

Position Paper**Oral Features of Mucocutaneous Disorders***

Part of periodontology involves the diagnosis and treatment of a variety of non-plaque-related diseases of the periodontium. The International Workshop for a Classification of Periodontal Diseases and Conditions noted that the periodontist may be called upon to manage non-plaque-related mucocutaneous disorders either alone, or as part of a treatment team consisting of physicians, dentists or other allied health care professionals. This informational paper will review the etiology, clinical manifestations, diagnosis, and treatment of the most common chronic mucocutaneous diseases, including those that may present as desquamative gingivitis or intra-oral vesiculobullous lesions. This paper is intended for the use of periodontists and other members of the dental profession. *J Periodontol* 2003;74:1545-1556.

DESQUAMATIVE GINGIVITIS

Desquamative gingivitis is a clinical feature of a variety of diseases. It is characterized by epithelial desquamation, erythema, ulceration, and/or the presence of vesiculobullous lesions of gingiva and other oral tissues. This phenomenon can be a manifestation of a number of dermatoses, most commonly lichen planus, cicatricial pemphigoid (benign mucous membrane pemphigoid), and pemphigus vulgaris¹⁻³ (Tables 1 and 2). Biopsy specimens obtained from mucosal lesions may sometimes provide equivocal histopathologic findings and are often inadequate as a single examination to establish the correct diagnosis because several diseases can produce a subepithelial blister. Therefore, direct immunofluorescence examination is necessary to establish a definitive diagnosis. Oral lesions may occur first or very early in several mucocutaneous disorders.⁴⁻⁶ Accurate diagnosis and effective treatment of these lesions may greatly diminish or reverse disease progression.

LICHEN PLANUS

Lichen planus is a relatively common dermatologic disease that affects the skin and mucous membranes, including the oral cavity. Although the etiology of lichen planus is unknown, its immunologic features suggest a cell-mediated immune response to intraepithelial antigens.^{7,8} Lichen planus generally develops between the ages of 40 and 70, and it is more common in females than males.^{9,10} Skin and oral lesions of lichen planus in children are rare but have been reported.^{11,12} Oral manifestations occur in approximately 2.0% of the general population,¹³ while cuta-

neous lesions occur in 0.4%.¹⁴ Ten percent to 20% of patients with lichen planus demonstrate oral as well as cutaneous lesions.¹⁵

Intraoral features of lichen planus include reticular, papular, plaque-like, atrophic, ulcerative, and bullous lesions. The reticular pattern occurs most frequently¹⁶ and is often seen as white lace-like lesions located bilaterally on the buccal mucosa. The reticular, plaque-like, and papular forms are generally asymptomatic and may require no treatment. Patients with these types of lesions may report a change in surface texture or roughness in the area that is affected. The atrophic, ulcerative, and bullous forms of the disease are referred to as erosive lichen planus. It is usually the onset of erosive lesions that motivates patients to seek treatment. Patients often present with a combination of painful erosive lesions in conjunction with white lesions. Patients with erosive lichen planus may exhibit desquamative gingivitis and a positive Nikolsky's sign, characterized by epithelial separation from the underlying connective tissue as a result of minor trauma. A small percentage of patients with lichen planus will experience transient small bullae or vesicles involving the mucosal surfaces.¹⁷

In addition to the oral cavity, lesions may also be seen on the skin, esophagus, genitalia, and rarely the eyes.^{18,19} Skin lesions occur alone or in combination with intraoral lesions and present as recurrent violaceous, keratotic, pruritic patches. Vulvovaginal-gingival and peno-gingival syndromes refer to a variant of lichen planus that affects the gingiva as well as the genitourinary tract of either men or women.^{20,21}

In lichen planus, as well as other dermatologic diseases affecting the oral mucosa, biopsy specimens are essential in establishing a diagnosis for erosive and plaque-like forms and very helpful for reticular forms.

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Table 1.

