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**Original Research Article**

# IMMUNE MEDIATED LESIONS OF THE ORAL CAVITY

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## Introduction

Lesions of the oral cavity are a common presenting complaint for patients seeking care at an otolaryngologist's office. It is imperative that otolaryngologists have an understanding of all the possible diagnoses. Lesions may vary from benign ulcerations to malignancies. Less commonly, immune mediated diseases may initially present with lesions in the oral cavity. The purpose of this article is to explore several specific forms of immune mediated lesions of the oral cavity. The clinical appearance of these lesions may not provide a clear diagnosis. The most important step in achieving a diagnosis for these lesions is obtaining a proper biopsy of 4mm in diameter at the perimeter.

We will be studying the following lesions: Lichen Planus, Bullous Pemphigoid, Mucous membrane Pemphigoid (Cicatricial Pemphigoid), Pemphigus Vulgaris, Linear IgA Disease.

## Lichen Planus

Lichen planus is an idiopathic inflammatory disorder involving the skin and mucous membranes. The age of onset is about 40 years in men, and 46 years in women. It is rarely found under the age of 5 years. There is positive family history in 10% of patients, and an increased frequency of HLA-B7 has been associated. There may be an association with hepatitis C virus. The pathogenesis of lichen planus appears to be T cell-mediated immune response to an unknown cause. Deposits of IgG, IgM, IgA, and complement as well as fibrin and fibrinogen are found in the basement membrane zone.

There are many forms of lichen planus that may be present over body surfaces. The lesions of lichen planus vary from few papules to generalized disease. Clinical features of cutaneous lichen planus are primary lesions measuring 2 to 10 mm, appearing flat topped with an irregular angulated border. A reticular pattern may be seen on close examination. The 5 P's of lichen planus are pruritis, planar, polyangular, and purple papules. These violaceous papules may aggregate into an arborizing pattern or in clusters. Vesicobullous formation may occur over previous lesions or normal mucosa.

Mucosal involvement may occur without cutaneous disease, usually presenting in the sixth decade. The ratio of females to males affected is more than 2:1. Greater than half the cases. of lichen planus involve the oral cavity. Lesions may be asymptomatic or have a burning sensation. The most common site affected is the buccal mucosa but may also include the tongue and lips. Lesions may be classified as reticular, plaque-like, atrophic, papular, erosive, and bullous. The most common form of oral lichen planus is reticular, which appears dendritic or lacy in a white arborizing pattern on the buccal mucosa and is generally asymptomatic. The whitish lines are known as Wickhams striae and are areas of epidermal thickening. Erosive lichen planus results in localized or extensive ulcers of the oral cavity. The Koebner phenomenon, where lesions develop in response to trauma, is a characteristic of cutaneous lichen planus and is also exhibited on mucosal surfaces. Cheek chewing, friction from sharp cusps and dental prostheses and dental procedures may precede oral lesions. Malignant transformation to oral SCCA has been detected in previous lichen planus sites in 0.8% of

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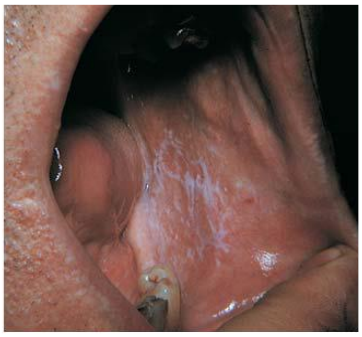
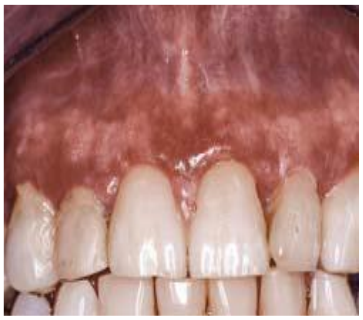
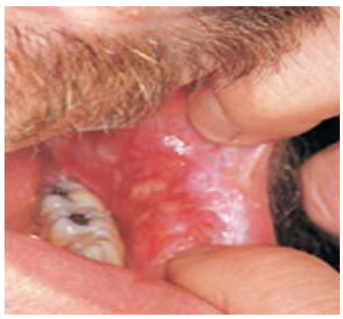
patients.



**Reticular, lace-like pattern Lichen planus**



**Atrophic Lichen planus**



**Erosive Lichen planus**

Diagnosis of mucosal and cutaneous lichen planus may be established clinically. A perilesional biopsy offers definitive diagnosis. Histology indicates loss of the rete appendages with epidermal thinning and lymphocytic (lichenoid) infiltration into the dermis. Direct immunofluorescence indicates ovoid globular deposits of IgG, IgM, IgA, and complement. In addition, a linear pattern of fibrin and fibrinogen is present in the basement membrane zone. Indirect immunofluorescence is negative as no circulating antibodies have been detected.

