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ORAL LICHEN PLANUS AND POSTINFLAMMATORY PIGMENTATION - A REVIEW

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ABSTRACT Oral lichen planus (OLP) is a chronic inflammatory disease caused by autoimmune mechanisms and clinically presents as a reticular, atrophic/erythematous, or erosive/ulcerative lesion. Postinflammatory pigmentation is not a rare disease, particularly in populations with dark skin. When inflammation associated with OLP is inhibited by medication, tissue macrophages phagocytose melanin pigments in subepithelial connective tissues and cause the persistent deposition of melanin, postinflammatory pigmentation, at the site of OLP lesions. Therefore, the global prevalence and prognosis of OLP-related postinflammatory pigmentation need to be investigated.

KEYWORDS : oral lichen planus, postinflammatory pigmentation

INTRODUCTION:

Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease in which cell-mediated immunity plays a major role. It is most common in adult females and the prevalence is estimated between 0.1 and 2.2%.[1-6] As a typical clinical feature, OLP presents with a papuloreticular pattern with striae and is bilaterally located on the buccal mucosa, but also occurs on other mucosal sites, such as the lips, tongue, and gingiva. Three major clinical forms of OLP: reticular, atrophic/erythematous, and erosive/ulcerative, have been reported to date and may alternatively overlap in the dynamic state with disease progression. Although reticular lesions are generally asymptomatic, patients with erosive OLP often exhibit pain and a burning sensation in the oral mucosa, which interferes with eating and speaking, leading to a decline in the quality of life. The histological changes associated with OLP are mainly characterized by a band-like infiltrate of lymphocytes immediately underlying the basement membrane and the apoptosis of keratiocytes in the basal cell layer. The ratio of malignant transformation is reportedly 0-6.25%.[2,3,5] OLP is generally not accompanied by melanin pigmentation. However, chronic inflammatory conditions, such as OLP, may be associated with the deposition of melanin in connective tissue, which presents clinically as multiple brown-black areas at the site of the original lesion, and is referred to as postinflammaotry pigmentation.[7-10]

Melanin pigmentation is commonly observed in the oral cavity and has various clinical patterns ranging from physiological conditions to the oral symptoms of systemic diseases and malignant tumors.[11-15] In acquired melanin pigmented diseases, postinflammatory pigmentation is not a rare disease, particularly in populations with dark skin.[10,14] OLP has been extensively examined its pathogenesis, the ratio of malignant transformation, and treatment modalities. However, few studies have been conducted on the clinical and pathological features of mucosal pigmentation that occurs at the site of OLP. Therefore, melanin production in the epithelium, pigmented diseases of the oral mucosa, pigmentary lichen planus, and postinflammatory pigmentation associated with OLP were reviewed herein.

MELANIN PRODUCTION AND TRANSPORT:

The color of the skin and mucosa depends on the number and melanogenic activity of melanocytes in the basal cell layer of the epithelium, the size and distribution of melanosomes formed in melanocytes, the type of melanin, and the masking effect of a heavily keratinized epithelium. Melanosomes contain all the proteins required for melanin biosynthesis and the maturation of melanosomes, including tryosinase, tyrosinase-related protein -1 (TRP-1) and TRP-2, gp100, and melanoma antigen recognizable by T lymphocytes (MART-1). In the basal cell layer of the epithelium, melanocytes and keratinocytes form epithelial melanin units and the ratio of melanocytes to keratinocytes ranges between 1:10 and 1:15.[16,17]

Melanin is synthesized from the amino acid tyrosine in melanosomes. The first step in the biosynthetic pathway for black eumelanins and brown pheomelanins is catalyzed by tyrosinase. Tyrosine is converted to dihydroxyphenylalanine (DOPA), which may be converted to dopaquinone. At this point, when cysteine is present, brown pheomelanin is synthesized from dopaquinone via cysteinyl DOPA. Dopaquinone is also converted to leucodopachrome and then converted from quinine into black eumelanin by two pathways. Melanosomes are transferred to keratinocytes via a network of melanocyte denderitic processes. Along with cell differentiation, keratinocytes ascend through epithelial cell layers and their melanosomes are digested by lysosome enzymes and finally released from the surface of the epithelium.[18]