Mucocutaneous Diseases That May Present with Desquamative Gingivitis

Chronic ulcerative stomatitis	Linear IgA disease	Pemphigus
Dermatitis herpetiformis	Lupus erythematosus	-Vulgaris
Drug induced	Pemphigoid	- Vegetans
Epidermolysis bullosa aquisita	- Bullous	- Follicaceus
Erythema multiforme	- Cicatricial	- Erythematosus
Graft-versus-host disease	- Ocular	- Paraneoplastic
Lichen planus	- Anti-epilgren	- Benign famial
		Psoriasis

Table 2.

Medications for the Treatment of Diseases Associated with Desquamative Gingivitis

Topical	Intralesional	Systemic
Triamcinolone	Triamcinolone	Prednisone
Fluocinonide		Azathioprine
Clobetasol		Cyclophosphamide
Betamethasone		Methotrexate
Halobetasol		Gold
Retinoids		Dapsone
Tacrolimus		Cyclosporin

The histologic features of lichen planus include epithelial acanthosis and hyperkeratosis, liquifaction degeneration of the epithelial basal cells, saw-tooth rete ridges, and a dense, band-like, sub-basilar infiltrate of T lymphocytes.²²⁻²⁴ These classic histologic features are more commonly seen in skin biopsies, while mucosal biopsy specimens are often less distinctive in character. Although immunofluorescence studies of lichen planus do not suggest pathognomonic features associated with the disease, direct immunofluorescence examination may be of value in supporting the diagnosis or ruling out other diseases.^{6,25,26} A linear or a shaggy deposit of fibrin or fibrinogen at the basement membrane is often observed in biopsy specimens, which are examined using direct immunofluorescence tech-

niques. In addition, cytoid bodies are commonly seen at the epithelial-connective tissue interface and are thought to represent necrotic keratinocytes.²⁷⁻²⁹ Although the etiology remains elusive, these histologic and immunofluorescence features suggest that the condition represents a cell-mediated autoimmune response to basal keratinocytes that express a foreign or altered self-antigen.^{30,31} This suggestion is supported by recent data which indicate that external substances such as mercury in dental amalgams may induce keratinocyte ICAM-1 expression, increased binding of T cells to normal keratinocytes, and increased production of TNF- α in vitro.³²

Lichenoid lesions resembling lichen planus may occur in association with the use of medications, including antimalarial drugs, anti-hypertensives, and non-steroidal anti-inflammatory agents.³³ Lichenoid lesions demonstrate clinical, histologic, and immunofluorescence patterns similar to idiopathic lichen planus, and they often resolve without recurrence following discontinuation of the identified medication.³⁴

Exposure to dental restorative materials and cinnamon flavoring agents has also been reported to induce lichenoid reactions.³⁵⁻⁵⁰ Lichen planus may be associated with systemic diseases including hypertension and diabetes mellitus as well as hepatitis B and C.⁵¹⁻⁶⁴ Lesions identical to lichen planus are seen in patients with acute and chronic graft-versus-host disease and lupus erythematosus.⁶⁵⁻⁷²

Treatment of oral lichen planus requires elimination of potential factors associated with lichenoid reactions, elimination or control of local irritants, and the effective use of therapeutic agents that suppress excessive lymphocyte function. Patients with erosive lichen planus are often successfully treated with corticosteroids. Topically applied medications such as fluocinonide and clobetasol gel, beclomethasone dipropionate spray (inhaler), or dexamethasone mouthrinses are effective in inducing remission of lesions.^{31,73-75} Short-term tapering doses of systemic corticosteroids such as prednisone or intralesional injections are useful in severe episodes as well as in recalcitrant cases.⁷⁶ Although expensive to use, systemic and topically administered cyclosporin has shown promising results.^{77,78} Recently, topical tacrolimus has been shown to be an effective form of treatment for oral lichen planus.⁷⁹⁻⁸³ Other medications such as griseofulvin, azathioprine, cyclophosphamide, dapsone, retinoids, metronidazole, lev-

amisole, thalidomide, and low molecular weight heparin have shown some treatment efficacy, but evidence based data are lacking. In addition, the potential for significant side effects may limit their use.⁸⁴⁻⁹⁴ Periodontists who administer these drugs should be aware of reported side effects and be prepared to take appropriate action should any occur. A physician may need to be involved in diagnosis of associated systemic disease and in provision of systemic therapy. In these circumstances, coordinated follow-up involving both the dentist and physician is important. Although some patients experience complete remission following therapy, lichen planus is more often persistent/recurrent in nature and is likely to require periodic retreatment.