Lichen planus is usually a self-limited process that resolved in 8 to 12 months. However, recurrence may be present in up to half of affected individuals. Topical, intralesional, and systemic

steroids have been used to treat lichen planus. Fluocinolone gel, triamcinolone (orabase), and clobestasol are effective topical agents for mucosal disease. Submucosal intralesional steroids are effective for erosive lesions (methyl prednisolone 20-40 mg). Oral prednisone is an effective systemic therapy but may result in recurrence when tapered. Dapsone is alternative to steroid therapy (50-150 mg daily). Plaquenil and azathioprine is used for resistant, debilitating lesions.

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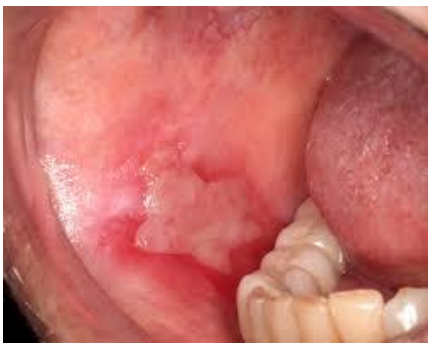
Isotretinoin and acitretin have also been used for therapy.

**Bullous Pemphigoid**

Bullous pemphigoid (BP) is a rare autoimmune subepidermal bullous disease primarily affecting the elderly population after 60 years of age. Males are equally as affected as females. In many cases, the cause of BP is suspected to be medications. BP is mediated by the formation of autoantibodies binding to bullous pemphigoid antigens 230 and 180, cytoplasmic and transmembrane portions hemidesmosomes of basal cells in the epidermis. IgG autoantibodies are found in circulation and bound to the lamina lucida layer of the basement membrane. These antigen-antibody complexes trigger the release and activation of complement with leukocyte chemotaxis and subsequent degranulation. The release of proteolytic enzymes results in the degradation of the BMZ with separation of the epidermis from the dermis.

The presentation of BP is commonly oral blisters (24%) and is usually transient. Initially there may be a localized erythematous plaque which may be pruritic, and subsequently enlarges with edema to become tense bullae. These lesions are usually generalized an most commonly affecting the lower abdomen, groin, and flexor surfaces. There is a negative Nikolsky sign.

These bullae usually rupture in a week, which leaves a localized are of erosion which heals quickly. There are multiple variants of BP with vesicular, vegetating, hyperkeratotic, and erythrodermic appearances. However, they all share the same histologic and immunologic.



The diagnosis of BP is dependent on skin biopsy. A subepidermal cleft with the present of eosinophils in the dermis and bullous regions are common histologic findings. Direct immunofluorescence indicates the deposition of IgG, and/or C3, and variably IgA, IgM, and fibrin in a linear fashion at the BMZ. Indirect immunofluorescence is needed to differentiate BP from other bullous diseases. Circulation IgG antibodies targeting the BP230 and BP180 antigens found in BP.

BP may remain localized and undergo remission or become generalized. Generalized BP has a poor prognosis. Mortality at 1 year is near 19% with treatment. Remission is near 30% at 2 years and 50% at 3 years. Interestingly, the presence of autoantibodies to BP180 but not BP230 has been found more frequently in patients with BP that died in the first year.

Treatment of BP is dependent on the extent and severity of disease. The use of tetracycline, minocycline, or erythromycin with or without niacinamide has indicated excellent clinical

response for localized and generalized disease. It is believed that these medications suppress inflammation at the BMZ. Thus, neutrophil chemotaxis is inhibited and the hemidesmosomes of the basal cells remain functional. Topical steroid therapy has been to be effective for all forms of BP and is superior to oral corticosteroids. Clobetasol proprionate cream (0.05%) has been effectively used as a topical agent in treating BP. Prednisone (0.5-1 mg/mg/daily) may be used in generalized BP and/or

