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Review Article

Oral lichen planus: A review study

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Abstract

Lichen planus (LP) is a chronic inflammatory condition affecting the skin and the mucous membrane. LP is a multifactorial condition and the pathogenesis depends mainly on the evoked cellular immunity. Most cases develop on the oral mucosa. Oral lichen planus (OLP) has several clinical patterns and the symptoms range from no symptoms to aches and burning sensations. The histopathological picture is considered a characteristic feature of OLO. OLP is incurable and the treatment aims to reduce the patient's complaints and enhance the quality of the patient's life. Although there is no uniform protocol for treatment, corticosteroids and adjuvant treatment are commonly used for OLP management. Malignant transformation is suspected in each OLP, despite the type and location of the OLP inside the mouth. Periodic follow up is required. Updating the data about the OLP is always needed to improve the outcomes of management.

Key words
Lichen planus, Oral lichen planus.

Introduction

LP is a chronic inflammatory disease commonly present on the skin and mucous membranes with the possibility of a malignant transformation. It is associated with a T-cell mediated response against epithelial basal cells.[1] Globally, the incidence ranges from 0.1 to 4.0 per 100 people.[2] LP lesions within the oral mucosa are called OLP.[3] Although the lesion microscopic picture is the same, the clinical picture and prognosis of LP differs between the oral mucosa and the skin. OLP diagnosis and treatment requires special consideration in dentistry as this chronic disease has a negative impact on the quality of life and has a potential for malignant transformation.[4] A clinical and histopathological examination are required for OLP diagnosis.[5] Oral lichenoid reaction (OLR) is a term applied when the causative is medications or dental materials. OLR and OLP are share a nearly same clinical manifestations and histopathological features.[6] The purpose of this review was to highlight the most important aspects of OLP, such as epidemiology, pathogenesis, clinical and histopathology features, treatment, as well as prognosis.

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Epidemiology

OLP without skin or other mucous membrane lesions occupied the main portion (more than 75%) of the total LP cases.[7] Previous studies have shown that the incidence of OLP may reach 4% of the total population and that females are more affected by lesions than males.[8] Most cases were found to have appeared from the third decade to the sixth decade, although children with OLP lesions were also reported.[9] Black individuals suffer from OLP less than white individuals.[10]

Etiology

OLP's true cause is unknown, and only a few

risk factors are now known to play a role in its pathogenesis.[11] Since multiple familial cases of OLP have been described, genetic factors may play a role in the disease's development.[12] The association, however, has not been strong. Human leukocyte antigen (HLA) and cytokines with genetic polymorphism have been reported to be associated with LP. Several studies have highlighted interferon-gamma (IFN-ɣ) and Tumor necrosis factor- α (TNF-α) polymorphism in OLP cases. HLADBQ1, HLA-DR9, and HLA-A3 are highly linked to LP cases.[13]

Hepatitis C virus infection

OLP is one of the extra hepatic signs that have been most frequently reported in hepatitis C virus (HCV) patients.[14] The pathogenesis of OLP in HCV patients may have contributed to the HCV viral sequences and/ or HCV-specific T cells being present in the serum of patients and in the oral mucosa. Since not all HCV cases show OLP, genetic predisposition may play a role. In most cases of HCV with OLP, the patient is present with the HLA class II allele HLA-DR6. This might help to explain the unusual regional heterogeneity of the HCV-OLP connection.[15] Interferon and ribavirin therapy, which are used to treat HCV infection, are also proposed to aggravate the OLP.[16]

Psychological status

Discomfort, anxiety, and stress were obvious in most OLP patients.[17] The question is whether these adverse psychological markers are associated with OLP development or come as a consequence after the lesions arise.[18] Previous studies have shown that the drop in psychological status could be associated with the chronicity and prognosis of the disease, a lack of knowledge and faire from malignant potential.[19]

Thyroid disorders

The outcomes of the studies on the association between OLP and thyroid gland disorder showed a positive correlation between the two diseases.[20] However, other studies found no connection between thyroid disorders and the development of LP lesions.[21] Hypothyroidism and Hashimoto's thyroiditis are the conditions most often noted to be associated with OLP.[22]

Graft versus host disease

Hematological cell transplantation (HCT) is one of the approaches to treating hematological disorders. 15,000 to 25,000 HCTs have been conducted per year. Graft versus host disease (GVHD) is a fatal complication found in 40-70% of total HCT, the donor cells include T cells (CD8 and CD4).[23] Unfortunately, these lymphocytes start an immune response since the tissue of recipient patients is marked as foreign material.[24] Clinically, GVHD is associated with multiple immune-mediated conditions and is classified into acute and chronic forms. OLP appears in more than 75% of GVHD.[25]