Melanocyte stem cells have self-renewal and differentiation potentials and maintain a population of mature melanocytes.[19] In the epidermis, melanocyte stem cells reside in the bulge region of hair follicles; however, the site of the niche in the oral mucosa currently remains unknown.[20] Pre-dermal melanocytes pass through the basement membrane and migrate to the epidermis. If melanocyte precursor cells remain in the lamina propria/dermis and have melanogenic and aggregating potentials, they will form a nevus.[21]

Melanocytes are stimulated to synthesize melanin by many inflammatory factors, such as prostanoids, cytokines, chemokines, and reactive oxygen species (ROS). Leukotrienes (LT)-C4 and -D4, prostaglandins E2 and D2, thromboxane-2, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, epidermal growth factor, and nitric oxide are included in these factors.[22-24]

Melanin influences the color of the skin, hair, and eyes and provides protection against stress factors, such as ultraviolet

(UV) radiation, ROS, and free radicals in the environment. Melanin also has the ability to sequester metal ions and bind certain drugs and organic molecules. Since melanin synthesis is a process that depends on oxygen, paradoxically, ROS are also produced. UV radiation promotes the generation of ROS during melanin biosynthesis. Therefore, melanin has both antioxidant and ROS-dependent cytotoxic properties. Furthermore, melanocytes serve as antigen-presenting cells for T cells and microbial phagocytosis.[18,25,26]

PIGMENTATED LESIONS IN THE ORAL MUCOSA:

Oral pigmentation may be physiological or pathological. Pathological pigmentation may be classified as endogenous and exogenous based on the underlying cause. Endogenous pigmentation may be associated with an endocrine disorder, syndrome, infection, chronic irritation, reactive lesion, or neoplasia. Exogenous pigmentation may be induced by drugs, tobacco smoking, amalgam, or heavy metals.[13-15]

The stimulating effects of tobacco components on melanocytes has been proposed as a mechanism responsible for tobacco-related oral pigmentation (smoker's melanosis).[27,28] In the histology of smoker's melanosis, increased melanin is found in the basal layer of the epithelium and melanophages are present in the subjacent connective tissue. Pigmentation is reported to disappear with the cessation of smoking. Oral melanoachanthoma is a rare benign lesion composed of keratinocytes and pigment-laden melanocytes. This lesion is considered to have a reactive nature and generally regresses spontaneously or after incomplete removal, such as insicional biopsy. Chronic inflammatory conditions are sometimes associated with the deposition of melanin within connective tissue, resulting in postinflammatory pigmentation.[29] Fixed drug reactions after the administration of cotrymazole, tetracycline, chochicine, and ketoconazole may also be involved in the development of postinflammatory pigmentation.[30] In human immunodeficiency virus (HIV) infection, melanin plaques appear in the buccal mucosa, palate, gingiva, and lips, and are caused by cytokine abnormalities and dysfunctions in the adrenal cortex due to HIV infection.[31] Melanotic macules, a relatively common lesion in the oral cavity, are caused by the increased production and deposition of melanin in the basal cell layer, the lamina propria, or both.

Addison's disease is a congenital or acquired adrenal gland disease in which the secretion of the adrenal cortex hormone decreases, while the secretion of a melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH) increases in a feedback function. This stimulates melanin production in melanocytes, leading to diffuse dark pigmentation of the skin and oral mucosa. Other systemic diseases and syndromes, including Peutz-Jeghers disease, McCune-Albright disease, hyperthyroidism, Nelson syndrome, Laugier-Hunziker syndrome, and Carney complex, are generally accompanied by melanin pigmentation of the oral mucosa.

Pigmentation may occur after treatments with hormones, oral contraceptives, chemotherapeutic agents V (cyclophosp hamide, busulfan, belomycin, and fluorouracil), tranqulizers, antimalarials (clofazamine, chloroquine, and amodiaquine), the anti-microbial agent minocycline, anti-retroviral agent zidovudine, and the antifungal agent ketaconazole.[14,15] Recent studies reported that the molecular target drug imatinib for chronic myeloid leukemia caused blue-gray pigmentation in tissues, such as the oral mucosa, skin, and nails.[32-34] Hematomas, petechiae, purpurae, and ecchymoses may cause the deposition of bilirubin and biliverdin as products of hemoglobin degradation. The colors of lesions depend on the length of time from trauma and may range from red to black.[35,36]

The deposition of amalgam and heavy metals, including arsenic, leads, bismuth, mercury, silver, and gold, cause exogenous pigmentation.[37-39] Amalgam tattoo is one of the most common pigmentations, clinically presenting as a localized blue-gray lesion. The gingiva and alveolar mucosa are the most commonly involved. Amalgam particles disperse in the connective tissue and sometimes exist in the walls of vessels. Pigmentation due to lead poisoning appears as a blue-black line along the marginal gingiva, known as the Burtonian line.