Controversy exists regarding the potential for malignant transformation in patients with lichen planus.⁹⁵⁻⁹⁸ Some clinical investigations have demonstrated an increased incidence of oral cancer in lichen planus lesions ranging from 0.4% to 5.6%.⁹⁹⁻¹⁰⁵ Others, however, have questioned the validity of histologic features used to establish the initial diagnosis. Some early precancerous (dysplastic) lesions may present with lichenoid features, and create the impression of malignant transformation from preexisting lichen planus lesions.¹⁰⁶ A recent systematic analysis, however, indicated that individuals with oral lichen planus may have a 10-fold increased risk of developing squamous cell carcinoma when compared to the general population.¹⁰⁷ Regardless of the dispute, it is clear that regular recalls are important to assess the character of recurrent lichen planus or lichenoid lesions, and periodic biopsies are often necessary for areas that do not respond to treatment.

MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid (benign mucous membrane pemphigoid, cicatricial pemphigoid) is a humoral autoimmune disorder that predominantly affects the oral cavity. Other mucosal surfaces may also be involved, including the conjunctiva, nares, larynx, esophagus, upper respiratory tract, rectum, or genitalia.¹⁰⁸⁻¹¹³ The mean age of onset is 50 years or older. However, case reports of mucous membrane pemphigoid in children and young adults exist.¹¹⁴ Females are affected more often than males, at a ratio of 2:1.^{115,116}

The oral cavity usually represents the first and often the only site of disease involvement. Intraoral manifestations of mucous membrane pemphigoid include desquamative gingivitis, vesiculobullous lesions, and ulcerations. Patients often exhibit a positive Nikolsky's sign with epithelial sloughing and exposure of painful

bleeding surfaces beneath. Periods of exacerbation and remission are common, although some lesions may remain unrelenting for years.^{117,118} The gingiva is by far the most common intraoral site affected,^{116,119} and the lesions tend to heal with insignificant scarring.

In contrast, ocular lesions often exhibit progressive scarring leading to fusion of ocular and eyelid conjunctiva (symblepharon formation).^{120,121} Continued scar formation may ultimately result in blindness if untreated.^{122,123} Ocular lesions have been reported to occur in 11% to 61% of patients with mucous membrane pemphigoid, while skin lesions occur in 0% to 11%.¹²⁴⁻¹²⁶ Related conditions such as bullous pemphigoid primarily affects the skin, while antiepiligrin cicatricial pemphigoid characteristically involves the eyes as well as the oral mucosa and/or skin and may represent a paraneoplastic form of the disease.

In mucous membrane pemphigoid, one or more of several heterogeneous antigens (BP180, BP230, laminin 5, and others) found within the basement membrane adhesion complex may be targeted, resulting in an immune response.^{31,118,127,128}

Histologically, biopsy specimens from patients with mucous membrane pemphigoid demonstrate a sub-basilar separation of the epithelium from the underlying connective tissue. Subepithelial vesicle formation and vacuolation in the basal lamina occur below intact epithelium. In contrast to lichen planus, the inflammatory infiltrate is non-specific in nature, consisting of lymphocytes, plasma cells, and neutrophils.¹²⁹

