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Review Article

INTEGRATING IMMUNOLOGICAL INSIGHTS INTO THE ETIOPATHOGENESIS WITH CLINICAL REPRESENTATION AND FUTURE DIRECTIONS FOR ORAL LICHEN PLANUS

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ABSTRACT

Oral Lichen Planus (OLP) is an immune-mediated, chronic mucosal condition that has been associated with malignant transformation in certain cases. In this review, we will explore more about the etiopathogenesis of OLP, including immunological parameters, genetic aspects, and environmental influences, which are the major important reasons for the development of lesions in the oral cavity. A key player in OLP pathogenesis is the T cell-mediated autoimmune attack, which leads to CD8+ cytotoxic T lymphocyte recruitment and basal keratinocyte apoptosis. OLP risk is also associated with genetic predisposition, e.g., certain Human Leukocyte Antigen (HLA) alleles and cytokine gene polymorphisms. Environmental aspects: Factors from the environment, such as psychological stress and some medications are also involved in disease worsening. This interplay creates a spectrum of immunological milieu, resulting in clinical and histopathological features. This review also evaluates the clinical presentation, histopathologic characteristics, and diagnostic methods of OLP as well as contemporary management options. In conclusion, we also discuss the severity, indication, and prevention of OLP.

Keywords: Autoimmune mucosal condition, corticosteroid therapy, histopathological features, malignant transformation potential, oral lichen planus, T-cell-mediated pathogenesis.

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INTRODUCTION

Oral lichen planus (OLP) is taken to a chronic immune-mediated condition affecting mucous membranes in the oral cavity, hence also bearing a wide range of clinical indications. It falls under the category of lichen planus, whereby it affects the mucocutaneous sites such as the skin, mucous membrane, scalp, and nails [1,2]. OLP is also called a precursor of malignancy by the World Health Organization, with an incidence rate of over 0.05–0.10% of the population because of its slight development and also because it has a significant risk of malignant change [2]. OLP affects the female population more than it does with males, and researchers have shown that it even has a higher prevalence in certain populations [3]. The mean age of onset is generally reported to be between 50 and 55 years of age.

That does not mean that OLP has only alone led to malignant transformation; its further development toward the erosive nature will have the possibility of transformation into a malignant cause [4]. This erosive nature is often associated with Lichenoid Drug Eruptions (LDE) in the oral mucosa. For example, a certain class of drugs such as anti-hypertensive, nonsteroidal anti-inflammatory drugs, and hypoglycemic drugs, has been responsible for the development of LDE [5].

PubMed and other specialized databases such as Elsevier and Cambridge were used to search with the help of terms such as "Oral lichen planus," "Autoimmune mucosal condition," and "T-cell-mediated pathogenesis" for selecting the publications that are included in this review. More options include online published journals like The Lancet Respiratory Medicine, Medscape, Stat Pearls, Springer, and Wiley data from internet sources.

ETIOPATHOGENESIS OF OLP

While a number of studies have been conducted on the pathogenesis of OLP, its exact etiology has not yet been unraveled. On the basis of the understanding hitherto available related to this pathology, it is being attributed to the interplay of such factors as immunology, genetics, and environment, which designates OLP as a multi-factorial disease [6]. Central to the pathogenesis of OLP is a T-cell-mediated autoimmune response in which cytotoxic T cells (CD8+) become activated by some unidentified antigen presented by basal keratinocytes. It provides an activation signal for basal keratinocyte apoptosis mediated by numerous mechanisms, which include Fas-FasL interactions and granzyme B release [7]. This inflammatory process is further amplified through the involvement of the pro-inflammatory cytokines involved in T-cell recruitment and perpetuation of the inflammatory response. Other studies have also reported on circulating auto-antibodies in OLP patients, supporting further its autoimmune nature [8,9].

Genetic predisposition has been an essential factor in the susceptibility and severity of OLP. The association of certain Human Leukocyte Antigen (HLA) alleles, such as HLA-DR6, HLA-DQA1*0501, and HLA-DQB1*0201, with an increased risk of OLP has been identified in various populations [10]. Other genetic polymorphisms to cytokine genes, including Tumour Necrosis Factor (TNF-α) and interferon gamma,and immune-related genes, have also been recognized as risk genes for OLP. Although rare, familial cases of OLP have also been described, thus suggesting a genetic component of the disease. Important environmental triggers in the initiation and exacerbation of OLP are noted [11]. There is an unequivocal association of psychological stress with the onset and flaring-up of OLP. This can be mediated through complex neuroendocrine-immune interactions. Thus, lichenoid reactions are clinically indistinguishable from OLP, which were caused by certain medications such as Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), beta-blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, dental materials, and associated contact hypersensitivity in some cases of OLP [12,13].

