

A Review of Common Mucocutaneous Disorders Affecting the Mouth and Lips

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Abstract

Most oral involvement in the mucocutaneous diseases is related mainly to disorders with a prominent immunological component, especially lichen planus and pemphigoid. However, less common conditions such as pemphigus, dermatitis herpetiformis, linear IgA disease, erythema multiforme, chronic ulcerative stomatitis and other conditions may need to be excluded.

Diagnosis is initially clinical, based on a full history, general, and oral examination but precise diagnosis can be difficult without further data and therefore biopsy and immunological studies are invariably required to confirm the specific diagnosis.

Apart from improving oral hygiene, immunosuppressive therapy is typically required to control many of these conditions.

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Introduction

Most of the mucocutaneous diseases are confined to the stratified squamous epithelia and thus may involve oral, genital and other mucosae and skin. Most of these conditions are acquired and have an immunological basis but there is often a hereditary predisposition.* The precipitating factors are often unclear but drugs, possibly viruses and other environmental factors are presumably important though often as yet not identified.

An elementary knowledge of the biology of the oral epithelium is crucial to the understanding of the pathogenesis of these disorders. The oral epithelium is a complex structure consisting mainly of keratinocytes adherent to adjacent cells and, via an epithelial basement membrane, to the underlying lamina propria. Each morphologically identifiable component of the attachment apparatus itself contains several proteins with important functions. Cell-cell contact is via adherens (desmosomes and adhesion plaques), occludens (tight junctions), and nexus junctions (gap junctions). Cell-basement membrane contact is largely via hemidesmosomes which contact the superficial part of the basement membrane (the lamina lucida) (Fig. 1).^{2,3}

Damage to any of these epithelial proteins may result in loss of attachment, either defective cell-cell adhesion or cell-basement membrane adhesion. Whichever, the

result can be vesiculation leading eventually to erosions or ulcers. This is the underlying pathology of the vesiculobullous disorders such as pemphigus and pemphigoid.

Several of the vesiculobullous conditions are of autoimmune aetiology and may affect other stratified squamous epithelia and may have systemic manifestations.^{4,5} Clinically they can be fairly distinct but at times can be difficult to differentiate without further investigation⁶.

The management of these conditions can only be carried out appropriately if there is an accurate diagnosis.

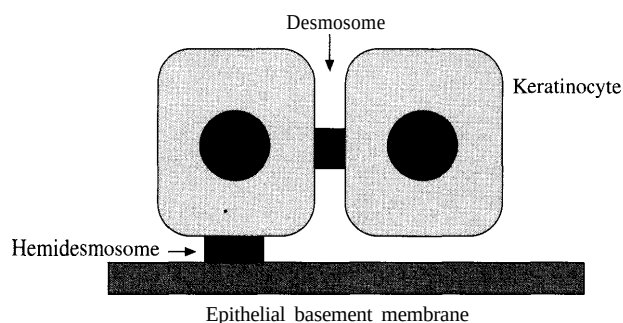


Fig. 1. Epithelial structure.

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This is based on the history, examination, and biopsy with immunological studies.

This paper discusses the main mucocutaneous disorders of pemphigus, pemphigoid, lichen planus and erythema multiforme. There are also a host of rare conditions that may involve these tissues; details are found elsewhere.⁷

Pemphigus

Aetiopathogenesis

Pemphigus is found mainly in middle-aged and elderly patients. There is a fairly strong genetic background to pemphigus; certain ethnic groups, such as Ashkenazian Jews and those of Mediterranean origin are especially liable to pemphigus.⁸ Pemphigus is an autoimmune disorder in which there is damage to desmosomes by antibodies directed against epithelial cell adhesion molecules,⁹ particularly desmoglein-3. The antibody-antigen reaction results in immune deposits intra-epithelially, especially IgG and C3, and loss of cell-cell contact (acantholysis), leading to intra-epithelial vesiculation. The appearance of antibodies against desmoglein-1 as well, heralds involvement of skin and other mucosae¹⁰ (Table I).

TABLE I: EPITHELIAL ANTIGENS IMPLICATED IN AUTOIMMUNE VESICULOBULLOUS DISORDERS (MODIFIED FROM NOUSARI AND ANHALT¹¹)

Disease	Antigens
Pemphigus vulgaris localised to mucosae	desmoglein 3
Pemphigus vulgaris also involving skin/other mucosae	desmoglein 3 desmoglein 1
Bullous pemphigoid	BP1 BP2
Mucous membrane pemphigoid	BP2 Laminin 5* 200 kDa 168 kDa

* Also known as epiligrin/nicein/kalinin/BM600.

Clinical Features

Pemphigus vulgaris (PV) is the most severe variant, and typically runs a chronic course, causing blisters, erosions and ulcers on the mucosae and skin. There can be a positive Nikolsky sign. Before the introduction of corticosteroids, it typically was fatal.¹²

Oral lesions are common,¹³⁻¹⁵ and may be the sole initial manifestations of pemphigus vulgaris. Initially vesiculobullous, the lesions readily rupture, new bullae developing as the older ones rupture and ulcerate.¹⁶ Irregular chronic erosions remain. In the absence of systemic treatment, such lesions are almost invariably

followed by involvement of the skin or occasionally other epithelia such as the oesophagus.¹⁷

Management

Biopsy of perilesional tissue, with histological and immunostaining examination, are essential to the diagnosis. Current treatment, largely based on systemic immunosuppression, has significantly reduced the mortality. Hence, unless there are only localised oral lesions, when topical corticosteroids may suffice for a time, systemic corticosteroids (e.g. prednisolone) are usually essential.^{14,15,18,19}

Pemphigoid

Aetiopathogenesis

Pemphigoid is the term given to a group of autoimmune sub-epithelial vesiculobullous disorders of late middle age. However, a number of other sub-epithelial vesiculobullous disorders may produce clinical pictures similar to the several pemphigoid variants.²⁰ The main variants are mucous membrane pemphigoid (MMP), in which mucosal lesions predominate but skin lesions are rare, and bullous pemphigoid (BP), which affects mainly the skin. Mucous membrane pemphigoid is sometimes termed cicatricial pemphigoid (CI') since the variant that affects the eyes may cause serious scarring as symblepharon or ankylo-blepharon. However, oral pemphigoid rarely scars.