Direct immunofluorescence testing reveals a linear deposition of complement (usually C₃) and IgG or other immunoglobulins at the basement membrane zone.¹³⁰⁻¹³³ Intact epithelium and connective tissue are critical in evaluating a specimen with direct immunofluorescence techniques. Because desquamation can often be induced by minor trauma, perilesional areas may be chosen as an appropriate site to biopsy, and repeat biopsies may be required if desquamation occurs. Serum indirect immunofluorescence testing has been believed to be of little diagnostic value in mucous membrane pemphigoid since circulating basement membrane antibodies are often not detected.¹³⁴ However, improved techniques have recently demonstrated small quantities of circulating serum antibodies in patients with the disease.¹³⁵

Pemphigoid-like lesions have been identified in patients taking systemic medications such as captopril, carbamazepine, clonidine, furosemide, penicillamine, and practolol.¹³⁶⁻¹⁴⁵ Elimination of the targeted medication by a physician should be considered when drug reactions are suspected. A form of paraneoplastic

pemphigoid associated with internal malignancy has also been described. These findings indicate that a diagnosis of mucous membrane pemphigoid warrants a medical referral and complete evaluation.^{146,147}

Treatment of mucous membrane pemphigoid often includes potent topical corticosteroids alone or in combination with systemic corticosteroids.¹²⁴ Dapsone, an antimicrobial agent with immunosuppressive activity, has shown some promise.^{129,148,149} Periodic blood studies are necessary, however, when administering dapsone due to its potential to induce hemolytic anemia. Other systemic medications, including immunosuppressive agents such as azathioprine, methotrexate, levamisole, cyclophosphamide, and mycophenolate mofetil may also be effective in the treatment of pemphigoid,¹⁵⁰⁻¹⁵² but the potential for side effects must be considered and managed should they occur. Successful treatment with a tetracycline derivative or a combination of tetracycline and niacinamide has been reported.¹⁵³⁻¹⁵⁵ Control of dental plaque and local irritants is important in the management of patients with mucous membrane pemphigoid.¹⁵⁶ Coordinated effort between the dentist and physician is important in developing the most effective treatment regimen for patients requiring systemic therapy. In addition, it is important to refer pemphigoid patients to an ophthalmologist for evaluation.

PEMPHIGUS VULGARIS

Pemphigus vulgaris is a potentially life-threatening autoimmune disease that results in bullae formation involving the skin and/or mucous membranes. It occurs most frequently between the fourth and sixth decades of life and affects individuals of Jewish or Mediterranean descent more frequently than others. The overall incidence of pemphigus vulgaris has been estimated to be 0.5 to 3.2 per 100,000 persons,¹⁵⁷ affecting both genders equally.

Intraoral manifestations of pemphigus vulgaris include intraepithelial separation resulting in the formation of bullous lesions. The bullae soon rupture, leaving painful erosions with ragged borders. Gingival lesions can occur and, along with other oral lesions, may represent the first manifestations of the disease. Lip lesions are typical, in contrast to pemphigoid where they are rare.^{158,159} Minor insults to any oral tissues, however, can result in desquamation (Nikolsky's sign).

Skin lesions feature the formation of bullae which quickly rupture, leaving multiple areas of ulceration. The ulcers may cover a significant portion of the body and result in death due to septicemia or fluid and electrolyte loss.¹⁶⁰ In approximately 70% of patients,

the initial lesions of pemphigus vulgaris occur in the oral cavity, and oral involvement is evident in almost all patients with advanced disease.¹⁶⁰⁻¹⁶²

Histologically, pemphigus vulgaris is characterized by acantholysis and suprabasilar bullae formation. The basal cells lining the floor of the bullae are often arranged in a tombstone pattern, and acantholytic keratinocytes (Tzanck cells)¹⁶³ float freely within the blister fluid. The inflammatory infiltrate in pemphigus vulgaris is predominantly mononuclear.

Examination of specimens with direct immunofluorescence techniques reveals the deposition of complement and IgG, IgM, or IgA¹⁶⁴ within the intercellular spaces of the epithelium, resulting in a reticular pattern diagnostic of pemphigus vulgaris. The antigenic stimulus is desmoglein III, an intercellular desmosomal adhesion molecule.³¹ Serum indirect immunofluorescence testing also typically shows epithelial cell surface antibody in substrate tissue. However, circulating anti-epithelial antibodies may not be present in patients with early lesions involving the oral cavity.

