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Literature Review

Stress-induced Oral Lichen Planus Immunopathogenesis and Potential Therapy: A Narrative Review

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ABSTRACT

Background: Oral lichen planus is a chronic inflammatory condition that only involves in the oral cavity and is mediated by the cellular immune system. The etiology of OLP is unclear but autoreactive T lymphocytes are considered to play an important role in the development of OLP. Factors like stress and psychological anxiety have been associated with OLP but their roles in the development of OLP is yet explored**. Purpose:** To describe stress-induced OLP immunopathogenesis and therapeutic potential. **Reviews:** In the early stages, the mechanism of OLP involves the expression of keratinocyte antigens or exposure to an antigen in the form of self-peptide or heat shock protein (HSP). HSP90 is the most expressed heat shock protein in the basal layer of keratinocytes and plays a role in recruitment of cellular immune cells through the production of cytokines due to TLR2/4 and CD91 activation, inflammatory cell migration due to 4 integrin activation, and increased antigen presentation due to HSP90-peptide binding to MHC class I/II. Stress as a physiological response triggers the release of the hormone cortisol from the adrenal cortex and catecholamine hormones such as epinephrine/adrenaline and norepinephrine/noradrenaline from the adrenal medulla. Catecholamines increase the migration of T lymphocyte cells through the interaction of integrins and integrin ligands on the endothelium through the expression of 2-integrin after binding to adrenergic receptors on the cell membrane. **Conclusion:** Oral lichen planus is a chronic inflammatory condition caused by various factors where stress increases the migration of T lymphocyte cells on the side that expresses self-peptides and antigens through the interaction of immune cells with catecholamines. Topical non-selective beta blockers can be supporting therapy in reducing pain and size of OLP lesions.

Keywords: Immunopathogenesis; oral lichen planus; stress; medicine; dentistry

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INTRODUCTION

Lichen planus (LP) is *mucocutaneous* inflammatory disease whose exact etiopathogenesis is remained unclear, presumably due to chronic autoimmune disorders relapsing, pruritic and non-infectious.[1] Oral lichen planus (OLP) is an LP that only involves the oral mucosa, precisely in the stratified squamous epithelia. The incidence of OLP in the general population ranges circa from 1 to 2%, often appears in the 4th decade of life, can affects all types of races, gender and usually more common in women with a ratio of 1.4:1. As many as 70% of affected women are between the ages of 30 and 60 years. The cause of OLP is still not known with certainty. Over the years, the immune system have been shown to play a major role in the disease progression. Autoreactive T lymphocytes can play an important role in the development of OLP. These cells cant it distinguish among molecules attached to the body and foreign antigens.[2] Other factors such as stress and psychological anxiety are associated with OLP in most of the studies that have been conducted so far.

Stress is an organism's response to potentially damaging external influences such as environmental conditions or stimuli. The stress response is the body's way of reacting to a problem. Based to a stressful case, the body's way of responding into stressful conditions is when the sympathetic nervous system activates resulting in a fight or flight response. For the reason that body cannot maintain a state for long periods of time, the parasympathetic system restores the body's physiological conditions to normal (homeostasis). Autonomic activity and an increase produced by the HPA axis play a role in the immune mechanism that controls the inflammatory process.[3,4]

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As a chronic inflammatory oral mucosal disease, OLP has the potential to transform into a malignancy. Immunological factors play a major role in the pathogenesis of OLP whose can exacerbated by host conditions. Prolonged stress conditions in the host can result in HPA axis dysregulation which can trigger an increase in the production of proinflammatory cytokines, as well as over-activation of the immune and inflammatory systems, thus supporting the development of Oral Lichen Planus (OLP).[3–5] This literature review was made to describe the role of stress on the immunopathogenesis of Oral Lichen Planus and the treatment that may prescribe to the patients with stress-induced OLP.

