



## Review

## Oral mucosal manifestations of autoimmune skin diseases

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## ABSTRACT

A group of autoimmune diseases is characterised by autoantibodies against epithelial adhesion structures and/or tissue-tropic lymphocytes driving inflammatory processes resulting in specific pathology at the mucosal surfaces and the skin. The most frequent site of mucosal involvement in autoimmune diseases is the oral cavity. Broadly, these diseases include conditions affecting the cell-cell adhesion causing intra-epithelial blistering and those where autoantibodies or infiltration lymphocytes cause a loss of cell-matrix adhesion or interface inflammation. Clinically, patients present with blistering, erosions and ulcers that may affect the skin as well as further mucosal surfaces of the eyes, nose and genitalia. While the autoimmune disease may be suspected based on clinical manifestations, demonstration of tissue-bound and circulating autoantibodies, or lymphocytic infiltrates, by various methods including histological examination, direct and indirect immunofluorescence microscopy, immunoblotting and quantitative immunoassay is a prerequisite for definitive diagnosis. Given the frequency of oral involvement and the fact that oral mucosa is the initially affected site in many cases, the informed practitioner should be well acquainted with diagnostic and therapeutic aspects of autoimmune dermatosis with oral involvement. This paper reviews the pathogenesis and clinical presentation of these conditions in the oral cavity with a specific emphasis on their differential diagnosis and current management approaches.

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*Abbreviations:* BP, bullous pemphigoid; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; ELISA, enzyme-linked immunosorbent assay; IF, immunofluorescence; LAD, linear IgA disease; MMP, mucous membrane pemphigoid; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris.

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**1. Introduction**

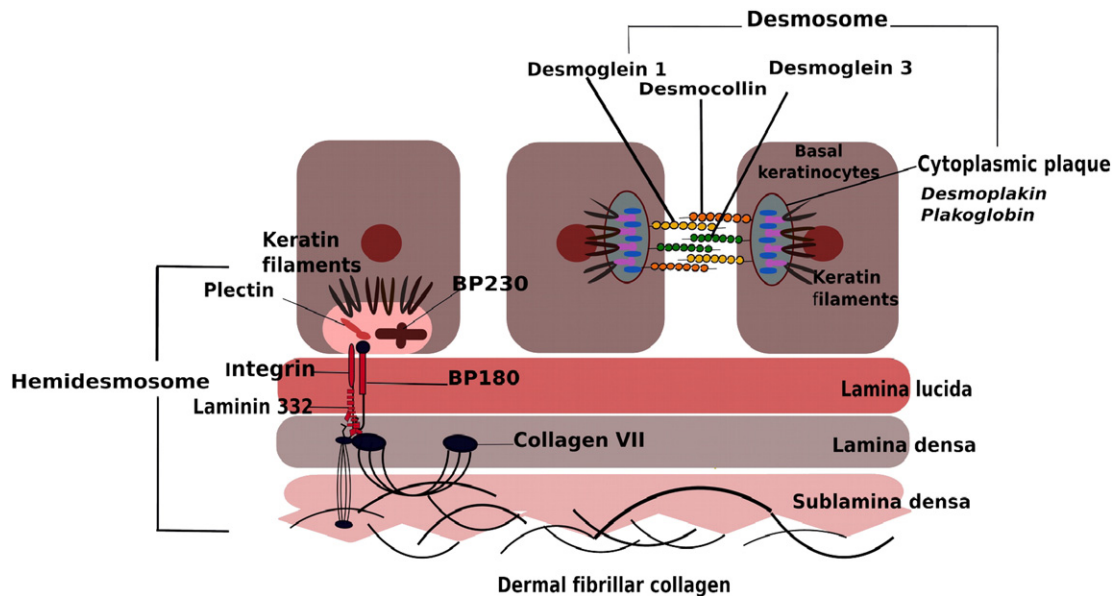
Oral mucosa and skin are composed of highly specialized stratified epithelium that functions as a first-line barrier against physical and chemical damage. The integrity of this epithelial barrier is essentially dependent on structures maintaining cell-cell and cell-matrix adhesion [1]. Autoimmune bullous diseases are associated with autoantibodies directed against structures that mediate cell-cell and cell-matrix adhesion in skin and mucous membranes [2]. In pemphigus diseases tissue injury is mediated by autoantibodies against the cell-cell junction causing intra-epithelial blistering, whereas in subepidermal autoimmune diseases autoantibodies are directed against the epithelial – connective tissue junction at the basement membrane zone (BMZ) [3]. Primary or extensive oral involvement is the hallmark of further inflammatory autoimmune conditions, including lichen planus (LP), erythema multiforme (EM), lupus erythematosus (LE) and chronic ulcerative stomatitis (CUS).

