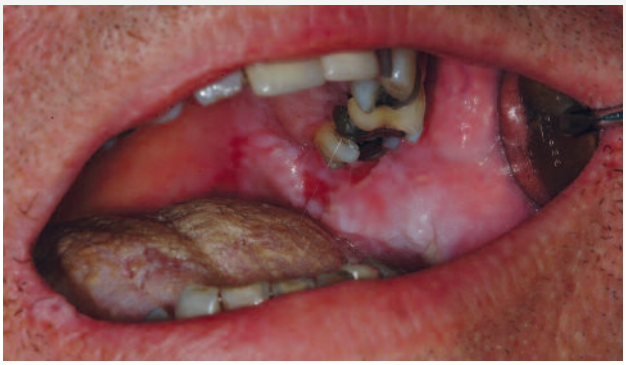

Figure 1: Pemphigus

Activation of HLA class II restricted, desmoglein-specific CD4 T effector lymphocytes drives autoreactive B-cell activity and autoantibody production and the ST18 gene regulates apoptosis and inflammation.

Pemphigus affects stratified squamous epithelia of skin and malpighian mucous membranes.

Pemphigus vulgaris manifests with skin blistering and mucosal lesions and, if left untreated, has a high mortality. Oral lesions are invariable and seen early. They include blisters that rupture to erosions as well as persistent ulcers.

Lesions are seen mainly where there is trauma and Nikolsky's sign is positive – pressure on the blister causes it to spread. Irregular red erosions seen early on have a whitish surround due to necrotic epithelium (Figure 1) but there is a fibrinous slough on older erosions.

People with PV have an increased incidence of other autoimmune disorders themselves (especially myasthenia gravis, Basedow disease, rheumatoid arthritis, systemic lupus erythematosus) and in their blood relatives (type 1 diabetes, autoimmune thyroid disease, less commonly PV).

Diagnosis is confirmed by histopathology, mainly. Biopsy is essential and shows acantholysis. Immunostaining by direct immunofluorescence (DIF) microscopy shows a net-like appearance of deposited IgG and C3. Indirect immunofluorescence (IIF) microscopy shows pemphigus antibodies.

Depending upon involvement of eyes, larynx, skin, and genitalia, appropriate referral to physicians is essential.
Management is by using:

- Systemic immunosuppression
- Corticosteroids
- Alternates
  - Azathioprine
  - Dapsone
  - Intravenous immunoglobulins
  - Rituximab
- Autoantibody removal
  - Immunoadsorption
  - Plasmapheresis.

Oral lesions may be helped also by use of:

- Topical corticosteroids (fluocinolone acetonide or clobetasol)
- Intralesional steroids
- Topical tacrolimus.

Pemphigus variants

Paraneoplastic pemphigus is the most important other pemphigus variant, seen usually in the sixth decade.

Associated with anti-plakin (plectin, desmoplakin I, desmoplakin II, bullous pemphigoid antigen I, envoplakin, and periplakin) antibodies plus DSG-1 and DSG-3, it often causes oral ulceration on the lips and tongue, along with palmar/plantar bullous lesions.

The prognosis is poor with a mortality of approximately 90% because of the presence of lymphoproliferative disorders such as:

- Non-Hodgkin's lymphoma
- Castleman's disease
- Chronic lymphoid leukaemia
- Adenocarcinomas, Kaposi and other sarcomas
- Bronchiolitis obliterans.

Immune-mediated subepithelial bullous diseases

Immune-mediated subepithelial bullous diseases (IMSEBD) is a group of blistering diseases, less dangerous than PV, in which autoantibodies to various components of the hemidesmosomes that link keratinocytes to the epithelial basement membrane zone (EBMZ) cause subepithelial vesiculation and blistering of squamous epithelia.

Often in the past these IMSEBD have all been called pemphigoid but it is now recognised that other disorders can cause a similar clinical picture. Even pemphigoid has several variants.

Pemphigoid

Pemphigoid is an autoimmune disorder that affects skin and/or mucosae associated with HLA-DQB1*0301. It may affect one or several sites, and oral lesions predominate in mucous membrane pemphigoid (MMP) subtypes.