REVIEWS

Oral lichen planus (OLP) is an LP that only involves the oral mucosa, precisely in the stratified squamous epithelia. Oral lichen planus lesions that can be seen as white or red and white lesions[3] appear bilaterally distributed, asymmetrically,[4] and can be reticular, papular, plaque, bullous, erythematous/ erosive, or ulcerative.[1,2]

In the literature, various prevalence rates in OLP have been reported, but the prevalence is around 0.5% and 2% in different populations. Oral lesions occur in approximately 50-60% lichen planus on the patient's skin. In contrast, skin lesions occur in 10-15% of people with OLP. The percentage of women is higher than that of men, with a ratio of 3:2. This condition usually occurs in people older than 40 years, the median age of onset of OLP is 53 years. It is very rare in children, and there are no hereditary predisposing factors.[2]

The incidence of OLP in the general population ranges from 1 to 2%, often appears in the 4th decade of life, can affects all types of races, gender and usually more common in women with a ratio of 1.4:1. As many as 70% of affected women are between the ages of 30 and 60 years. Oral lichen planus can also occur in children, although it is rare.[5,6]

The etiology of OLP is still unknown. Over the years, it has been shown that the immune system has a major role in the development of this disease. Autoreactive T lymphocytes can play an important role in the development of OLP. These cells are unable to differentiate between body-attached molecules and foreign antigens.[2]

Other factors such as stress and psychological anxiety are associated with OLP in most of the studies that have been conducted so far. In general, patients report that they have been exposed to negative social events months before the onset of illness. Overall, the etiology behind the occurrence of OLP involving a multifactorial process consisting of events that may occur at different time points and therefore difficult to investigate.[1] The severity of the disease often parallels the stress level of the patient, although there is no evidence to suggest that stress is the cause of this condition.[7]

Histopathological manifestation

Histological appearance in OLP patients as a whole showed hydropic degeneration of the basal layer and a band-like chronic subepithelial lymphocytic inflammatory infiltrate (Figure1). In some preparations, plasma cells in the connective tissue can also be observed (42%-62%), epithelial hyperkeratosis (50%-78%), epithelial hyperplasia (20%-59%), acanthosis (39%-57%), hypergranulosis (47%), civatte bodies (6%), flattened epithelial cristae (20%) and fibrin deposits in the epithelium (5%).[8–10]

Several histological exclusion criteria for the diagnosis of OLP does not reveal basal cell liquefaction degeneration, polyclonal inflammatory infiltrates, abnormal dysplasia, abnormal keratinization, flat rete ridges and the absence of colloid bodies.[11]

Immunopathogenesis of Oral Lichen Planus

The cause of OLP is remain indefinite but there are several things that trigger the pathogenesis of OLP. Immunity plays a considerable role in disease progression and it is postulated as an autoimmune disease mediated by cellular immune system attacking keratinocytes, especially those in basal layer. The mechanism of OLP initially involves the expression of keratinocyte antigens or exposure to an antigen in the form of self-peptide or heat shock protein.[12]

Heat Shock Proteins (HSPs) are cellular protective responses that prevent protein denaturation and degradation and support cellular repair. Protein denaturation can occur due to a number of stressors such as environmental (heat,

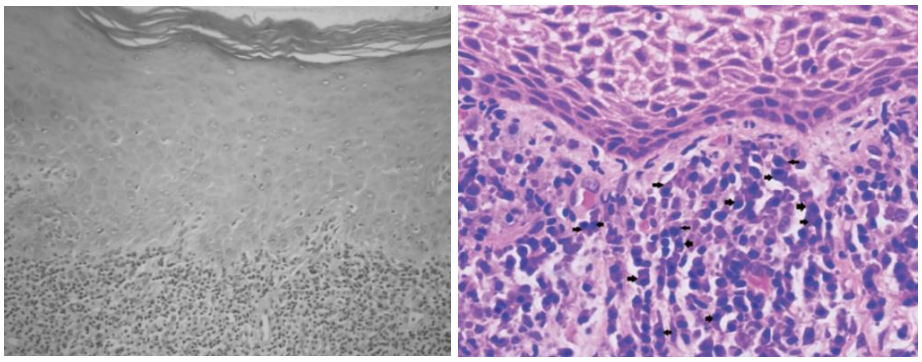

Figure 1. Histopathological picture of OLP shows a lymphocyte infiltrate in the basal layer and accumulation of plasma cells in the connective tissue.