Skin and oral mucosa are stratified epithelia, in which the cell-cell adhesion is mainly mediated by desmosomes and adherens junctions, whereas the adhesion of basal epithelial cells on the underlying basement membrane essentially depends on hemidesmosomes and focal contacts (Fig. 1) [4]. Desmosomes are anchoring complexes that link epithelial cells to each other and attach the keratin filaments to the cell surface. Desmosomes consist of calcium-dependent adhesion molecules called cadherins, including desmogleins and desmocollins, which are transmembrane proteins that extend across the plasma

membrane and mediate cell-cell adhesion by homo- or heterophilic interactions between their extracellular protein domains. An additional group of intracellular proteins resides on the cytoplasmic face of desmosomes and constitutes the desmosomal plaque. Desmosomal plaque is associated with different types of proteins including plakoglobin, the desmoplakins, the plakophilins, envoplakin, and periplakin. It provides adhesion by linking the desmosomal transmembrane cadherin proteins to the cytoplasmic keratin filaments [1,5].

Hemidesmosomes are specialized junctional complexes on the ventral surface of the basal keratinocytes that maintain the epithelial cell attachment to the underlying basement membrane. In the oral cavity they can also be found in the junctional epithelium in contact to the tooth surface [6]. The basement membrane zone comprises the basal cell plasma membrane, the lamina lucida, the lamina densa and the sublamina densa. Anchoring filaments traverse the lamina lucida perpendicularly from the basal cell membrane to the underlying lamina densa [3]. At molecular levels, the basement membrane zone contains a mixture of structural components and antigens including collagen VII, which is the major structural component of anchoring fibrils, and collagen IV, which is a major ubiquitous component of vertebrate basement membranes. Laminins, which exist in various molecular forms as abundant non-collagenous glycoproteins of basement membranes, are heterotrimers consisting of alpha, beta and gamma chains [3,6].

Hemidesmosomes, together with the anchoring filaments, form the hemidesmosomes anchoring filament complex, which plays an important role in cell-basement membrane adhesion. The molecular



**Fig. 1.** Schematic representation of major autoantigens found in the skin and mucous membranes. Autoantigens are molecules that maintain cell-cell and cell-matrix adhesion. Desmosomes consist of cadherins, including desmogleins and desmocollins, which are transmembrane proteins that extend across the plasma membrane and confer adhesion by calcium-dependent interactions between their extracellular protein domains. On the cytoplasmic sides of desmosomes, resides the desmosomal plaque, through which the carboxy-terminal regions of cadherins are rooted and composed of different types of proteins such as plakoglobin and desmoplakin, which provide adhesion by linking the desmosomal transmembrane cadherin proteins to the cytoplasmic keratin filaments. Hemidesmosomes have an important role in cell-basement membrane adhesion and are organized in three classes of proteins. The first class is the cytoplasmic plaque proteins, which connect the intermediate filament cytoskeleton to the plasma membrane. These include bullous pemphigoid antigens BP230 (BPAG 1) and plectin. The second class includes  $\alpha 6 \beta 4$  integrin and BP180 (also termed BPAG 2 or type XVII collagen), which are transmembrane proteins involved in the assembly of hemidesmosomes, connecting the cell interior to the extracellular matrix and serving as cell receptors. The final class of proteins consists of basement membrane associated proteins of the extracellular matrix, which include different laminin isoforms. Laminin (Ln) 332 is a major component of the lamina densa. Laminin  $\gamma 1$  chain, present in the vessel walls and also in the structure of laminin 511, may also function as autoantigen. Laminins interact with different subsets of integrins such as  $\alpha 6 \beta 1$ ,  $\alpha 3 \beta 1$  or  $\alpha 6 \beta 4$  and regulate cellular adhesion and function. Collagen VII is the main constituent of the anchoring fibrils, which connect lamina densa to the collagen fibers of the upper dermis.

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