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Abstract
Desquamation of the gingiva is a sign that may be encountered in clinical practice. Various diseases can affect the gingival tissues. Mild desquamation that is localized may be associated with mechanical irritation or induced by trauma. Moderate to severe generalized desquamation associated with ulceration and erythema may be indicative of a more serious systemic condition. Although often overlooked, mucocutaneous diseases frequently present with gingival desquamation as an early presenting symptom. The most common mucocutaneous diseases that affect the oral cavity are lichen planus, pemphigus, and mucous membrane pemphigoid. This article reviews the etiology, signs and symptoms, and therapies for these disorders. Increased knowledge of mucocutaneous diseases can help the clinician recognize these disorders and enable the patient to receive appropriate therapy.

Keywords
desquamative gingivitis, erosive lichen planus, mucous membrane pemphigoid, pemphigus vulgaris, reticular lichen planus

Disciplines
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Desquamative gingivitis: Early presenting symptom of mucocutaneous disease

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Desquamation of the gingiva is a sign that may be encountered in clinical practice. Various diseases can affect the gingival tissues. Mild desquamation that is localized may be associated with mechanical irritation or induced by trauma. Moderate to severe generalized desquamation associated with ulceration and erythema may be indicative of a more serious systemic condition. Although often overlooked, mucocutaneous diseases frequently present with gingival desquamation as an early presenting symptom. The most common mucocutaneous diseases that affect the oral cavity are lichen planus, pemphigus, and mucous membrane pemphigoid. This article reviews the etiology, signs and symptoms, and therapies for these disorders. Increased knowledge of mucocutaneous diseases can help the clinician recognize these disorders and enable the patient to receive appropriate therapy. (Quintessence Int 2003;34:582-586)

Key words: desquamative gingivitis, erosive lichen planus, mucous membrane pemphigoid, pemphigus vulgaris, reticular lichen planus

Gingival tissue can be differentiated based on its anatomic position. The free gingiva comprises the gingival tissue at the vestibular and lingual/palatal aspects of the teeth and in health, is coral pink and has a dull surface and firm consistency.¹ The attached gingiva extends apically from the free gingiva to the mucogingival junction, where it becomes contiguous with the darker red alveolar mucosa. The alveolar mucosa is loosely bound to the underlying bone and is relatively mobile. The attached gingiva is firmly adherent to the underlying alveolar bone and in health, is coral pink and often shows a fine, surface stippling, giving it the appearance of an orange peel.¹

Desquamation or peeling of the epithelial tissue usually occurs mainly on the free and attached gingiva. Mild cases that are localized and display minimal loss of tissue with mild erythema and no ulceration may be attributed to mechanical abrasion or irritation. Aggressive toothbrushing or parafunctional habits may cause these localized forms of gingival desquamation. Various oral hygiene products may also cause a mild superficial peeling of the gingiva. Toothpaste hypersensitivity, especially to tartar-control products, has been reported as an etiology of desquamative gingivitis.² The patient should be educated on proper toothbrushing techniques and encouraged to discontinue parafunctional habits if these are the suspected etiologies. More severe desquamation may be generalized and accompanied by intense erythema and ulcerations on the free and attached gingiva, as well as the alveolar mucosa. When local factors cannot be attributed to the etiology of the desquamation, systemic conditions must be considered. Three common mucocutaneous diseases that can present with initial symptoms of desquamative gingivitis (peeling of the gingival tissue usually accompanied by erythema, ulceration, and pain) are lichen planus, pemphigus, and mucous membrane pemphigoid. These conditions are immune mediated and are managed via topical and/or systemic medications. Knowledge of the etiology, signs and symptoms, and therapies for these diseases will enable the clinician to more effectively recognize and diagnose these conditions.

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LICHEN PLANUS

Lichen planus (LP) is a relatively common dermatologic disorder that occurs on the skin and oral mucous membranes. There are several forms of this disease, including reticular, papular, atrophic, bullous, and erosive patterns. This discussion will focus on the reticular and erosive forms of LP.

The reticular form of LP is the most common and most readily recognized form of the disease. It consists of slightly elevated, fine, whitish lines (Wickham’s striae) that produce a lace-like lesion. Reticular LP is most commonly seen bilaterally on the cheeks and is usually asymptomatic requiring no treatment.

Erosive LP presents as chronic multiple oral mucosal ulcers. A significant number of cases of erosive LP presents with an initial sign of erythema and/or desquamative gingivitis. Figure 1 demonstrates generalized desquamative gingivitis in a patient diagnosed with erosive LP. In some cases, the lesions start as vesicles or bullae (bullous LP), and in others, the disease is characterized solely by erythema or ulcers (erosive LP). The etiology of LP is idiopathic, which distinguishes itself from lichenoid reactions. Lichenoid reactions have a similar clinical presentation to LP but are differentiated on the basis of the association of the reactions with administration of a drug, systemic disease, or contact allergy, and they may slowly resolve when the allergen is discontinued or the disease is treated. Drugs that have been reported to induce lichenoid reactions are penicillamine, ACE inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs), although, less commonly, numerous other drugs have been implicated. Contact allergens such as cinnamon and peppermint, as well as mercury and gold in select dental materials have been reported to cause a lichenoid reaction due to contact allergy. Hepatitis C is a systemic condition that has been implicated with induction of LP-like lesions.