ultraviolet radiation, heavy metals, nutritional deficiencies, systemic drugs, allergens and oxidative stress), pathological (acute or chronic inflammatory disease, viral infections, bacterial infections, ischemia, and trauma). mechanical) or physiological (growth factors, cell differentiation, exercise activity, and gravity). Under normal conditions, Heat Shock Factor (HSF), which is an HSP transcription factor, is suppressed by the Heat Shock Protein present in the cytoplasm. Protein denaturation during heat shock causes phosphorylation and trimerization of HSF to be translocated to the nucleus.[13,14]

Extracellularly released HSPs (ex-HSPs) have an important role in intercellular communication in the immune system and various pathological conditions. HSPs can be released from cells either passively (such as through cell damage, stressed cells or cell death) or actively through the secretion of HSP-containing exosomes. These free extracellular HSPs, also known as alarmins or chaperokines, include HSP90 which is highly expressed in the basal layer of normal keratinocytes and is elevated in OLP conditions. HSP90 has a role in T lymphocyte activation in the pathogenesis of OLP.[15–18]

HSP90, including gp96, which is an endoplasmic reticulum resident of the HSP90 family, can bind to TLR2/4 and CD91. HSP90 in the cytosol and gp96 that bind to Toll-like receptors (TLRs) on APCs stimulate pro-inflammatory cytokines and Th1-type cytokines (TNF-alpha, IL-1beta, and IL-12). HSP90 and gp96 also interact with CD91 which triggers phosphorylation and activation of NF-kB and p38 MAPK. This activation enables APC maturation, cytokine release and T-helper cell recruitment. These two processes are thought to play an important role in multiple T cell responses.[19,20]

HSP90 can selectively bind to the cytoplasmic 4 end and induce the binding of talin and kindlin-3 which triggers alpha4 integrin activation via outer and inner signaling. The N and C-terminal domains of the HSP90 molecule simultaneously bind to the two alpha4 ends causing dimerization and assembly of alpha4 integrins on T cell membranes and activates the FAK-Rhoa signaling pathway to support cell migration.[21] Activation of integrins by talin and kindlin allows strong interactions between immune cells such as T cells or neutrophils and endothelial cells expressing integrin ligands such as ICAMs, VCAM-1 and MAdCAM which have increased expression due to the release of TNF-a, IL-1b, IFN-g and others.[22,23] Increased expression of ELAM-1.[11]

T lymphocytes (dominantly T cytotoxic and some T helper) relocate to the epithelial layer when they incidentally detect antigen during periodic surveillance or specifically migrate via chemokine signal to basal keratinocyte. Antigen binding to major histocompatibility complex (MHC)-I on keratinocyte or the activation of T helper may directly activate the migrating T cytotoxic. The total of Langerhan cells in OLP lesions is also increased when MHC-II expression upregulates; Furthermore, T helper and Interleukin (IL)-12 activate T cytotoxic cells through the interaction of receptors, interferon (INF) and IL-2. Activated T cytotoxic cells destroy basal keratinocytes via the production of tumor necrosis factor (TNF)-α.[12]