Mucous membrane pemphigoid is of unknown aetiology but occasionally triggered by drugs.²¹ It is characterised histologically by junctional separation at the basement membrane zone, giving rise to a sub-basilar split and usually there is deposition of IgG and C3 at the basement membrane zone.²²⁻²⁶

As emphasised above, a range of variants exist, with antibodies directed against various hemi-desmosomal components or components of the lamina lucida^{26,27} (Table I), the oral variant being associated particularly with anti-epiligrin.^{28,29} Patients with mucous membrane pemphigoid rarely have circulating autoantibodies to basement membrane zone components detectable by standard methods.

Clinical Features

Commonly, patients with oral pemphigoid have desquamative gingivitis.³⁰ Vesicles and chronic erosions may also occur elsewhere, and there can be a positive Nikolsky sign.

Management

Biopsy of perilesional tissue, with histological and immunostaining examination, are essential to the diagnosis. The management of oral pemphigoid should include oral hygiene improvement as secondary infection

may inhibit healing. Topical corticosteroids are the usual treatment.^{20,30,31} If there is extensive oral or systemic involvement, patients may require systemic corticosteroids, azathioprine, cyclosporin or other adjuncts.

Lichen Planus

Aetiopathogenesis

Lichen planus (LP) is a relatively common condition, affecting mainly adult females. It is the most common dermatological disorder affecting the mouth and the underlying cause of much desquamative gingivitis.^{30,32} The precise aetiology and immunopathogenesis of oral LP are unclear.³⁰ There is no definitive immunogenetic basis and current evidence suggests that there is a local cell-mediated immunological response characterised by a profound CD8+T cell infiltrate of the lamina propria, and an increased population of activated dendritic cells within the epithelium.³⁰

Clinical Features

LP presents with a spectrum of clinical manifestations but, almost invariably, lesions are seen bilaterally. Clinically oral LP lesions are observed mainly on the buccal mucosa and lateral borders of the tongue, but the gingiva may also be affected. Six main clinical types of oral LP have been reported: reticular, papular, plaque-like, atrophic, ulcerative and bullous.^{30,33,34} White lesions are usually asymptomatic but mild oral discomfort or a burning sensation are the most common complaints in symptomatic cases. The atrophic and ulcerative forms which account for about 10% to 15% of all oral LP lesions are usually painful.

Management

The diagnosis of LP relies upon biopsy and histopathological examination of lesional tissue, occasionally aided by direct immunostaining, more to exclude other conditions than to specifically diagnose LP. Exclusion of agents that can produce lichenoid reactions, especially non-steroidal anti-inflammatory agents and dental materials, is important and possible associated disorders such as diabetes mellitus, HIV or hepatic disease may occasionally need to be excluded.

Improvement in oral hygiene may result in some subjective benefit³⁵ and it is worth considering replacement of amalgam with another material. Topical corticosteroids (e.g. hydrocortisone hemisuccinate or triamcinolone acetate) are the mainstay of therapy, though lesions are often recalcitrant. Thus potent topical corticosteroids such as fluocinonide may be required and antifungals may help.³⁶ If there is extensive oral or systemic involvement, patients may require systemic corticosteroids, azathioprine, cyclosporin or other adjuncts. There is a small malignant potential.

Erythema Multiforme

Aetiopathogenesis

Erythema multiforme (EM) is a vesiculobullous disorder that most frequently affects young adult males. It may be recurrent and appears to be an immunological reaction triggered by drugs such as sulphonamides, barbiturates or hydantoin, or by infective agents such as herpes simplex virus, or mycoplasma.

It has recently been suggested that EM with acral or facial raised lesions is caused by herpes simplex, and distinct from that presenting with widespread flattish lesions on the torso, which is usually drug-related and falling into the category of Stevens-Johnson syndrome.^{37,38} The degree of mucosal involvement is used to distinguish major and minor forms of erythema multiforme.³⁹ Erythema multiforme major almost invariably involves the oral mucosa, though oral lesions are also seen in some erythema multiforme minor.^{40,41}

Clinical Features

Oral lesions of erythema multiforme may precede lesions on other stratified squamous epithelia, or may arise in isolation. The clinical presentation is typically with swollen lips, and labial erosions with bloodstained yellowish white pseudomembranes (serosanguinous exudates). There are also widespread intraoral blisters and erosions particularly anteriorly.^{42,43}

Management

Biopsy of perilesional tissue, with histological and immunostaining examination are essential if a specific diagnosis is required. The condition may be self-resolving but healing is slow-up to 3 weeks in minor forms and as long as 6 weeks in major erythema multiforme.⁴⁴ Treatment is thus indicated but controversial. For those patients in whom the episodes are related to herpes simplex virus, there is substantial evidence that prophylactic aciclovir may help abort the attacks.⁴⁵ Corticosteroids are often used to control other erythema multiforme though opinion is divided as to their efficacy.⁴⁶ If there is extensive oral or systemic involvement however, there is often little alternative but to use systemic corticosteroids, azathioprine, cyclosporin or other adjuncts.

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