Masilana et al.[40]investigated the physiological pigmentation of the oral mucosa in South Africa. Among 430 participants, 182 (42%) were diagnosed with physiological pigmentation: 54% blacks, 16% Indians, and 21% whites. There were no gender differences. Although all oral mucosae were involved, the gingiva was the most visible site (73%). Hassona et al.[14] examined the prevalence of pigmented oral lesions in a university hospital in the UK. A total of 386 (30.2%) patients were found to have oral pigmentation. Of these, racial/physiological pigmentation was noted in 39.9% of patients and smokers' melanosis in 32.9%, indicating that they were the most common causes of oral pigmentation. Other causes included amalgam tattoo (18.9%), focal melanotic macules (5.7%), postinflammatory pigmentation (1.6%), pigmentation due to medication or systemic disease (0.52%), heavy metal deposits (0.26%), and an oral nevus (0.26%). The gingival and buccal mucosae were the most common sites for oral pigmentation.

LICHEN PLANUS PIGMENTOSUS IN THE SKIN AND ORAL MUCOSA:

Lichen planus pigmentosus is an uncommon variant of lichen planus of the skin and is characterized by the insidious onset of dark brown macules in sun-exposed areas and flexural folds with or without slight pruritus.[41-43] Although this disease was originally reported in India, it occurs in darker skinned individuals in other racial and ethnic groups, such as Latin American, Middle Eastern, Japanese, and Korean populations. Kanwar et al.[42] conducted a retrospective analysis of the medical records of patients in central India and found that the disease was present in 4.1% (124/3020) of patients referred to the pigmentary clinic. The face and neck were the most commonly affected sites, followed by the upper limbs, trunk, and lower limbs. The oral mucosa was involved in only four patients, three of whom showed bluish black pigmentation diffusely on both sides of the buccal mucosa and along the lateral borders of the tongue. The fourth patient had speckled pigmentation present only on the tongue. Another four intraoral lesions have been reported in Kuwait, India, and Japan.[41,44-46]

Lichen planus pigmentosus-inversus is a recently described rare variant of lichen planus. It was initially reported in European Caucasians of the Czech Republic in 2001.[47] Although lichen planus pigmentosus appears in sun-exposed areas of the skin, the lesions of lichen planus pigmentosus-inversus predominantly arise in intertriginous areas, such as the axilla and groin. Only 41 cases have been reported to date in the literature.[48] Lichen planus pigmentosus-inversus was originally considered to only affect Caucasians; however, similar cases have been reported in Asians and Africans. The nails, hair, and mucous membranes are generally not affected.

Lichenoid infiltrates of lymphocytes and histiocytes of various densities with epithelial atrophy and prominent pigment incontinence characterized by the presence of melanin within macrophages in the superficial dermis have been reported in the histologies of lichen planus pigmentosus and lichen planus pigmentosus-inversus.

POSTINFLAMMATORY PIGMENTATION IN THE SKIN AND ORAL MUCOSA:

Postinflammatory pigmentation is an acquired hypermelanosis occurring after inflammation in or injury to the skin. It may develop in all skin types, but more frequently appears in colored patients, including African American, Hispanic/Latin, Asian, Native American, Pacific Islander, and Middle Eastern populations.[49] According to the Fitzpatrick skin types, natural skin color is classified as white skin type I to black skin type VI. Postinflammatory pigmentation occurs more frequently and becomes severe in populations with Fitzpatrick dark skin types IV through VI.[24,50,51] In a study conducted in Singapore, postinflammatory pigmentation was slightly more common in Asians with darker skin colors, such as Malaysians and Indians, than in those with lighter skin, such as Chinese, suggesting that the degree of skin color was contributary to the development of postinflammatory pigmentation.[52] Common causes of postinflammatory pigmentation in the skin are acne vulgaris, atopic dermatitis, and impetigo.[53]