The role of stress in Oral Lichen Planus

Stress is a notion of emotional strain and pressure that at small-scale may be favourable and healthy. Positive stress may aid improvement in performance, play a role in motivation, adaptation and reaction to external circumstances which excessive amounts can cause damage to the body. Stress may be associated with increased risk of stroke, heart attack, ulcers and mental conditions such as depression. It may be external in relation to the surrounding environment but it may also be resulted from perceptions to cause anxiety and negative emotions following the situation including pressure, discomfort, which perceives as stress. Stress, or perceiving thing as a threat, may also be experience when a person lack of confidence upon their abilities to overcome obstacles (stimuli, people, situations, etc). Stress can occur when we think that the problem we get is beyond our ability to overcome.[24]

Physiologically or biologically, stress is an individual response to a destructive external influence (a stressor) such as environmental conditions or a stimulus. Depend on stressful circumstances, body mechanism in responding to stressful conditions begin when autonomic nervous system particularly symphatetic nervous system is activated resulting in a fight or flight response. This response will not last for long periods of time where parasymphatetic system returns body condition into the state of homeostasis. In humans, stress is commonly considered into a positive or negative condition affecting individual health mentally or physically.[24]

Not only occur at the level of organism, stress also appears at tissue level and cells. It is a form of body reaction to manage the continuity of life. Any presence of stress can indicate a new balance or an adaptation phenomenon. If the cell or organ can handle the stressor well and is still in a state of balance, it is called eustress, whereas if life cannot cope in the transaction process, the cell or organ will experience distress.[24]

Physiologically, stress hormones are released in sufficient amount throughout the day but increase dramatically in the encounter of stressful condition. Both physical and physiological stress can increase the secretion of ACTH which in turn elevate the level of cortisol. Corticotrophin Releasing Factor (CRF) is the initial stress hormone to be released in response to stress. It is secreted by hypothalamus in the brain to blood circulation where it reaches the pituitary gland located below the hypothalamus. CRF then stimulates the secretion of adenocorticotrophin hormone (ACTH) by the pituitary that further stimulates adrenal gland to produce and release various hormones, one of which is cortisol. Circulated in the body, cortisol plays a role in coping mechanisms. When hypothalamus process intense stressor, CRF secretion will escalate so that the stimulation in putuitary gland will also increase. This phenomenone will also be followed by the increase of cortisol secretion in adrenal gland as well. At the time

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the emotional state stabilized, the coping mechanism will shift into positive axis in which brain signals inhibit CRF release until the stress-hormone cycle repeated.[25]

There is a domino effect of stress affecting the endocrine system where glands in this system will secrete substances called hormone directly to the circulation. Several endocrine glands are involved in body response to stress. Firstly, there is a small structure in the brain called hypothalamus which is responsible in secreting hormone to produce adrenocorticotrophine hormone (ACTH) after the stimulation of the nearest hypophysis. ACTH further stimulates adrenal glands which are located above the kidneys. By the influence of ACTH, the outer layer of the adrenal glands known as adrenal cortex release a group of hormones called cortical steroids. Cortical steroids (also called corticosteroids) possesses diverse functions in the body namely increasing resistance to stress, promoting the development of muscle and encouraging the release of sugar to provide energy burst in responding to a threatening stressor (e.g. a lurking predator or attacker) or emergency situation and assisting the body to defend against allergic reaction and inflammation. The sympathetic branch of autonomic nervous system may stimulate the inner lining of adrenal gland (or adrenal medulla) to release a mixture of epinephrine and norepinephrine that funtion as hormone as it is released to the bloodstream. Concurrently, norepinephrine is also produced in the nercous system to function as a neurotransmitter. Both epinephrine and norepinephrine incite the body to manage threatening stress through the acceleration of the heart rate and the stimulation of liver to release stored glucosa, generates available energy that is useful to protect oneself in threatening situation. The stress hormone produced by the adrenal glands helps the body prepare for an upcoming threat or stress. After the stressor has passed, the body returns to its physiological state which is a normal and adaptive condition, but when stress persists or recurs, the body regularly secretes stress hormones and mobilizes other systems, which gradually can overload the body's energy and damage health.[26,27]