The diagnosis of LP and lichenoid reactions is made by biopsy. Three characteristic features of LP are seen histologically: a dense subepithelial band of lymphocytes; liquefactive degeneration of the basal cell layer; and areas of hyperorthokeratosis and hyperparakeratosis with a saw tooth appearance to the rete pegs. Lichenoid reactions cannot always be distinguished from LP but may show deep, as well as superficial lymphocytic infiltrates, rather than the classic band-like infiltrate of LP, as well as eosinophils, neutrophils, and plasma cells. Direct immunofluorescence can be performed to rule out other mucocutaneous diseases, such as pemphigus or mucous membrane pemphigoid. Subepithelial deposits of fibrinogen are the most consistent feature of LP when analyzed via immunofluorescence.

Treatment of LP/lichenoid reactions can be wide ranging. If the patient has been using flavoring agents, they should be advised to discontinue the use of such products. If the patient has started a new medication that correlates to the onset of LP, they should discuss changing classes of medication with their physician. The erosive type of LP should be managed more aggressively with the use of high potency (flucinonide) and ultra high potency (clobetasol) topical steroid gels. These agents may be placed in an occlusive dental splint that covers the affected area of the gingiva to increase healing time and decrease pain. Topical steroid rinses and topical steroids applied to gauze pads are other methods of administering medication. Intralesional steroid injections may be necessary to treat lesions that are recalcitrant to conventional therapy; however, this may be difficult for gingival lesions. A short course of systemic steroids may be considered for extremely indolent lesions. Recently, several reports have been published regarding the use of topical tacrolimus in treating oral lichen planus. Tacrolimus is an immunosuppressive agent used in the prevention of solid organ transplant rejection, and several reports have been published demonstrating the effectiveness of the topical formulation in managing oral LP, especially lesions recalcitrant to conventional therapy. There is evidence that suggests that patients with erosive LP are of a higher risk for developing squamous cell carcinoma. Therefore, it is important to evaluate these patients on a standard recall basis. This recall should be based on the patient’s response to treatment. Areas unresponsive to treatment should be biopsied to rule out dysplasia. Often, the recall will be more frequent than that usually performed for periodontal disease, usually every 1 to 3 months.
An important aspect of LP that must be appreciated by the clinician is the chronic nature of this disease. Lichen planus, when properly managed, can undergo periods of quiescence where the patient does not experience any symptoms. When the condition becomes exacerbated, it can cause desquamation of the gingiva, which may lead to severe and painful gingivitis. This may cause the patient to neglect daily oral hygiene due to the painful nature of these symptoms and may, in turn, lead to an increase in gingival inflammation and periodontal disease. More frequent professional prophylaxis may be indicated. Due to the chronic nature of LP, periodontal therapy becomes more integral in the maintenance of oral health in these patients, as poor periodontal health makes the management of erosive LP extremely difficult.

**PEMPHIGUS**

Pemphigus is an autoimmune disease characterized by blisters, peeling, and erosions of the skin and mucous membranes. The highest incidence of the disease occurs in the fifth and sixth decades of life. This discussion will be limited to the most common form of the disease, pemphigus vulgaris (PV), which accounts for over 80% of cases. The other forms of pemphigus are pemphigus vegetans, pemphigus foliaceus, pemphigus erythematous, paraneoplastic pemphigus (a condition where patients with neoplasms, such as lymphoma, present with pemphigus), and drug-related pemphigus.

Lesions associated with PV are intraepithelial, and blister formation is initiated by the binding of IgG autoantibodies to desmoglein 3, a transmembrane glycoprotein adhesion molecule present on desmosomes. Once desmoglein 3 is bound by the autoantibody, there is loss of cell-to-cell adhesion, and blister formation begins. As blister formation progresses, it results in a suprabasilar bulla, which can involve loss of large areas of skin and mucosa.

Initial signs of PV may include generalized desquamatative gingivitis, as seen in Fig 2. The classical oral lesion of pemphigus is a thin-walled bulla with associated erythema. The lesions are commonly seen on the gingival and buccal mucosa, and the edges of the lesion can continue to extend peripherally until they involve large areas of the oral mucosa. It is common for the oral lesions to present up to 4 months before the skin lesions appear. If treatment is instituted during this time, the disease will be easier to control, and the chance for early remission is enhanced.

Biopsy is the standard for diagnosing PV. Ideally, the biopsy specimen should be taken from an intact vesicle less than 24 hours old. Since these types of lesions are rarely present in the mouth, the biopsy should be taken from the advancing edge of the lesion where the characteristic suprabasilar splitting of the epithelium may be observed. A second biopsy specimen should be taken from clinically normal-appearing intact perilesional mucosa and sent for direct immunofluorescence studies (DIF). Direct immunofluorescence is performed by placing fluorescene-labeled antihuman immunoglobulins over the patient's tissue specimen in order to detect antibodies bound to the surface of keratinocytes. If the patient is positive for PV, the immunofluorescence pattern will reveal a lace-like pattern around the epithelial cells of the tissue specimen.