Vitamins

In a previous study, vitamin A, B12, C, and C deficiency were observed in significant correlation with OLP.[26] The role of Vitamin D in OLP pathogenesis is unclear and needs further investigation. The role of vitamin D in enhancing the work of lymphocytes was established and studies were successful in highlighting the association between vitamin D deficiency and OLP.[27] Another study found individuals with vitamin D supplements were at greater risk of developing OLP than those without a recoded intake of vitamin supplements.[28] Having a low level of vitamin D is a sign that you should take a supplement, so it could be that vitamin D deficiency is a risk

factor for OLP.[8]

Dental products

Hypersensitivity reaction type IV has been documented with various dental products such as amalgam, composite, and materials involved in fabricating removable dentures.[29] The allergy reaction occurs due to alteration in basal cell epithelial cells after interaction of dental products with deep epithelial layers. The immune response may have appeared clinically and histopathologically as OLP and was called OLR.[30] A skin patch test can be used to distinguish between de nova OLP and OLR, with a positive test indicating OLR. The negative results should not exclude OLR, especially if the lesions are found near fillings or any dental prosthesis. The removal or replacement of the dental products, followed by the lesion disappearance, confirms the OLR.[31]

Medications

Many medications are reported to induce OLR. Several studies showed that anti-hypertensive, non-steroidal anti-inflammatory drugs (NSAIDs), and antiretroviral medications were associated with OLR development.[5] Other drugs have been shown to have been correlated with OLR through single case reports. Part of OLR diagnosis and treatment depends on the withdrawal of the causative drugs.[32]

Pathogenesis

The apoptosis of basal epithelial cells and clinicohistopathological findings of the OLP may have contributed to one or several mechanisms. Cellular immunity is a mainstay mechanism in the pathogenesis of OLP.[33] The histopathological finding showed that the OLP lesion included a band of T cells, mainly cytotoxic (CD8) T cells close to the destruction epithelial cells, and this picture is not found in normal tissue.[34]

Cellular immunity

Activation of T cells

The key to OLP induction is epithelial cells with altered or extrinsic antigens.[35] The extrinsic antigens are taken up by Langerhans cells, which then travel to the lymph nodes under the influence of TNF-α released by epithelial and inflammatory cells.[36] In the lymph node, the activation and recruitment of helper (CD4) T cells will occur in response to the presenting antigen through Langerhans cells' major histocompatibility type II (MHC II). In addition, the MHC II of the epithelial cells is also involved in CD4 T cell activation.[37] According to the presumed receptor interaction between CD4 and CD8 T cells as well as the mediators released from CD4 T cells, INF–γ and IL-2, will lead to the activation of CD8 T cells.[38] The direct activation of CD8 T cells by epithelial cells is well documented. The intrinsic foreign antigen, accumulation of heat shock proteins (HSP), and the malignant transformation makes epithelial cells a target for immune cells, especially CD8 T cells.[39] Even though HSP plays a protective role, when this protein is too high, it may be an autoantigen and cause an immune response.[40]

Attracting the pathogenic lymphocytes

The migration of lymphocytes from the vascular network to the lymphocytes at the epithelium–connective tissue interface has been thought to be caused by the cytokine-mediated overproduction of adhesion molecules on endothelial cells and the production of receptor molecules by circulating lymphocytes.[41] The vascular adhesion molecules (VAM) of the endothelial cells of the underlying connective

tissue include CD62E, CD54, and CD106, and the receptors of the lymphocyte, CD11a, act reciprocally with VAM. The migration of T cells across the basement membrane depends on the release of matrix metalloproteinases (MMPs), MMP-1 and MMP-7, which result in BM disruption.[33,42,43] Furthermore, the presence of mast cells in a high proportion in the lesional area aids lymphocytes in crossing the BM. Mast cell degranulation promotes T cell transmigration and MMP-9 synthesis via degranulation molecules such as TNF-α and chymase.[44]

The apoptosis mechanism

Interaction between Fas molecules and their Fas-ligands, which are found on cytotoxic T cells and epithelial cells, is one of the apoptosis mechanisms of basal epithelial cells. This interaction leads to the induction of a caspase cascade and cell death.[45] The apoptosis action is also documented to be triggered by T cells but by different mechanisms. The cytotoxic lymphocyte secretes two molecules: perforin, which causes holes in the walls of epithelial cells, and granzyme B, which has the ability to break down cellular proteins.[46] The presence of TNF can contribute to cell death because this mediator stimulates the activity of cytotoxic lymphocytes while also having cytotoxic effects on epithelial cells.[47]

Basement membrane disruption

The relationship between the epithelial cells and the basement membrane is a reciprocal relationship, and each of them is required to maintain the integrity of the other.[42,48] The activated and required T cells secrete RANTES. This chemical agent aids in recruitment and degranulation of the mast cells. The degranulation materials include MMPs and TNF, which, as we mentioned before, are involved in BM disruption and attract more T cells.[49] These cyclic events were pinpointed as the cause of the chronic nature of OLP.[50]

Humoral immunity

A number of studies are being undertaken to better understand the role of autoantibodies. Antibodies against smooth muscle and desmoglein (DSG) have been found to be linked to the presence of the LP.[51] Further studies still required to established the role of the humoral immunity in LP pathogenesis.