MMP is uncommon, with a female predisposition and seen in the fifth to sixth decade of life. Rarely, it is drug-induced. MMP affects mainly oral, ocular, nasal, nasopharyngeal, anogenital, laryngeal, and oesophageal mucosae. Sub-sets of patients with MMP have autoantibodies targeting antigens of the EBMZ, such as epiligrin and integrins. These may differ, depending on sites mainly involved:

- Oral MMP: α-6 integrin

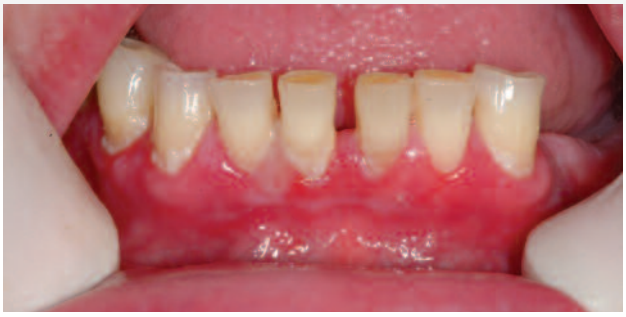

Figure 2: Pemphigoid causing desquamative gingivitis

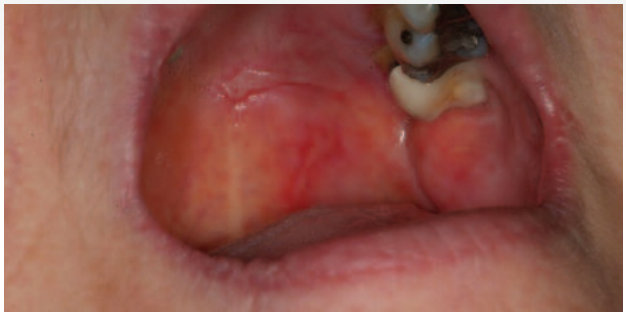

Figure 3: Erosions in pemphigoid

- Ocular MMP: β-4 integrin.

MMP with oral lesions affects mainly the gingiva, soft and hard palate as well as buccal mucosae.

MMP is a common cause of:

- Desquamative gingivitis – erythematous, ulcerated, tender gingiva, patchy distribution (Figure 2)
- Erosions, arising from vesicles that burst within several days, causing persistent ulcers or erosions covered with yellowish slough and surrounding erythema (Figure 3). Blood-filled blisters are sometimes seen.

Diagnosis is from a positive Nikolsky sign (ie, pressure on a blister causes it to spread). However, this is non-specific, therefore the following are also necessary:

- Biopsy – oral (not ocular) mucosal biopsy
- Immunostaining; shows linearly deposited IgG, IgA, or C3 at EBMZ.

Management may be with:

- Topical corticosteroids (fluocinolone acetonide or clobetasol)
- Intralesional steroids
- Topical tacrolimus
- Systemic immunosuppressants in advanced cases (corticosteroid or alternates – azathioprine, dapsone, high dose IV Ig, rituximab).

Appropriate referral to physicians (depending upon involvement of eyes, larynx, skin, and genitalia), and need for systemic immunosuppression (severe or widespread disease) may be necessary.

Patients with apparently exclusive oral involvement may later develop ocular lesions. There is a higher relative cancer risk in MMP patients with autoantibodies to epiligrin/laminin-332 but a lower than expected relative cancer risk in patients with:

- Exclusive oral mucosal disease (autoantibodies to α-6 integrin)
- Exclusive ocular mucosal disease (autoantibodies to β-4 integrin).

Dermatitis herpetiformis

Dermatitis herpetiformis is an IMSEBD in which autoantibodies against epithelial transglutaminase cause an itchy rash on extensor surfaces, along with gluten sensitive enteropathy and oral blisters or desquamative gingivitis. Lesional biopsy on direct immunofluorescence shows granular deposits of IgA at basement membrane zone (BMZ).

Linear IgA disease

Linear IgA disease (LAD) or chronic bullous disease of childhood is an IMSEBD similar to dermatitis herpetiformis but antibodies are against ladinin in the EBMZ, with linear IgA deposition.

References

Gandolfo S, Scully C, Carrozzo M (2006) Oral medicine. Elsevier Churchill Livingstone (Edinburgh and London). ISBN 13: 29780443100376

Scully C, Almeida ODP, Bagan J, Diz PD, Mosqueda A (2010) Oral medicine and pathology at a glance. Wiley-Blackwell (Oxford) ISBN 978-1-4051-9985-8

Scully C, Flint S, Bagan JV, Porter SR, Moos K (2010) Oral and maxillofacial diseases. Informa Healthcare (London and New York). ISBN-13: 9780415414944

Scully C, Bagan JV, Carrozzo M, Flaitz C, Gandolfo S (2012) Pocketbook of oral disease. Elsevier, London. ISBN 978-0-702-04649-0

Scully C (2013) Oral and maxillofacial medicine. 3rd edition. Churchill Livingstone (Edinburgh). ISBN 9780702049484

Scully C (2012) Aide memoires in oral diagnosis: mnemonics and acronyms (the Scully system). Journal of Investigative and Clinical Dentistry 3(4): 262-3

Scully C (2013) RULE for cancer diagnosis. British Dental Journal 215: 265-6

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