Such mechanisms may involve, for example, the potential role of viral infections like hepatitis C virus and human papillomavirus in the pathogenesis of OLP, which remains still under considerable debate.

The interplay of these factors leads to a complex immunological environment that finally results in the clinical and histopathological features of OLP [14,75]. T-cells, particularly CD8+ cytotoxic T-cells, accumulate in the sub-epithelial region and initiate apoptosis of basal keratinocytes through the action of several molecules, including perforin, granzyme B, and Fas ligand [15,79].

This finally results in the weakening of this epithelial-connective tissue interface, which is clinically manifest as Wickham's striae. During this period of activation, there is a release of cytokines and chemokines by these activated T-cells and keratinocytes, which may perpetuate the inflammatory response and thus contribute to chronicity in OLP. The role of Tregs in the pathogenesis of OLP has also been explored; some studies have found that there is a dysregulation in the function of Tregs participating in persistent inflammation [16] (Fig. 1).

It is these intricate mechanisms of pathogenesis that must be further elucidated in terms of targeted treatment modalities that would advantage patients with OLP and enhance their quality of life. This could be in the way of determining the precise antigens that initiate the autoimmune response, the role or contribution of epigenetic factors to OLP susceptibility, and the creation of novel therapeutic strategies able to modulate immune responses effectively with fewer side effects [80].

CLINICAL PRESENTATION OF OLP

OLP is manifested in several clinical forms, lots of symptoms, and certain localization or distribution inside the oral cavity. In general, reticular, erosive, atrophic, plaque-like, bullous, and papular OLP represent the more common clinical forms. One of the most typical clinical forms, though not comprehensive, is reticular OLP [17]. It usually manifests as white, lace-like striae Wickham's striae on the oral mucosa; in this form, it usually remains asymptomatic and is discovered during the process of routine dental examination.

Erosive OLP presents as erythematous areas with central ulcerations and fine, white radiating striae around them. It is usually painful and erosive in nature. Atrophic OLP is characterized by scattered red regions of mucosal thinning, usually with white striae surrounding the area. This can be uncomfortable and elicit burning feelings [18]. The plaque-like type of OLP appears like leukoplakia with white, slightly raised plaques, primarily on the dorsum of the tongue or buccal mucosa. The rare bullous form is characterized by fluid-filled vesicles or bullae that rupture soon to leave painful erosions. In papular OLP, there are small white papules that may coalesce to form larger lesions [19] (Fig. 2).

Symptoms and signs of OLP have wide variations between the different forms it takes clinically and the extent of involvement. Pain and discomfort are particularly associated with erosive and atrophic forms. The character of pain varies from mild sensitivity to severe pain that may hamper eating and speaking. Common complaints of burning sensation in atrophic and erosive forms include exacerbation by spicy or acidic foods [20].

Bleeding is common in erosive forms at the time of oral hygiene procedures or during eating. The patient may report changes in mucosal texture and characteristically roughness of the involved mucosa. Some patients also complain of taste alteration, mostly when the lesion involves the tongue [21,72]. It is worth realizing that the intensity of symptoms could greatly affect the quality of life of a patient and necessitate proper management.

OLP can be associated with any intra-oral site, which is known to manifest with site-specific distribution patterns. The most common site involved is buccal mucosa, which presents bilaterally. The involvement of the tongue generally occurs in the dorsum and the lateral borders. Gingival involvement, usually in the form of desquamative gingivitis, can be noted in both attached and marginal gingiva [22]. Much less commonly, labial mucosa is also involved, but sometimes it is.

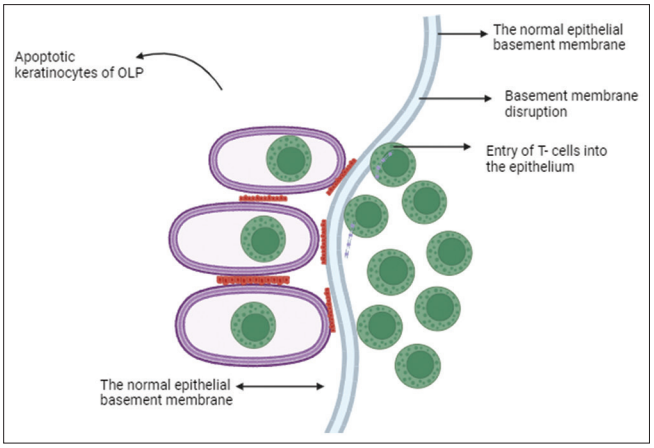

Fig. 1: Migration of T cells into the oral epithelium after the expression antigen in the keratinocytes. When the antigen binds to the keratinocytes after the activation of the T cell