The mainstay of treatment is high doses of systemic corticosteroids. Prednisone is initially used to bring the disease under control and once this is achieved, the dose of prednisone is decreased to the lowest possible maintenance level. A critical aspect of patient management is early diagnosis; this allows the clinician to use lower doses of medication for shorter periods of time to control the disease. Azathioprine and cyclophosphamide are immunosuppressive drugs used as adjuvant therapies in conjunction with prednisone to reduce side effects of the steroid by allowing the clinician to administer lower doses of systemic steroid. Studies have shown that adjuvant therapy decreases mortality when used with systemic corticosteroids. Mycophenolate mofetil, a newer immunosuppressive drug, has been effective in managing patients resistant to other adjuvants. Current studies have demonstrated the effectiveness of mycophenolate in combination with prednisone to successfully manage PV while managing adverse side effects of medication.
MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid (MMP), also commonly referred to as cicatricial pemphigoid, is a chronic, autoimmune disease that results in mucosal ulceration and subsequent scarring. It primarily affects the mucous membranes of patients over the age of 50 and is considered a subepithelial disease.\textsuperscript{15} Autoantibodies, usually of the IgG class, cause subepithelial blistering by cleaving fibrils in the basement membrane zone, as well as activating complement and recruiting neutrophils.\textsuperscript{21} Subsets of MMP have been identified using sophisticated immunology testing and salt-split skin. These subsets are based on the location and molecular weight of the antigens involved in MMP, and the majority of cases have antigens on the epidermal side of salt-split skin.\textsuperscript{22} Today, MMP is considered a family of closely related autoimmune disorders in which the various autoantigens are found in the BMZ and are involved in the attachment of basal epithelial cells to the underlying connective tissue.

Oral manifestations of MMP include desquamative gingivitis and erosion or ulcerations of buccal and labial mucosa, palate, and tongue. Figure 3 demonstrates intense erythema and an area of hemorrhage in the gingiva of a patient with MMP. Extraoral manifestations include ulceration and scarring of the conjunctiva, corneal damage, and mucosal lesions of the genitals, esophagus, larynx, and trachea.\textsuperscript{23} Skin involvement is seen in a low percentage of patients with MMP.\textsuperscript{15}

Any patient suspected of having MMP must have two biopsy specimens taken for both routine histology and direct immunofluorescence study. Routine histopathology will demonstrate sub-basilar cleavage and immunofluorescence will show positive fluorescence for immunoglobulin and complement in the basement membrane zone in 50\% to 80\% of patients.\textsuperscript{15} Clinical correlation with routine and immunofluorescence studies should be interpreted together to arrive at a diagnosis of MMP.

Management of MMP depends on the severity of symptoms. Patients with mild oral disease may be managed by topical and intralesional steroids. Desquamative gingivitis is often managed with topical steroids in a soft occlusive splint that covers the gingiva. An adverse sequela of chronic topical steroid use is candidal infection, and the clinician must closely monitor the patient for development of infection.

If topical therapies prove ineffective, systemic medications may be used for treatment. Like PV, systemic steroids are often effective. Dapsone is a synthetic sulfone with anti-inflammatory properties that is found to be most effective in diseases associated with significant neutrophil infiltration. It has been in clinical use for many years to treat leprosy and malaria. Studies have demonstrated its effectiveness in treating mucous membrane pemphigoid.\textsuperscript{21,24} The major adverse effect of dapsone is hemolysis, and prior to initiating therapy, patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency. This is a key enzyme that prevents oxidation of hemoglobin to methemoglobin, and individuals who are G6PD deficient may develop extensive hemolysis.\textsuperscript{25} Minocycline, a member of the tetracycline family of antibiotics, also has been shown to be effective in treating MMP.\textsuperscript{26} Reported adverse effects include nausea, vomiting, dizziness, photosensitivity, and hyperpigmentation.\textsuperscript{25} Combination therapies consisting of nicotinamide and tetracycline also have been reported as effective therapy for MMP.\textsuperscript{27} It is very important for the clinician to thoroughly examine all skin surfaces and the patient’s eyes to determine the extent of the MMP. If extraoral manifestations are observed, it is imperative that the patient be referred to the appropriate specialist for further evaluation. It is important to remember that approximately 10\% of patients with MMP will develop eye lesions which often result in scarring and can lead to blindness.

CONCLUSION

Gingival desquamation can be indicative of local trauma/irritation or systemic disease. Lichen planus, pemphigus, and mucous membrane pemphigoid are three mucocutaneous diseases that can present with gingival desquamation as their initial symptom. With a comprehensive history and physical exam, as well as the use of gingival biopsy, diagnosis of these disorders will not be delayed.
REFERENCES