Clinical features

OLP can be raised at any site within the oral cavity. OLP mostly developed in the buccal mucosa and the lesions were on both sides and symmetrical.[52] OLR could be differentiated from OLP; the lesions of the former appeared unilateral rather than bilateral and located near dental filling or at area when the chemical agent usually contacts such as cinnamon gum.[53] The tongue, gingiva, and labial mucosa are also documented as common sites for OLP, followed by the buccal mucosa. OLP is uncommonly diagnosed on the mouth floor and the palate, as well as the upper lip.[54]

The reticular forms of OLP form the most common presentation of OLP, mostly found in the buccal mucosa of the tongue.[5] The clinical picture of the reticular form consists of a network of fine keratotic lines called Wickham's striae, enclosing an area of papules with over keratin. Some authors prefer to describe this form as reticular-papular LP. The network could have boundaries of erythematous areas blending into the normal mucosa.[24] The redness areas represent epithelial atrophy.[55] In general, the reticular form is asymptomatic, but in the case of tongue involvement, the patient may complain of a burning sensation.[56]

OLP is represented as an atrophic erythematous lesion with central erosion or ulcer. A white radiating line may have appeared around the atrophic lesion. Previous studies showed that this form of OLP is not common like the reticular form, but because the patient complains of burning sensations and impairment in food intake, therefore, the medical records showed OLP with atrophic and erosive/ ulcerative are the major cases registered.[57] OLP rarely may appeared as bullae (bullous form) with the tendency to rapture, it will give the erosive/ulcerative form. Desquamative gingivitis is indicated when the atrophic and erosive/ ulcerative OLP are confined to the gingiva.[58] Clinically, other immune-mediated conditions such as mucous membrane pemphigoid (MMP) and mucous pemphigus vulgaris (m PV) may appear as ulceration and have relapses and remissions periods like OLP, therefore direct immune fluorescent (DIF) may be needed to confirm the diagnosis.[59]

People who have OLP with plaque form look like leukoplakia and frictional keratosis.[60] It usually shows up on the tongue and the buccal mucosa. The plaque lesions are present as homogeneous, elevated, hyperkeratotic areas with whitish color. The presence of both plaque and reticular form may provide facilities to confirm the OLP diagnosis rather than other conditions.[61] A significant correlation was reported between the plaque form of OLP and smoking. The suggestion was that smoking induces over-keratin production.[62]

The multiple small, pinpoint, and white papules indicate the papular form of OLP. It is a rare presentation since the small sized lesions are difficult to diagnose and, with progression of disease, some of the papules fuse with each other to give a striae picture of the reticular form.[63]

Microscopic picture

The biopsy should avoid the ulcerative part of the lesion because of the absence of the epithelial cells that are required for diagnosis.[64] The microscopic examination revealed that hyperkeratosis had progressed to involve half of the epithelial full thickness. The keratin may be either parakeratin or orthokeratin. Some cases showed both types of keratin. The cells of the basal layer of the epithelium showed degeneration to produce eosinophilic globules called Civatte bodies (colloid, cytoid, hyaline).[65]

The epithelium-connective tissue contact may show an elongated epithelium rete-ridge described as a tooth-saw.[4] At the underlying CT, just underneath the epithelium, there is a band of infiltrated lymphocytes, predominately T cells. Investigated for candida hyphae is needed, as several studies reported OLP cases with superimposed candida infection, which may have an effect on the prognosis.[66]

If dysplastic change is found at the basal layer, the term "lichenoid dysplasia" is preferred to be used instead of "OLP." The presence of the dysplasia could be a mark of the malignancy potential of OLP.[67]

Infiltration of lymphocytes high into the epithelium, as well as more extensive liquefactive degeneration of basal cells, are distinguishing hallmarks of OLR. A mixed infiltration of lymphocytes, plasma cells, and eosinophils, as well as perivascular chronic inflammation, are more common in lichenoid drug reactions than in OLP.[68]

Treatment

General principles

LP is an incurable condition, and the treatment

offered is to treat the symptoms associated with this disease.[69] A medical and dental history are required. Healing due to withdrawal medications, removal or replacement of therapeutic dental materials inside the oral cavity comes with ORL.[70] The family history is also important if a similar condition is found among the relatives.[71]