Catecholamines are hormones produced in both the medulla of the adrenal glands and the central nervous system. In addition to having hormonal and neurotransmitter functions, catecholamines also affect the immune system by binding to adrenergic receptors that are expressed on immune cells. Catecholamine signaling in immune cells exhibits a number of effects including cell activation, proliferation and apoptosis. Both innate and adaptive immune cells express adrenergic receptors, especially 2-adrenergic receptors (ADRB2), which enable these cells to respond directly to neurotransmitters, especially norepinephrine, which is secreted by the sympathetic nervous system and the adrenal medulla. Secretion of sympathetic agonists such as norepinephrine and prostaglandin E2 supports T cells to express 2-integrin on their cell surface.

Potential therapy of Oral Lichen Planus

Oral lichen planus can last for several years or even a lifetime. There is no treatment for oral lichen planus. Management is still symptomatic and mostly in the form of topical corticosteroids and can also be systemic. Use of other drugs such as tacrolimus, thalidomide, topical aloe vera, oral curcuminoids and lysopine have been reported. However, the results of the treatment are still questionable**.** Irritating foods, drinks and oral hygiene products (such as mint toothpaste) should be avoided. Maintaining oral hygiene and cleaning teeth and mouth regularly can help reduce plaque formation and gum inflammation with the potential to exacerbate OLP conditions. Pharmacotherapy is indicated when symptoms are severe, persistent and interfere with daily functions (such as brushing teeth and eating). The rationale for administering therapy is based on the pathogenesis of OLP which is an immune-mediated disease associated with T lymphocyte dysfunction and with the implication of cytokines such as TNF-alpha, IFN-gamma, IL-6 and IL-8 for immunosuppressant use. Therefore, corticosteroids are given for the initial management of symptomatic OLP. If topical therapy fails, systemic therapy is then considered.[28]

In stress-induced OLP, the ability to verbalize and process awareness of the problem at hand and the awareness that there are people who care to listen can often lift the patient's burden, tension, anxiety and stress. Operators can improve the quality of care for patients such as through this approach and refer patients with psychological risk factors to psychologists or psychiatrists to evaluate and treat these patients. The reason for the need for referral should be conveyed to the patient carefully to avoid defensiveness from the patient and increase patient cooperation.[18] Topical administration of timolol along with triamcinolone acetonide has also been reported to show significant improvement in lesions both in terms of pain, lesion size and patient quality of life. Timolol is a non-selective propranolol beta-blocker that has an inhibitory effect that can reduce lymphocyte infiltration in cases of OLP. This is related to the role of catecholamines as non-traditional cytokines that can activate immune cells through b-adrenergic receptors on immune cells.[29]

DISCUSSION

Oral lichen planus is an inflammatory condition that can be caused by various factors where stress can increase the accumulation of T lymphocytes at sites that express self-peptides and antigens. The stress response is the body's way of reacting to a problem. Autonomic activity and the resulting increase in the HPA axis play a role in immune mechanisms that control the inflammatory process.[3,13,14]

As a chronic inflammatory disease of the oral mucosa, OLP has the potential to turn into malignancy. Prolonged stress conditions in the host can result in dysregulation of the HPA axis which can trigger increased production of proinflammatory cytokines, as well as over-activation of the immune and inflammatory systems, thus supporting the development of Oral Lichen Planus (OLP).[24,25]

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Management of stress-induced oral lichen planus can be done by avoiding agents that can trigger the release of HSP90 and minimizing the migration of T lymphocytes due to binding of adrenergic receptors with catecholamines. Topical non-selective beta blockers can be adjunctive therapy in symptomatic OLP to reduce pain and lesion size.[3,29]

CONCLUSION

From the narrative review above can be concluded that OLP is a chronic inflammatory condition caused by various factors where stress increases the migration of T lymphocyte cells on the side that expresses self-peptides and antigens through the interaction of immune cells with catecholamines. Topical non-selective beta blockers can be supporting therapy in reducing pain and size of OLP lesions.

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