Oral Features of Mucocutaneous Disorders

Committee on Research, Science and Therapy

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PREFACE

Periodontology usually involves the diagnosis and treatment of gingivitis, periodontitis, or other periodontal infections, A variety of non-plaque related diseases, however, also affect the periodontium, Periodontists may be called upon to manage them either alone or as a part of a treatment team of physicians and dentists, This informational paper will review the etiology, clinical manifestations, diagnosis, and treatment of the most common mucocutaneous diseases, including those that present as desquamative gingivitis or intraoral vesiculobullous lesions.

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 vulgaris.[1] When biopsy specimens from mucosal lesions provide equivocal histopathologic findings, direct immunofluorescence may be beneficial in establishing a definitive diagnosis, Oral lesions may occur first or very early in several mucocutaneous disorders, Accurate diagnosis and effective treatment of these lesions may greatly diminish or reverse disease progression,

LICHEN PLANUS

Lichen planus is a disease of unknown etiology that affects the skin and mucous membranes. It generally develops between the ages of 40 and 70, and is more common in females than males.[2] Oral manifestations of lichen planus occur in approximately 2,0% of the general population[3] while cutaneous lesions occur in 0,4%.[4] Ten to 20% of patients with lichen planus demonstrate oral as well as cutaneous lesions.[5]

Intraoral features of lichen planus include reticular, papular, plaque-like, atrophic, ulcerative, and bullous lesions, The reticular pattern occurs most frequently[6] and is often seen as white lace-like lesions located bilaterally on the buccal mucosa, The reticular and plaque-like forms are asymptomatic and may require no treatment, The atrophic, ulcerative, and bullous forms of the disease are referred to as erosive lichen planus, and it is usually the onset of erosive lesions that motivates patients to seek treatment, 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, Skin lesions occur alone or in combination with intraoral lesions and present as recurrent violaceous, keratotic pruritic patches.

In lichen planus, as well as other dermatologic diseases affecting the oral mucosa, biopsy specimens are valuable in establishing a diagnosis. The histologic features of lichen planus include epithelial acanthosis and hyperkeratosis, basal cell layer vacuolation, sawtooth rete ridges, and a dense band-like sub-basilar infiltrate of T-lymphocytes.[7-9] A linear deposit of fibrinogen at the basement membrane can be observed when biopsy specimens are examined using direct immunofluorescence. In addition, cytoid bodies are commonly seen at the epithelial-connective tissue interface which represent necrotic keratinocytes.[10-12]

Lichen planus-like ("lichenoid") lesions may occur in association with the use of medications, including antimalarial drugs, antihypertensives, and nonsteroidal anti-inflammatory agents.[13] Lichenoid lesions demonstrate clinical, histologic, and immunofluorescence patterns similar to idiopathic lichen planus and often resolve without recurrence following discontinuation of the identified medication.[14] Dental restorative materials have also been repotred to induce lichenoid reactions.[15]

Patients with erosive lichen planus are often successfully treated with corticosteroids. Topically applied medications such as fluocinonide and clobetasol gel and beclomethasone dipropionate spray (inhaler) are effective in inducing remission of lesions,[16-18] while short-term tapering doses of

systemic corticosteroids such as prednisone are useful in severe episodes as well as in recalcitrant cases.[19] Although expensive to use, systemic and topically-administered cyclosporin has shown promising results.[20,21] Other systemic medications such as griseofulvin,[22,23] azathioprine,[24] and retinoids[25] have shown some treatment efficacy, but the potential for significant side-effects limit their use. A physician may need to be involved in systemic therapy, and 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 re-treatment.

Controversy exists regarding the potential for malignant transformation in patients with lichen planus. Some clinical investigations have demonstrated an increased incidence of oral cancer in lichen planus lesions ranging from 0.4% to 5.6%.[26-30] Others, however, have questioned the validity of histologic features used to establish the initial diagnosis.[31] Some early dysplastic lesions may mimic lichen planus, and create the impression of malignant transformation in pre-existing lesions. 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 may be necessary in areas that do not respond to treatment.

CICATRICIAL PEMPHIGOID

Cicatricial pemphigoid, commonly referred to as benign mucous membrane pemphigoid, is an autoimmune disorder that predominately affects the mucous membranes and infrequently, the skin. The mean age of onset is 50 years or older, and females are affected more often than males, at a ratio of 2:1.[32,33]

Intraoral manifestations of cicatricial pemphigoid include desquamative gingivitis, vesiculobullous lesions, and ulcerations. The gingiva is the most common intraoral site affected,[33,34] 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). Continued scar formation may ultimately result in blindness if untreated.[35,36] Ocular lesions have been reported to occur in 11 - 61% of patients with cicatricial pemphigoid, while skin lesions occur in 0 - 11% [37-39]