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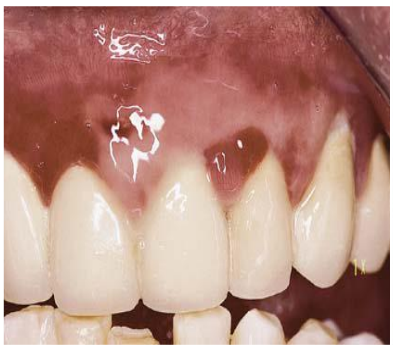
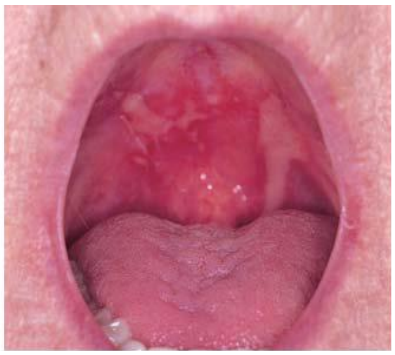
for lesions resistant to topical therapy. Dapsone (50-200 mg/daily) has been used to treat BP, but, its efficacy is limited. Additional adjuvant therapy to corticosteroids for cases of generalized BP unresponsive to topical steroids includes immunosuppressants.
Azathioprine (1-2.5 mg/kg/day), Mycophenolate mofetil (0.5-1g twice daily), cyclophosphamide, methotrexate (5-12.5 mg/week), cyclosporine, and chlorambucil have been used when initial therapy with topical and/or systemic therapy is ineffective. In addition, plasmapheresis and immunoglobulin treatment have been used with some success.

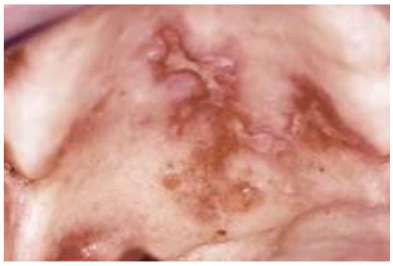
**Mucous Membrane Pemphigoid (Cicatricial Pemphigoid)**
Mucous membrane pemphigoid (MMP), or cicatricial pemphigoid, is a rare chronic immune-mediated disease characterized by blistering, ulcers, and scarring. This disease usually affects adults from the age of 40 to 60 and there is found in twice as often in woman than men.

It results from the production of autoantibodies against antigens within the basement membrane zone of the lamina lucida. Theses antigens are proteins involved in the adhesion of human keratinocytes to extrasellar matrix. Bullous pemphigoid antigen 1 and 2 (BPAG1, BPAG2), laminin 5, β4 integrin subunit, and bullous pemphigoid hemidesmosomal antigen 180 have been implicated in this process. In addition, patients with MMP have been found to have the HLA- DQB1*0301 allele.

The most commonly involved sites in MMP are the oral cavity (85%) and eyes (65%). In the oral cavity, lesions are present commonly in keratinized tissue of the gingival (90%) and palate, and less often in the buccal mucosa. Gingival involvement results in diffuse or patchy erythema with vesicle or bullae formation. These lesions then rupture, leaving noninflamed ulcers that are painless and do not interfere with mastication. These lesions generally heal in 7-10 days. In contrast to pemphigus, the vermilion of the lips is spared. Hoarseness, when present, may indicate involvement of the larynx (8%).







With eye involvement in MMP, unilateral conjunctivitis precedes further destruction. Bilateral involvement may occur within two years and fibrosis is the primary process beneath the conjunctiva that leads to complications. This may include obliteration of the conjunctival sac and erosion of the

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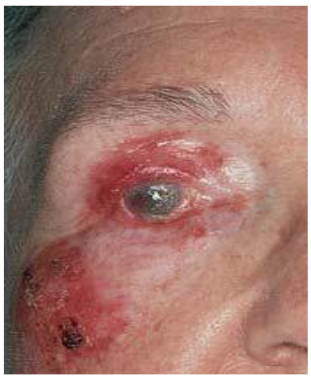
cornea. Subsequently, neovascularization and reduced tearing may opacify of the cornea and result in perforation. Fibrous conjunctival adhesions result in scarring that may lead to blindness in 20% of affected individuals.

Skin involvement may be present in 25% of patients and are clinically evident as tense vesicles or bullae arising over an erythematous base. These lesions may be on the face, neck and scalp and eventually rupture leaving ulcers that heal with or without scars. Genetalia may be involved in 17% of cases.



Diagnosis of MMP is established on biopsy taken from the lesion edge that includes ulcerated and nonulcerated portions. Hematoxylin and eosin staining typically indicates separation of the mucosal epithelium from the underlying tissue at the level of the lamina lucida between the basal cell layer and the lamina densa. There are usually minimal, if any, inflammatory cells present in the underlying tissues. Definitive diagnosis requires clinical correlation with direct immunofluorescence findings. There are linear deposits of one or a combination of IgG, IgA, and C3 at the basement membrane zone in a continuous and homogeneous pattern. MMP may be distinguished histologically from pemphigus by the location of blisters. Pemphigus has acanthosis with cleavage at the spinous cell layer in the epithelium.