Postinflammatory pigmentation in the oral cavity is a change in the color of the oral mucosa occasionally associated with chronic inflammatory disorders, such as OLP, oral lichenoid lesions, periodontal disease, Steven-Johnson syndrome, and graft-versus-host disease. Muri at al.[54] reported that 11% of 99 patients affected by OLP presented with oral pigmentation. Chitturi et al.[10] examined the relationship between pigmentation and OLP in a South Indian population. Among 58 patients with OLP, more than 60% patients had pigmentation associated with OLP, indicating a high prevalence of oral postinflammatory pigmentation in dark skin populations. Mergoni et al.[9] reported 7 cases of oral postinflammatory pigmentation at universities in Italy and Turkey. The original disease was OLP in 4 cases, lichenoid lesions in 2, and proliferative verrucous leukoplakia in 1. A 60-year-old white woman with mucocutaneous lichen planus had bilateral ulcerative lesions of the buccal mucosa. During the treatment period, a brown pigmented lesion not previously noted appeared in the buccal mucosa. Another 32-year-old white woman with erosive lesions in the hard palate was histologically diagnosed with lichenoid stomatitis. An asymptomatic pigmented lesion of the hard palate was detected after treatment for 2 months. In these patients, pigmented lesions appeared after the amelioration of the primary diseases through treatments with corticosteroids. Histologically, the presence of subepithelial melanophages is the characteristic feature, causing the clinically detectable mucosal pigmentation.

TACROLIMUS TREATMENT FOR OLP AND PIGMENTATION:

A wide range of treatments have been proposed in the management of symptomatic OLP; however, topical corticosteroids are still the mainstay of therapy. When the lesion is refractory to topical corticosteroids, other treatments with immunosuppressive drugs, such as cyclosporine, tacrolimus, and picrolimus, are required. Tacrolimus was initially applied in the prevention of allograft rejection. Significant therapeutic effects were subsequently observed in the treatment of cutaneous diseases, such as atopic dermatitis, contact dermatitis, psoriasis, and pyoderma gangrenoum. It has been also reported that 0.1% tacrolimus ointment is tolerated well and effective for erosive OLP that does not respond to topical corticosteroids.[2,55,56]

Hodgson et al.[57] assessed the long-term safety of topical tacroliums in the treatment of erosive OLP. Adverse effects were local, including a burning sensation (16%) at the site of application and transient taste disturbance (8%), but pigmentation of the oral mucosa did not occur. In 2004, Shen et al.[7] reported the first case of mucosal staining after the topical tacrolimus treatment of OLP. A 45-year-old woman visited the US Roger Williams Medical Center. Her erosive OLP was treated with 0.1% tacrolimus ointment twice daily for 9 months. Although she noted a significant improvement in OLP, lower gingiva gradually darkened. After stopping tacroliums, pigmentation resolved within 2 months. Fricain et al.[8] reported a 71-year-old Italian woman who was the first histologically documented case of oral mucosa pigmentation that occurred in association with tacroliums ointment. After being treated with tacrolimus for 15 days, the symptoms of OLP were attenuated and erosions disappeared. Brown mucosal staining appeared and increased during the 2-month application of tacrolimus. Biopsy of the pigmented zone showed a mild lymphocytic cell infiltrate, epithelial atrophy, and an orthoketatotic horny layer. Melanin staining showed pigmentation in the basal cell layer as well as pigment incontinence. Pigmentation clinically disappeared one month after the cession of tacrolimus. These cases suggest that topical tacrolimus for OLP contribute to the development of postinflammatory pigmentation.

MECHANISM OF POSTINFLAMMATORY PIGMENTATION ASSOCIATED WITH OLP:

Two processes are involved in the development of postinflammatory pigmentation: the first relates to the direct stimulation of melanocytes by inflammatory mediators, while the second is the abnormal distribution of melanin pigment. A frequent finding in specimens taken from tissue affected by postinflammatory pigmentation is the presence of melanin-laden macrophages, melanophages, in connective tissue underlying the epithelium. This indicates that melanin pigments are released from apoptotic keratinocytes into connective tissue and phagocytosed by tissue macrophages.[10]