Histologically, biopsy specimens from patients with cicatricial pemphigoid demonstrate a sub-basilar separation of the epithelium from the underlying connective tissue In contrast to lichen planus, the inflammatory infiltrate is non-specific in nature, consisting of Iymphocytes, plasma cells and neutrophils.[41] Direct immunofluorescence reveals a linear deposition of complement, IgG or other immunoglobulins at the basement membrane zone.[41-44] Intact epithelium and connective tissue are critical in evaluating a specimen with direct immunofluorescence. 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. Serum indirect immunofluorescence is of little diagnostic value in cicatricial pemphigoid since circulating basement membrane antibodies are often not detected.[45]

Treatment of cicatricial pemphigoid is similar to that used for erosive lichen planus, including topical corticosteroids alone or in combination with systemic corticosteroids.[37] Dapsone, an antimicrobial agent with immunosuppressive activity, has shown some promise.[40] 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, and cyclophosphamide, are also effective in the treatment of cicatricial pemphigoid,[46,47] but the potential for side effects must be considered. 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 prudent to refer cicatricial pemphigoid patients to an ophthalmologist for evaluation.

PEMPHIGUS VULGARIS

Pemphigus vulgaris is an autoimmune disease that results in bullae formation involving the skin and/or mucous membranes. It occurs most frequently between the 4th and 6th 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 - 3.2 per 100,000 persons.[48]

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.[49,50] 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.[5]1 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.[51]

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 (Tzank cells)[52] float freely within the blister fluid. The inflammatory infiltrate in pemphigus vulgaris is predominantly mononuclear. Examination of specimens with direct immunofluorescence reveals the deposition of complement and IgG, IgM, or IgA[53] within the intercellular spaces of the epithelium, resulting in a reticular pattern which is diagnostic of pemphigus vulgaris. Serum indirect immunofluorescence also typically shows intercellular antibody in substrate tissue.

Pemphigus vulgaris is treated by moderate to high doses of systemic corticosteroids alone or in combination with topical corticosteroids.[50,54-56] Imuran and other steroid sparing drugs may be introduced into the therapeutic regimen to help control recalcitrant cases. Since effective therapeutic results may require long-term treatment, this disease is probably best managed by a team approach involving both the dentist and physician. Other systemic medications including dapsone[57] and cyclosporin A[58] have shown some efficacy in the treatment of pemphigus vulgaris.

ERYTHEMA MULTIFORME

Erythema multiforme is a mucocutaneous disease that may affect the oral cavity as well as other mucous membranes. It occurs most frequently in children and young adults[59] in whom a specific etiologic agent is often not identified.[60,61]

The clinical course of erythema multiforme may include prodromal symptoms such as fever, headache, malaise, nausea, vomiting, and diarrhea. Characteristic "target" lesions of the skin consist

of concentric red and white rings and, occasionally, a central bullous lesion surrounded by an erythematous halo. Oral lesions usually appear as wide-spread superficial painful ulcerations. In a more severe form, prodromal symptoms are followed by the acute onset of bullous and ulcerative lesions involving the skin and mucous membranes (Stevens-Johnson syndrome). Intraorally, if blisters appear, they rupture quickly leaving ulcerations that become covered with a grayish pseudomembrane or a hemorrhagic crust. Healing generally occurs within two to three weeks; however, recurrent and chronic forms of the disease exist.

Although the etiology of erythema multiforme is not fully understood, many cases are believed to be related to allergic or hypersensitivity reactions. A variety of medications, including sulfonamides, have been implicated as potential causative factors.[62] In addition, many episodes of erythema multiforme are preceded by bacterial or viral infections such as mycoplasma pneumonia[63-66] and herpes simplex lesions,[67-69] suggesting a hypersensitivity reaction to an antigenic component of one of these microorganisms. As a result, a careful history of recent illnesses and medications can provide clues to aid in the prevention of recurrence experienced by 25% of affected patients.

In the treatment of erythema multiforme, drugs having the ability to precipitate lesions should be discontinued immediately. In addition, high-dose, short-term systemic corticosteroids typically hasten resolution of the lesions.[70-72] In patients who experience preceding recurrent herpes simplex infections, systemic acyclovir given prophylactically may reduce the chance of recurrence.[75] As with the management of other vesiculobullous lesions, a team approach involving both the physician and dentist is important.

RECURRENT APHTHOUS STOMATITIS

Recurrent aphthous stomatitis is a common intraoral condition that affects approximately 20% of the population.[74] Lesions can be classified into three groups based on their clinical appearance and behavior: 1) minor aphthae, 2) major aphthae, and 3) herpetiform aphthae.[75] Females are more frequently affected than males, and a familial pattern is often evident.[76,77] Aphthae occur predominantly on movable tissue such as the buccal mucosa, labial surfaces of the lips, soft palate, and tongue.[78] The gingiva and hard palate are rarely affected, except in immunodeficiency states.