Treatment for MMP is guided by location and disease severity. Cases involving ocular, laryngeal, esophageal, and genital regions are aggressively treated. Localized disease may be treated topically by debridement of necrotic tissue and oral rinses of hydrogen peroxide, elixir of dexamethasone, and elixir of diphenhydramine (diluted 1:4 or 1:6 with water. Before meals, hydrogen peroxide rinse with diphenhydramine may be used for cleaning and reducing pain. Meals may be followed by peroxide rinse and dexamethasone for reducing inflammation. Fluocinonide gel is an alternative and is adherent to ulcers with better patient compliance than triamcinolone in Orabase. A soft acrylic appliance may be used when there is gingival involvement. Topical treatment for eyes includes frequent lubrication and topical antibiotics. Additionally, intralesional steroids may be injected into oral cavity lesions (5-10 mg/ml) and repeated every other week or monthly. Systemic therapy with Dapsone (75-200mg/day) is the initial choice to control inflammation and achieve remission is some patients. Oral prednisone (0.75-1mg/kg/day) may be used, and tapered when new blister formation ceases. Cyclophosphamide (1.5-2.5mg/kg/day) may be used as adjuvant immunosuppressive therapy but may require 2-3 months for response. Systemic antibiotics may also be used in cases of superinfection by bacteria. Surgical intervention may also be needed in cases to prevent scarring that may lead to blindness, upper airway stenosis, or esophageal strictures. This is ideally performed when the disease process is not active.

**Pemphigus Vulgaris**

Pemphigus Vulgaris (PV) is a rare form of autoimmune blistering disease that involves skin and mucous membranes. It is related to pemphigus foliaceus, but differs at the level of acantholysis in the

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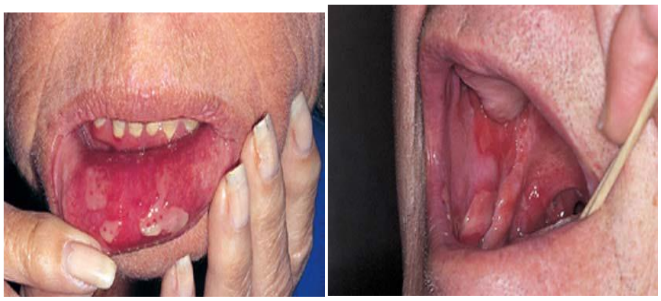
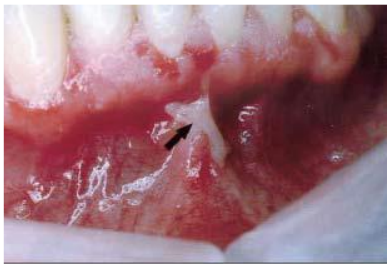
epithelium. In addition, paraneoplastic pemphigus may occur in patients with malignancy and drug-induced pemphigus is due to several agents, most commonly penicillamine. Pemphigus in general is a rare diagnosis, with 0.1-0.5 cases per 100,000/year.

There is an association to HLA-DR4. It is believed that pemphigus occurs in genetically predisposed individuals with an exogenous factor which triggers onset. The average age of onset is in the sixth decade with males and females equally affected. In pemphigus, the formation of autoantibodies to the desmosomes involved in cell-cell adhesion results in the destruction of cellular cohesion. Specifically, desmoglein 1 and 3 (Dsg1 and Dsg3) are found in stratified squamous mucosa where intraepidermal blistering occurs in pemphigus. The antibody-antigen complex destroys intercellular cohesion, and results in fluid accumulation. Mucosal involvement in pemphigus usually is due to formation of autoantibodies to Dsg3. Mucocutaneous involvement is to antibodies to Dsg1 and Dsg3.





PV is the most common form of pemphigus and initially presents clinically as painful erosions in the oral cavity, followed by blister formation in weeks to months. The soft palate is involved in 80% at onset. If left untreated, PV may become generalized, and fatal. Cutaneous involvement commonly occurs in the scalp, face, and axilla. All mucous membrane surfaces may be affected including the larynx, esophagus, and eye. The blisters have a thin roof, and easily rupture with a positive Nikolsky sign. Erosions may heal in a few weeks with hyperpigmentation but generally without scarring. Sunlight exposure may exacerbate the condition.

Diagnosis of PV is made by skin biopsy. There is intraepidermal bullae formation with acantholysis in the stratum spinosum layer with separation of basal cells from each other but not to the BMZ. In addition, there may be mild to moderate eosinophilia to the region. Two biopsies are recommended for direct immunofluorescence. One sample is from the edge of an active lesion while the second is from a normal region. Direct immunofluorescence reveals deposits of IgG and C3 in the intercellular spaces of the epidermis. Indirect immunofluorescence indicates the present of autoantibodies directed to Dsg3 in PV.