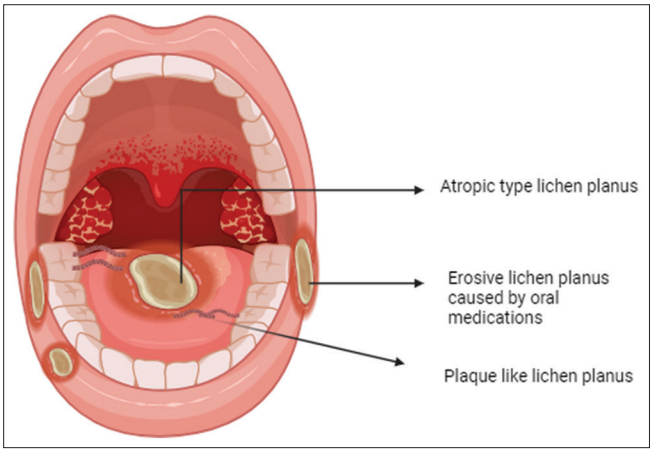

Fig. 2: Clinical manifestation of oral lichen planus

The palate and the floor of the mouth are the least common sites affected. The characteristic pattern of distribution that is often bilateral and symmetric may help in the clinical diagnosis and in distinguishing it from other conditions of the oral mucosa [23,24]. Knowledge about these clinical forms, symptoms, and patterns of distribution can help come up with an accurate diagnosis, the institution of appropriate management, and proper monitoring with reference to complications, including the rare but significant risk of malignant transformation [25].

THE HISTOPATHOLOGICAL FEATURES

The histopathological features of OLP are characteristic and form the basis for an accurate diagnosis. They reflect the immunological events underlying the process and may assist in differential diagnosis from other similar-appearing lesions. The epithelium in OLP usually presents hyperkeratosis, which represents a thickening of the stratum corneum that is usually either orthokeratotic or parakeratotic [26].

This often combines with saw-tooth rete ridges, in which the epithelial projections to the underlying connective tissue become elongated and pointed; it is particularly noticeable in plaque-like OLP lesions. All this goes to a key feature: liquefaction degeneration of the basal cell layer, the basal keratinocytes undergoing hydropic degeneration, and to weakening of the epithelial-connective tissue interface [27]. Such a weakening can lead to the creation of Max Joseph spaces, the focal regions of epithelium separation from connective tissue.

Perhaps the most typical feature of OLP is the existence of a dense, band-like lymphocytic infiltrate in the superficial lamina propria. This infiltrate is predominantly made up of T lymphocytes with an abundance of CD8+ cytotoxic T-cells. The infiltrate''s intensity and composition reflect the cell-mediated immune response central to the pathogenesis of OLP. Civatte bodies can be seen in the lower layers of the epithelium and upper connective tissue [28,29]. These represent degenerated keratinocytes appearing as homogeneous eosinophilic globules and correspond to apoptotic cells, the end result of immune-mediated damage to the epithelium [30].

These, therefore, have to be correlated to the clinical findings and sometimes supplemented by immune-fluorescence studies to help in making a definite diagnosis, more particularly in the differentiation of OLP from reactions due to lichenoid and other conditions that may occasionally show some histological similarities [31,76]. The proper interpretation of these histopathological features in light of the clinical data is of paramount importance in the proper diagnosis and management of OLP.

DIAGNOSIS OF OLP

The diagnosis of OLP is a fairly complex process, with the crucial diagnosis being the clinical examination. A good clinical examination is important in showing the typical features that characterize OLP and helps in distinguishing it from other conditions that affect the oral mucosa [32]. Several features are looked at in the process of clinical examination, and each is seen to play a vital role in forming an accurate diagnosis. The clinical examination relies on inspection, a careful inspection of the entire oral cavity with a view to the distribution, symmetry, and morphology of the lesions. Lesions are often bilateral and symmetrical in OLP, with many demonstrating the characteristic Wickham's striaea reticular network of thin white lines [33]. The location of the lesions has to be carefully noted.

The lesions may have variable forms: from the classic reticular form to erosive, atrophic, or plaque-like variants. Variables in color, size, and signs of ulceration or erythema should also be noted. The examination should continue with the palpation to further describe the texture and consistency of the lesions. Gently probing the affected areas provides an automatic estimation of the degree of firmness or softness. In most cases, OLP is nonindurated, which further helps to rule out malignant lesions [34,35]. The examiner should also note the tenderness or pain that the patient is experiencing upon palpation, which may be suggestive of the erosive or ulcerative forms of OLP.