Pemphigus vulgaris may be associated with systemic medications including captopril, penicillamine, rifampin, and interferon.¹⁶⁵ Paraneoplastic pemphigus is characterized by painful mucosal lesions similar to pemphigus vulgaris in patients suffering from an underlying neoplasia, most commonly lymphoma, leukemia, sarcoma, and squamous cell carcinoma.^{117,166-168}

Pemphigus vulgaris is treated by moderate to high doses of systemic corticosteroids alone or in combination with topical corticosteroids.^{160,169-171} Azathioprine and other corticosteroid sparing drugs may be introduced into the therapeutic regimen to help control recalcitrant cases.^{135,172} Other systemic medications including dapsone¹⁷³ and cyclosporin A¹⁷⁴ have shown some efficacy. Since effective therapeutic outcomes may require long-term treatment, this disease is probably best managed by a team approach involving both the dentist and physician. It is important to refer pemphigus patients to an ophthalmologist for evaluation.

PSORIASIS

Psoriasis is a chronic inflammatory mucocutaneous disorder that affects from 1% to 3% of the world population.¹⁷⁵ Skin lesions usually involve the elbows, knees, sacrum, and scalp. They present as localized or generalized erythematous plaques or papules covered with white hyperkeratotic scales. A pustular form of the disease also exists. Intraoral psoriatic lesions are relatively uncommon. They may occur in the presence or absence of cutaneous lesions, but they are most often found in association with skin manifestations.

Intraoral manifestations range from the presence of irregular erythematous lesions with raised yellow to white borders to frank ulcerations as well as desquamative gingivitis.¹⁷⁶⁻¹⁷⁸ Although most patients are asymptomatic, others may complain of tenderness, pain, burning, or roughness in the affected areas.¹⁷⁹

Lesions involving the gingiva may affect the periodontal status of patients with intraoral manifestations of psoriasis.¹⁸⁰⁻¹⁸² Psoriasiform lesions also include benign migratory glossitis, stomatitis areata migrans, and Reiter's syndrome.^{175,183-185} Histologically, these lesions demonstrate epithelial thickening with elongated rete ridges and a chronic lymphocytic inflammatory infiltrate. Intrapapillary microabscesses are a common presentation within the epithelium along with migrating polymorphonuclear leukocytes.¹⁸⁶ Direct immunofluorescence testing may reveal immunoreactants in the stratum corneum of the epithelium.

No definitive treatment for psoriasis has been established. Cutaneous lesions may be managed using a variety of topical and systemic agents. Systemic immunosuppressant drugs such as corticosteroids, cyclosporin, methotrexate, acitretin, and mycophenolate mofetil may be useful in recalcitrant cases, although their effectiveness may be limited due to adverse side effects or toxicity.^{187,188} Oral lesions may undergo spontaneous remission or remission in response to systemic therapy. Symptoms of persistent oral psoriasiform lesions may respond to topical corticosteroid therapy or palliative mouthrinses. Meticulous oral hygiene and control of any source of inflammation may be helpful, especially for gingival lesions.

GRAFT-VERSUS-HOST DISEASE

Oral complications occur in almost all patients receiving bone marrow transplantation.¹⁸⁹ Graft-versus-host disease (GVHD) is an immunologic reaction that occurs in 70% to 80% of bone marrow transplant patients and is an important cause of morbidity and mortality. Lesions may occur in various sites including the lungs, liver, gastrointestinal tract, skin, and mucous membranes. Intraoral manifestations of GVHD include lichenoid lesions that may become ulcerative, resulting in significant discomfort.^{72,190-194} These lesions are clinically and histologically similar to those associated with lichen planus, lichenoid drug eruptions, and lupus erythematosus.¹⁹⁵ Although primary care of GVHD is managed by the patient's medical team, treatment of oral complications of GVHD often includes the elimination of local irritants¹⁹⁶ and the use of topical medications such as corticosteroids, azathioprine, and cyclosporin.¹⁹⁷⁻¹⁹⁹