Macrophages are found in virtually all organs in the body, including the liver, brain, bones, and lungs. They have specific functions in each organ. Macrophages are considered to be continuously reproduced by blood-circulating monocytes, arising from the hematopoietic stem cells of adult bone marrow.[58] On the other hand, the existence of macrophages derived from the embryonic yolk sac and maintained in peripheral tissues by self-renewal has also been demonstrated.[59-61] These tissue macrophages are considered to be involved in the formation of melanophages in postinflammatory pigmentation associated with OLP. James et al.[41] reported a rare case of intraoral lichen planus pigmentosus with a mild chronic inflammatory infiltrate under the mucosal epithelium and focal pigment incontinence. Melanophages were all HLe-1 bone marrow-derived cells, eliminating the possibility of originating from keratinocytes, fibroblasts, or endothelial cells, and activated macrophages with T-cell activating and antigen-presenting abilities. These findings suggest that monocyte-derived macrophages contribute to the generation of melanophages that appear in pigmentary OLP.

Melanophage dynamics have been studied in a mouse tattoo model.[62] The tattoo process consists of inserting water-insoluble pigments of the desired colors into the dermal layer of the skin. Immediately after tattooing, a portion of the pigments is shed with the epidermis or transported away from the dermis via lymphatic vessels. The pigment particles that remain at the injection site, causing a long-term tattoo color, were exclusively detected within dermal macrophages. When tattoo pigment-laden macrophages die during the course of adult life, neighboring macrophages recapture the released pigments and ensure the macroscopic stability and long-term persistence of tattoos in a dynamic manner. In the case of melanophages found in the human dermis, they appear to persist for several years due to longevity rather than constitutional renewal within the tissue. When tattoos are no longer desired, they may be removed through the use of

quality-switched lasers. Laser pulses lyze tattoo pigment-laden cells, and pigment particles may fragment and be excreted via lymphatic vessels. Although several cycles of laser treatment are performed to achieve tattoo removal, some tattoos may not be completely removed. These difficulties are generally attributed to a fraction of fragmented pigments being recaptured by neighboring macrophages.

In active OLP lesions, melanin released from apoptotic keratinocytes may be eliminated from subepithelial connective tissues through lymphatic vessels. However, if the excretion mechanism for melanin pigments is lost by inhibiting the inflammatory response of OLP using an effective therapeutic agent, tissue macrophages may phagocytose the retaining melanin pigments and remain in place, thereby generating long-standing dark pigmentation of the oral mucosa (Figure 1).

CONCLUSIONS:

Melanin produced in melanocytes is supplied to keratinocytes in the basal cell layer. Melanin pigment released from apoptotic keratincytes into the subepithelial connective tissues is phagocytised by tissue macrophages, forming a new disease called postinflammatory pigmentation. Further studies are required to clarify the frequency of postinflam matory pigmentation in the population of each racial and ethnic group or skin color. It is also important to clarify whether its appearance indicates the efficacy of the therapeutic agent used or a healing stage of OLP lesions.

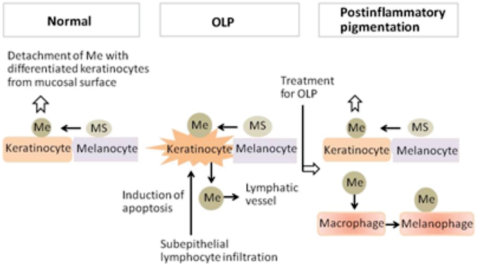

Fig. 1. A schematic representation of the mechanism by which OLP-associated postinflammatory pigmentation may be generated. Melanosomes (MS) are formed in melanocytes

associated postinflammatory pigmentation may be generated. Melanosomes (MS) are formed in melanocytes and transferred to neighboring keratinocytes via a network of melanocyte dendritic processes. Along with cell differentiation, keratinocytes ascend through the cell layers of the epithelium and melanin (Me) in keratinocytes is finally released from the surface of the epithelium. In active OLP lesions, lymphocyte-derived inflammatory mediators stimulate the activity of melanocytes. Lymphocytes that infiltrate subepithelially also induce the apoptotic cell death of keratinocytes in the basal cell layer. Melanin released from apoptotic cells may be eliminated through lymphatic vessels. If the excretion mechanism for melanin pigments is lost by inhibiting the inflammatory response of OLP using an effective therapeutic agent, tissue macrophages may phagocytose the retained melanin pigments and remain in place, thereby generating long-standing dark pigmentation of the oral mucosa.

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