Description of clinical findings is critical both for the initial diagnosis and long-term monitoring. This signifies that the health professional will give written descriptions of the lesions regarding their appearance, localization, and symptoms associated with them [36]. Photographic documentation can be a powerful tool since it shows a precise comparison over time and allows for communication with other health professionals or pathologists. The techniques in photography should be standardized for the accuracy of monitoring [37].

An extensive medical history is an important component of the diagnostic process. Aspects involving the review of the patient's overall health should include systemic conditions and medications, as well as potential environmental or lifestyle contributions that could be exacerbating to the oral lesions. Particular attention should be given to medications that are associated with lichenoid reactions, including many used in the treatment of hypertension, oral hypoglycemic, and nonsteroidal anti-inflammatory drugs [38,69]. Also to be noted would be the history of allergic conditions, recent dental procedures, and habits like tobacco use and alcohol consumption. This multifaceted approach in clinical examination becomes the basis of the diagnosis of OLP; clinical examination needs to be correlated with the histopathologic analysis done to confirm the diagnosis of OLP and rule out other conditions that mimic it [68]. The clinical examination guides, too, the selection of the most appropriate site for biopsy whenever such a measure is judged necessary [39]. Follow-up examinations are undeniably important to monitor the evolution of OLP and detect eventual signs of malignancy, which is a rare but severe complication of the disease.

MANAGEMENT OF OLP

OLP management is based on a multi-disciplinary approach oriented to alleviating symptoms and monitoring this chronic disease, which has no definite cure. The modalities of treatment are individualized after considering the severity of symptoms, the extent of oral involvement, and associated systemic conditions. Topical corticosteroids form the mainstay of first-line treatment for most cases of OLP [40]. The more potent formulations, such as clobetasol propionate 0.05% or fluocinonide 0.05%, are used for moderate to severe forms, while for the mild forms, a moderate-potency agent like triamcinolone acetonide 0.1% would be more than adequate [41]. Several application techniques, such as custom trays, adhesive pastes, or mouthwashes, may improve drug delivery and retention at the active site, enhancing the treatment's effectiveness. In patients where corticosteroids either are not effective or are contraindicated, there is evidence for the use of topical calcineurin inhibitors, such as tacrolimus 0.1% ointment and pimecrolimus 1% cream, as second-line therapy [42].

However, systemic treatments may be necessary in severe or refractory cases. Brief intermittent courses of oral corticosteroids, usually in the form of prednisone, are helpful in acute flare-ups or in those with extensive lesions [43]. In those cases in which the disease responds poorly to the usual topical and intralesional corticosteroid treatments, systemic immunosuppressants such as cyclosporine, mycophenolate mofetil, or azathioprine may be helpful; however, these drugs need to be monitored with concern for potential side effects [44].

During the past years, new and adjuvant therapies have been investigated in the management of OLP. Low-level laser treatment has been very promising in the management of symptoms and hastening healing. In severe diseases, biologics like rituximab have been tried, although evidence of their effectiveness is still very minimal [45,46] (Table 1). A few natural remedies, such as aloe vera gel and curcumin, showed the potential to alleviate symptoms, thus offering some alternatives for patients seeking complementary approaches.

Symptomatic relief is key to helping OLP patients improve their quality of life [67,71]. Topical anesthetics may help to alleviate the pain, mainly in the erosive or ulcerative forms of the disease. Keeping the mouth clean prevents further infection and minimizes discomfort. Modifications to the diet may also be of help by avoiding spicy, acidic, or abrasive meals that reduce painful symptoms [47,48].

OLP is a chronic process, and given its potential to be premalignant, follow-up, and tracking are integral to its management. This allows for periodic clinical examinations, probably every 3–6 months, or more often in at-risk cases, in order to enable the early detection of any alteration in lesion appearance or symptomatology [56]. Of core relevance is the role of educating patients on self-examination and reporting techniques. In other words, vigilance is the key to the long-term management of OLP; any unusual alterations or non-healing areas need to be biopsied to screen for malignancy [57].

In many cases, however, the management of OLP is truly multidisciplinary and needs the involvement of oral medicine specialists, dermatologists, and, sometimes, rheumatologists or immunologists. Although treatment success is most often defined by symptomatic relief and a decrease in clinical signs of inflammation, it is not necessarily defined by the complete resolution of lesions [58]. Proper education of the patients and long-term follow-up as a part of good care are needed due to the chronic nature of OLP and the small but important risk for malignant change.