Medical therapy in PV is important to control and limit the disease process. If left untreated, the mortality of PV has been documented to be as high as 50% at 2 years and 100% at 5 years. With therapy, mortality has been found to be 10%. The mainstay of therapy for PV is oral steroids (prednisone 0.5-0.1 mg/kg/daily). In addition, topical steroid cream, clobetasol proprionate 0.05%

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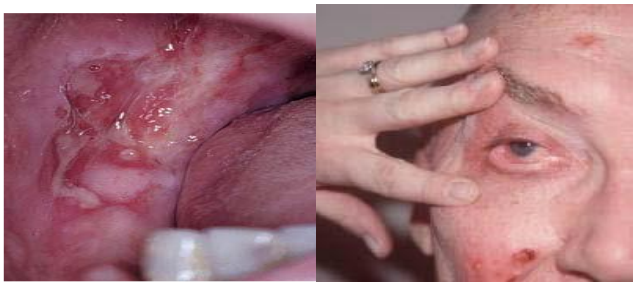
twice daily, has also shown to be effective. Immunosuppressants may also be used for severe disease. Cyclophosphamide (1.5 mg/kg/daily) is the most promising adjuvant therapy, while azathioprine (1.5-2.5 mg/kg/daily), and cyclosporine have been used with variable success. Immunoglobulin therapy may be used as monotherapy or as adjuvant. Therapy may be stopped when patients are clinically free of disease and there is a negative direct immunofluorescence examination. Remission at 10 years following onset is near 75%.

**Linear IgA Disease**

Linear IgA is an acquired blistering disorder without a definitive cause. There are two clinical types: chronic dermatosis of childhood occurs in the first ten years, adult linear IgA disease occurring later with peak between 60 to 65 years. These forms share the same histologic
and immunologic findings, and may share the same target antigen. HLA-B8 has been associated with childhood linear IgA disease. There are twice as many females affected by this disease than males and may affect any skin site. The lesions may be painful and pruritic. Elevated erythrocyte sedimentation rate and circulating IgA may be present.



This blistering disorder has a tendency to occur in the trunk, limbs, face, perioral region, and hands. This may clinically mimic dermatitis herpetiformis (also has IgA deposits), bullous pemphigoid, or other bullous diseases. The oral mucosa, conjunctiva, and genitalia may be affected and result in scarring. This may resemble the presentation of desquamative gingivitis. Vesicular lesions may become confluent and form large bullae, and finally burst leaving ulcerated areas.

IgA deposits have been found below the lamina densa, within the lamina lucida, and within both of these. There are multiple antigens involved in linear IgA disease, and the antibodies bind to multiple sites on a single antigen. The bullous pemphigoid antigen BP180 and its extracellular domain LAD1 are most often implicated in the disease process. Gluten sensitivity has been found in one quarter to one third of affected patients. Other associated diseases include rheumatoid arthritis, ulcerative colitis, immune glomerulonephritis, and malignancy including lymphoma. Drugs including antibiotics (Vancomycin) have also been implicated in the disease process.

Diagnosis of linear IgA disease depends upon biopsy of perilesional areas with immunofluorescence. Histologic appearance may indicate micro abscesses and infiltration of eosinophils in the superficial corium. There may also be few lymphocytes present surrounding
small vessels. A homogeneous deposition of IgA, and possibly C3, is present along the basement

membrane zone detected using direct immunofluorescence in skin biopsy. This contrasts with dermatitis herpetiformis, where IgA deposits are present usually at the tips of connective tissue papillae.

Treatment of linear IgA disease may require combination therapy. Topical and systemic steroids often do not effectively control this disease alone. Dapsone, adult dosing 25-150 mg daily, is effective in most cases for controlling symptoms of burning and itching but is not curative. Peripheral motor neuropathy and hemolytic anemia may result from dapsone therapy and should be discontinued if this

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occurs. Sulfapyridine, 500- 1500 mg daily, has also been used for therapy, and does not cause neuropathy. Colchicine, tetracycline, and nicotinamide have also been used as successful therapy. A large number of cases may resolve spontaneously.

## Conclusion

Lesions of the oral cavity are uncommonly due to immune mediated diseases. It is important for an otolaryngologist to be suspicious for all possible diagnoses. The most important diagnostic study for oral cavity lesions is an appropriate biopsy with possible direct and indirect immunofluorescence testing. In some cases, these lesions may be self-limited and undergo remission spontaneously, appropriate treatment may improve disease severity. These diseases may not be limited to the oral cavity, and it is imperative that appropriate consultations are made to ensure optimal patient care.

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