The type and dose of medication depend on the age and general health of the patient and also on the type of the lesion and its extension within the oral cavity.[72]

Reticular lesions are usually asymptomatic and no need for treatment. The patient only needs to be reassured and be followed up with periodic visits, which may be once a year. Follow-up is done to see if the pathological lesion changes in a suspicious way and also to see if there is a superimposed candida infection.[73]

Individuals with atrophic or erosive/ulcerative OLP forms complain of pain and burning sensations that affect food intake. Corticosteroids topical or systemic, are the first choice in the treatment.[48,74]

Topical treatments

Corticosteroids with topical application are widely used for OLP treatment.[75] Examples of CS are clobetasol propionate, fluocinonide, betamethasone, and triamcinolone acetonide.[76] There is no strong evidence that states that any drug from the aforementioned group has a greater effect than the rest.[77]

They come as mouthwash, ointment, spry, or orabase paste.[78] Application of mouthwash is suggested when the lesions are widely spread within the oral cavity and the application of the ointment is somewhat difficult.[79] Orabase paste is used for wet areas inside the body, but not for the lip vermillion border.[80]

Topical corticosteroids are well tolerated by most patients. Nausea, bad taste, mucosal atrophy, dryness, and sore throat are some of the side effects that have been observed. Candida infection is also reported as a side effect of topical CS use. Local antifungal agents such as nystatin and instructing the patient not to wear dentures while sleeping will help to prevent or reduce oral candidiasis.[81] Previous research has shown that the systemic absorption of topical corticosteroids is so low that it does not have clinical significance.[82] At the same time, adrenal insufficiency was found in some OLP patients who had used topical CS for a long time.[83]

The CS contraindication and no response to topical CS, as well as significant candida growth, required alternative medications such as Tacrolimus and cyclosporine.[84] Tacrolimus is an immunosuppressant drug used as a replacement for CS. The effectiveness of Tacrolimus is almost similar to that of CS in the treatment of OLP. The localized side effect is a transient burning sensation. The experimental study on mice shows that tacrolimus can cause squamous cell carcinoma, so the deal with this drug isn't clear.[42]

Cyclosporine is less effective than CS and tacrolimus. Although the high concentration of blood cyclosporine was not reported, the major side effect is kidney dysfunction due to chronic use. A transient burning sensation is also reported with topical cyclosporine application.[85] The financial aspect makes the use of cyclosporine limited to a small number of patients.[86]

Topical retinoids (synthetic vitamin A) are documented for OLP therapy. Authers stated that pain and inflammatory reactions could be retinoid side effects. The effectiveness of

retinoids is lower than that of CS, so the recommendation was to use it in combination with CS.[87]

Systemic treatments

In many OLP cases, topical CS was successful in achieving symptom-free status. Systemic CSs, for example, prednisolone, are justified for aggressive cases that do not respond to topical treatment.[88] The effective comparisons between topical and systemic CS varied between the previous studies. Studies showed systemic CS is more effective than topical CS, but other studies showed no difference between them.[89] The adverse side effects of systemic CS make them not the first choice for treatment and come clinicians preserve the systemic way for mucocutenous LP. Short duration of treatment and the periodic follow-up of the patient are mandatory during the reviving of the systemic CS. The most common side effects include gastrointestinal disturbances, mood changes, polyuria, fatigue, tremors, and changes in blood pressure and glucose concentrations. In some investigations, systemic mycophenolate mofetil, azathioprine, and methotrexat were also demonstrated to be useful in the management of persistent erosive OLP.[90]

Surgical intervention

Cryosurgery and laser application (carbon dioxide (CO_2) laser and ND: YAG laser) are suggested by some clinicians for OLP management, especially to remove the dysplastic tissue.[91] The choice of these two methods should not be a priority since the elimination of the cause is an unknown and recurrence will occur. Generally, the surgical approach is not applicable to atrophic and ulcerative/erosive OLP. The lesions in plaque form could be more suitable for surgical intervention.[92]

Prognosis

OLP shows remission and flare-up periods. This could be associated with the psychological status of the patients. Periodic follow-up once to six times per year is needed to reevaluate the effectiveness and drawbacks of the selected treatment. OLP has been classified as a premalignant disorder, especially when it is associated with candida infection.[93] Unfortunately, the clinical and histopathological features did not raise the alarm for malignancy development from preexisting OLP. Squamous cell carcinoma is the most common cancer associated with OLP.[23] First of all, the patient should be educated about the prognosis and that additional biopsy may be needed if oral cancer is suspected.[94]

Conclusion

OLP needed further and advanced studies to establish the definite etiological factor, exact mechanism of the disease, and appropriate treatment with minimum side effect. Advance and new investigations are required to detect the dysplastic and malignant features as early as possible.

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