Table 1: Administration and First-line treatment for the expression profiles in the association OLP

Management approach	Description	References
Topical corticosteroids	First-line treatment for symptomatic OLP. Examples: clobetasol, fluocinonide, triamcinolone Applied as gels, ointments, or mouth rinses	[49,73,74]
Systemic corticosteroids	Used for severe or widespread OLP Short courses of prednisone or prednisolone Reserved for cases unresponsive to topical treatment.	[50]
Topical calcineurin inhibitors	Second-line treatment Tacrolimus or pimecrolimus Used when corticosteroids are contraindicated or ineffective.	[51]
Retinoids	Topical or systemic May help in cases resistant to other treatments. Examples: tretinoin, isotretinoin	[52]
Immunosuppressants	For severe, recalcitrant cases Examples: cyclosporine, mycophenolate mofetil Used with caution due to potential side effects	[53,70]
Phototherapy	PUVA (Psoralen+UVA) therapy Low-level laser therapy May help reduce inflammation and pain	[54]
Symptomatic treatment	Analgesics for pain relief Anesthetic mouthwashes Avoiding spicy, acidic, or rough foods	[55,66]

FUTURE RESEARCH ON OLP

Research in the area of OLP is quickly moving on several fronts [65]. Investigation of novel treatments, especially biologics targeting definite components of the immune system, is underway [59]. These include TNF-α inhibitors such as etanercept and adalimumab for recalcitrant cases, anti-CD20 therapy like rituximab for severe OLP, and Janus Kinase (JAK) inhibitors like tofacitinib, which target the JAK-STAT (Janus Kinase - Signal Transducers and Activators of Transcription) pathway [60].

Genetic research in OLP is going on, searching for markers of a personalized treatment approach by studying the HLA associations and microRNA expression profiles in OLP patients. The relation of OLP with systemic diseases such as cardiovascular diseases and metabolic syndrome is under research [64]. As malignant transformation in OLP is possible, research is going on to find reliable biomarkers for its early detection and understanding of risk factors [61]. Finally, new diagnostic techniques are being evolved, including optical coherence tomography for noninvasive imaging and the use of salivary biomarkers in diagnosis and monitoring. Therefore, such manifold research directions might be able to improve understanding of pathogenesis, enhancing diagnostic accuracy and resulting in more effective and targeted treatments against this chronic inflammatory condition [62].

SUMMARY

OLP is an inflammatory disorder that is thought to be autoimmune, mediated primarily by T cells, particularly involving the activity of CD8+ cytotoxic T lymphocytes in targeting and inducing apoptosis in basal keratinocyte [63]. Males are comparatively less affected; females have more predisposition where the disease usually initiates with the genetic markers as specific HLA alleles or cytokine gene polymorphisms. OLP displays clinical presentations ranging from reticular, and erosive to atrophic, and bullous forms. The most affected sites are usually the buccal mucosa with specific bilateral and symmetry lesions of Wickham's striae [3,2]. The disorder's histopathological features include epithelial hyperkeratosis, saw-tooth rete ridges, liquefaction of the basal cell layer, and the presence of dense lymphocytic infiltrate in the superficial lamina propria, with Civatte bodies representing apoptotic keratinocytes [23,28]. At OLP, the treatment is directed mainly against the symptoms. The topical corticosteroids are the first-line treatment. Other therapies include systemic corticosteroids, topical calcineurin inhibitors, and new-age immunosuppressive and biological therapies [60]. This condition has one of the greatest ethical implications, leading to malignant transformation requiring considerable long-term follow-up [77,79].

CONCLUSION

OLP is a serious condition characterized by chronic inflammation that causes high morbidity to the affected patients. It could be of multifactorial etiology, including genetic, immunological, and environmental factors. Symptomatic control and prevention of complications can be primarily through management with topical corticosteroids. OLP is generally considered a benign lesion; nevertheless, its potential to undergo malignant transformation justifies long-term follow-up. This justifies further research into the pathogenesis and development of more targeted therapies for this rather challenging condition.

AUTHOR'S CONTRIBUTIONS

Praveen M: Literature review, Data curation, Writing-original draft, and Evaluation; Gurubaran S: Literature review, Data curation, and Writing-original draft; Sanjai Rajagopal: Writing-original draft, Conceptualization, Critical Evaluation; Nikam Kshitija Dilip: Writing-original draft, Conceptualization, Critical Evaluation; Kousalya S: Review and editing, Supervision, Evaluation, Visualization.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL STATEMENT

Nil.

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