Minor aphthae are characterized by small, shallow ulcerations covered by a white pseudomembrane and surrounded by erythematous borders. Patients may present with single or multiple lesions which heal within ten days without scarring. In contrast, major aphthae are larger in size (1 cm or more) and may take one month or longer to heal. The lesions are often indurated and frequently heal with scarring. Herpetiform aphthae occur as multiple small ulcerations which may coalesce in a pattern similar to herpetic stomatitis. These lesions generally heal within seven to ten days without scarring. A triad of oral, ocular, and genital lesions is referred to as Behcet's syndrome.[79]

Although the exact etiology of recurrent aphthous stomatitis is unknown, a variety of factors appear to be associated with the disease. In many instances, lesions may be precipitated by minor trauma[80,81] or stress.[82] Patients presenting with anemia due to deficiencies in vitamin B_{12}, folic acid, or iron may experience an increased incidence of aphthae.[83-85] In addition, recurrent aphthous stomatitis has been associated with hypersensitivity reactions to a variety of foods including chocolate, walnuts, and gluten-containing products.[86-88] Ulcerative diseases affecting the gastrointestinal tract such as ulcerative colitis, Crohn's disease, and coeliac disease[89-91] have been associated with the development

of aphthae, as have abnormalities in female sex hormone levels.[92] Although *Streptococcus sanguis* has been cultured from recurrent aphthae, a direct cause-and-effect relationship has yet to be established.[93]

Treatment of recurrent aphthous stomatitis is based on the severity of the disease and should begin with an evaluation of contributing factors. In patients with severe recurrent ulcerations, blood studies as well as referral for evaluation by a physician may be indicated to rule out systemic disease. Topical medicaments useful in the treatment of aphthae include tetracycline[94] and chlorhexidine gluconate,[95] although corticosteroids such as fluocinonide may be the most effective.[96] Systemic medications, especially corticosteroids, may be indicated for the treatment of severe episodes. Levamizole,[97] colchicine,[98] thalidomide,[99,100] chlorambucil,[101] and cyclosporin[102] may be considered if standard care fails.

PRIMARY HERPETIC GINGIVOSTOMATITIS AND RECURRENT HERPETIC LESIONS

The herpes viruses, including herpes simplex virus type one and type two, have the potential to initiate oral mucocutaneous lesions which are often painful and recurrent in nature. Most oral herpetic lesions are the result of herpes simplex type I infection.

Most patients are exposed to the herpes simplex type I virus during the first five years of life,[103] which usually results in nothing more than a subclinical infection. However, in approximately 5% of the population, this initial exposure results in primary herpetic gingivostomatitis. Affected patients present with acute onset of multiple vesicles and ulcerations, inflamed gingiva, cervical Iymphadenopathy, and an elevated temperature. Discomfort is often severe, inhibiting normal ingestion of food and liquids. As a result, dehydration may occur, necessitating fluid replacement therapy. Occasionally, primary herpetic gingivostomatitis occurs in adults who are exposed to the virus for the first time later in life. In these patients, the condition tends to run a more severe clinical course.

Following initial exposure, the virus follows neuronal pathways to immunoprivileged sites such as the trigeminal ganglion and a period of latency occurs. Although the mechanism remains unclear, reactivation of the virus may lead to the development of conditions such as recurrent herpetic stomatitis and herpes labialis. When recurrent lesions affect the oral cavity, they appear as multiple small vesicles that rupture, to form ulcerations which may coalesce to form larger lesions. In contrast to recurrent aphthous stomatitis, these lesions frequently occur on mucosa that is non-mobile such as the hard palate and attached gingiva. Occasionally precipitated by dental treatment, recurrent herpetic stomatitis lesions generally heal within 7 to 10 days.

Treatment of primary herpetic gingivostomatitis may include the use of systemic anti-viral therapy as well as palliative measures for relief of discomfort. Oral acyclovir is useful in reducing viral shedding; however, it does not always alter the clinical course of the disease. As a result, palliative therapy may be necessary. Topically-applied oral rinses containing an anesthetic solution may provide temporary pain relief. Analgesics and antipyretics are often indicated, and care must be taken to insure adequate fluid intake to prevent dehydration. Treatment of recurrent herpetic lesions may include the use of systemic and/or topically-applied acyclovir.[104-106] Orally-administered lysine has been reported to interfere with viral replication and has shown limited therapeutic benefit in some clinical trials.[107-110]

CONCLUSION

The oral mucosa may be affected by a variety of mucocutaneous diseases. The erosive gingival lesions associated with vesiculobullous diseases such as lichen planus, cicatricial 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, linear IgA disease, and psoriasis. Adequate treatment is predicated on establishing the correct diagnosis and eliminating potential etiologic factors. While biopsy specimens and laboratory tests are often 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 which have the ability to induce intraoral lesions.

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