# Autoimmune Disease Manifestations in the Oral Cavity

Kelly R. Magliocca, DDS, MPH[a,*], Sarah G. Fitzpatrick, DDS[b]

**KEYWORDS**

• Pemphigus • Pemphigoid • Pyostomatitis vegetans • Geographic tongue • Lichen planus

**Key points**

- Autoimmune diseases affecting the oral cavity may demonstrate clinical, histologic, and in some cases similar immunopathologic patterns.
- Infectious, reactive, and neoplastic entities may arise in the microscopic differential diagnosis of oral autoimmune disease.
- Identifying tissue reaction patterns, such as lichenoid, psoriasiform, spongiotic, and vesiculobullous, may form a component of the diagnostic algorithm for oral mucosal disease.

## ABSTRACT

Immune-related disorders of the oral cavity may occur as primary disease process, secondary to systemic disease or neoplasm, or as a reaction to medications and other agents. The entities represented within this group may vary significantly by severity, clinical presentation, microscopic presentation, and special testing results. The selected immune-related conditions of the oral cavity in this article are categorized and presented by their prototypical tissue reaction patterns: vesiculobullous, including acantholytic and subepithelial separation; psoriasiform; spongiotic; and lichenoid reaction patterns.

## OVERVIEW: IMMUNOPATHOLOGIC TESTING

Ancillary testing methods, such as special stains, immunohistochemical (IHC) testing, and immunopathologic and serologic testing, may be helpful in distinguishing between similar-appearing lesions. A brief overview of immunopathologic testing is provided: in direct immunofluorescence (DIF) testing, frozen perilesional tissue biopsy specimens are treated with fluorescein-labeled antibodies and evaluated under a fluorescence microscope.[1] Specimens for DIF must be transported to the laboratory in special medium, most commonly Michel solution, but other options include Zeus media, liquid nitrogen, or rarely saline (short-term storage only).[2] Fibrinogen, C3, IgA, IgM, and IgG represent the antibodies evaluated during the examination. In contrast, indirect immunofluorescence testing (IIF) uses patient serum applied to a secondary substrate tested for antibody presence with fluorescein labels.[1] The salt split technique can be performed either directly on patient tissue or indirectly using serum and is used to differentiate between certain entities with similar-appearing histology and DIF results.[3]

## VESICULOBULLOUS REACTION PATTERN — ACANTHOLYSIS

### PEMPHIGUS

Pemphigus is a group of autoimmune blistering diseases that may involve the skin and/or oral

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[a] Department of Pathology and Laboratory Medicine, Emory University, 500 Peachtree Street Northeast, Atlanta, GA 30308, USA; [b] Department of Oral & Maxillofacial Diagnostic Sciences, University of Florida, 1395 Center Drive, Gainesville, FL 32610, USA

* Corresponding author.

*E-mail address:* kmagliocca@emory.edu

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mucosa. Four major categories of pemphigus have been described: pemphigus vulgaris (PV), pemphigus foliaceus, IgA pemphigus (IgAP), and paraneoplastic pemphigus (PNP).[4] This article focuses on the 2 forms of pemphigus with almost invariable involvement of oral mucosal surfaces: PV and PNP.

PV is a potentially life-threatening chronic bullous disease affecting patients worldwide, and although possible in the pediatric population, a majority of cases affect adults in the fourth to sixth decades of life.[5] The best known mechanism for blister formation in PV involves the autoantibody attack against the intercellular keratinocyte adhesion molecules, or desmosomes. Desmoglein-3 (Dsg3), a 130-kDa cadherin component of the desmosome is the main target of attack in mucosal predominant PV, with desmoglein-1 (Dsg1), a 160-kDa protein, additionally targeted in mucocutaneous PV.[6] The antibody-antigen attack results in loss of intercellular adhesion, resultant epithelial acantholysis, and development of blisters and bullae.[4] The process or event(s) precipitating autoantibody formation are unknown.[7]