CHRONIC ULCERATIVE STOMATITIS

Chronic ulcerative stomatitis is a rare mucocutaneous disorder that was first described in the early 1990s. It primarily affects elderly females.²⁰⁰⁻²⁰³ Patients present with desquamative gingivitis that is refractory to treatment with corticosteroids. Direct immunofluorescence examination reveals deposition of IgG in the basal one-third of the epithelium, while indirect immunofluorescence demonstrates the presence of stratified epithelium-specific antinuclear antigen that is pathognomonic for chronic ulcerative stomatitis. Treatment appears to be most effective with systemic hydroxychloroquine.²⁰⁴⁻²⁰⁶ However, successful results have been reported using high-potency topical corticosteroids.²⁰⁷

LUPUS ERYTHEMATOSUS

Lupus erythematosus is an autoimmune disorder that may involve the oral cavity along with the skin and internal organs. Historically described as discoid or systemic forms, lupus erythematosus is now classified into the systemic form, a bullous form of systemic lupus erythematosus, a neonatal form, a chronic cutaneous form, and a subacute cutaneous form.²⁰⁸⁻²¹⁰ Lupus erythematosus is more common in women and blacks, and a genetic predisposition for the disease is apparent.²¹¹

The classic description of systemic lupus erythematosus includes chronic fever, weight loss, symptoms of arthritis, a malar or butterfly rash, effusion, and glomerulonephritis. Oral lesions are present in up to 40% of patients. Other skin conditions may be present, including discoid plaques on the face and scalp, alopecia, and vesiculobullous lesions.

Oral lesions are characterized by the presence of a central erythematous erosion or ulceration surrounded by a white rim with radiating keratotic striae. The most frequent sites of involvement are the hard and soft palate, buccal mucosa, and the vermilion border of the lips. The gingiva may take on a desquamative appearance, and patients may complain of burning or soreness. Other mucosal surfaces may also be affected including the oropharyngeal mucosa, nares, larynx, and epiglottis.²¹²⁻²¹⁶

Histologic findings suggestive of lupus erythematosus include keratinocyte vacuolization, subepithelial PAS-positive deposits, lamina propria edema, PAS-positive thickening of vascular basement membranes, and a severe or perivascular lymphocytic infiltrate.²¹⁷ Similar histopathologic features may be associated with lichen planus, and a lupus/lichen planus overlap syndrome has been described.⁶⁷⁻⁷⁰

Direct immunofluorescence testing reveals immunoreactants at the basement membrane zone with granular deposits of IgM, IgG, IgA, C3, and fibrinogen as well as the occasional presence of cytoid bodies.^{6,218}

Oral and skin lesions respond to topical and intralesional corticosteroids with variable results. Systemic corticosteroids alone or in combination with other immunosuppressive agents such as cyclophosphamide may be useful in severe cases. Antimalarial drugs may produce satisfactory control, and topical or systemic retinoids may be beneficial. Gold salts and cyclosporin have also been used successfully in the treatment of lupus erythematosus.²¹⁹

SUMMARY

The oral mucosa may be affected by a variety of mucocutaneous diseases. The erosive gingival lesions associated with vesiculobullous diseases such as lichen planus, mucous membrane pemphigoid, and pemphigus vulgaris have been collectively referred to as desquamative gingivitis. It must be remembered that other less common mucocutaneous conditions also affect the oral mucosa, including lupus erythematosus, bullous pemphigoid, epidermolysis bullosa acquisita, and linear IgA disease.

Adequate treatment is predicated on establishing the correct diagnosis and eliminating potential etiologic factors. While biopsy specimens and histologic examination including immunofluorescence tests are essential in arriving at a definitive diagnosis, the clinical appearance and history of the lesions provide very significant information. This paper has reviewed the features of common mucocutaneous diseases that have the ability to induce intraoral lesions.

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