PNP was first described in 1990 and most often occurs in association with an underlying neoplastic disorder.[8,9] Chronic lymphocytic lymphoma and other forms of non-Hodgkin lymphoma are often linked to PNP, but carcinoma and sarcoma, in addition to benign neoplasms, such as thymoma and Castleman disease, are reported.[9–11] The onset of PNP in relation to the identification of an underlying neoplasm is variable but in most cases the clinical history of neoplasm is known prior to the development of PNP.[12] In one-third of patients, oral mucosal lesions may be the first sign of any disease, with subsequent identification of a neoplasm during the diagnostic evaluation of the orocutaneous symptoms or within the ensuing months in approximately half of patients.[12,13] The average age of onset is 57 years with overall equal gender distribution.[10,13,14] The pathogenesis of PNP is complex and thought to occur as a result of the combined humoral autoimmune response and cellular immune response.[8,15] Antibody attack against a spectrum of targets, such as intercellular proteins (Dsg1 and Dsg3), plakin family proteins (envoplakin, periplakin, desmoplakin, plectin, and Bullous pemphigoid antigen 1 [BP230]), and the protease inhibitor alpha-2-macroglobulin-like antigen 1 (A2ML1), may be detected.[16] Of these, envoplakin and periplakin are most specific for PNP.[17]

## Gross/Clinical Features

In PV, mucosal lesions tend to precede the development of cutaneous manifestations and in some cases may be the only site affected. Delicate, superficial blisters and erosions affect any oral site but the palate, tongue, and labial/buccal mucosa are often involved.[5,12,18] Erosion of the lower lip vermillion is not uncommon. Nonoral mucosal sites, such as pharyngeal, laryngeal, nasal, conjunctival, and genital mucosa, can be affected.[4] Localized or generalized cutaneous lesions exhibit a symmetric predilection for the trunk, groin, axilla, scalp, and face[12,18] and present as flaccid vesicles or bullae on uninflamed skin reported to rupture easily and appear as erythematous erosions.

For PNP, the earliest and most striking clinical features of PNP are painful, florid oral mucosal erosions and ulcers.[17] Oral mucosal involvement can be identified in nearly all patients, but extraoral mucosal sites, such as conjunctiva, genital, pharyngeal, esophageal, nasopharyngeal, and laryngeal mucosa, may also occur[13,15] as well as cutaneous lesions (often sparing the face)[15,17] or viscera, justifying designation of paraneoplastic autoimmune multiorgan syndrome.[19] Pulmonary involvement is devastating and typically manifests as bronchiolitis obliterans.[10]

## Microscopic Features

A developing lesion of PV may demonstrate eosinophilic spongiosis, whereas the center of a deeply entrenched mucosal ulceration may show a nonspecific ulceration on microscopic examination. Clinicians carefully sampling the edge of the blister should include lesion and perilesional mucosa to confirm the level of the separation and demonstrate the presence of the characteristic suprabasilar acantholysis in PV.[18] Rounded acantholytic cells with eosinophilic cytoplasm and pyknotic nuclei are present within intraepithelial cleft spaces and lack overtly atypical features, despite their detachment (**Fig. 1**A). A mild to moderate mixed inflammatory infiltrate may be present in the subjacent connective tissue. The suprabasalar epithelial separation results in retention of only basal cells, an appearance that corresponds to the so-called tombstone effect.[4] Preservation of undulating connective tissue papillae lined by basal cells and devoid of suprabasal epithelium imparts a villous silhouette (**Fig. 1**B).

PNP shows variable morphologic features. The key and most frequent features include a combination of humoral mediated phenomena: suprabasal epithelial acantholysis, dyskeratosis, and cellular autoimmune phenomena: vacuolar interface change and lichenoid infiltrates. Dyskeratosis in the setting of suprabasal acantholysis may be an important clue to PNP.[8] In developing lesions,