Review Article

Oral Lichen Planus or Oral Lichenoid Reaction? A Literature Review

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Abstract

Background and Aim: Oral lichen planus (OLP) is a chronic, inflammatory, T-cell-mediated autoimmune oral mucosal disease. Oral lichenoid lesions develop as a type IV hypersensitivity reaction. Both of these entities are potential precancerous conditions; this adds to their clinical significance. The purpose of this literature review was to detect the similarities and the differences of these lesions to enhance the information of colleagues in managing these groups of patients.

Materials and Methods: For this review, we searched Cochrane, Medline, and Embase databases from January 1990 to the end of October 2018. A total of 96 published papers, including review papers, case reports, cohort studies, case-control studies, and meta-analysis studies, were included and analyzed.

Results: OLP and oral lichenoid reactions are two distinct diseases. They can be clinically similar but they have different etiologic factors. A histopathological study is necessary to differentiate them.

Conclusion: The definitive diagnosis of these conditions is extremely important given their potentially premalignant nature. A timely diagnosis probably results in proper management. Based on the present research, the final differentiation between OLP and oral Lichenoid reactions relies on both clinical and histopathological manifestations according to the modified World Health Organization (WHO) criteria.

Key Words: Oral Lichen Planus, Oral Lichenoid Reactions, Oral Lichenoid Lesions

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Introduction

Oral lichen planus (OLP) is a common chronic and recurrent immunologic inflammatory mucocutaneous disorder with unspecified etiology [1-3]. Recent data have attributed the etiopathogenesis to cell-mediated immune responses [4]. In contrast, lichenoid reactions are lesions with known etiology that may be clinically and histologically very similar to LP; this makes it difficult to differentiate these two entities [5-7].

LP was first described by Erasmus Wilson in 1869 and was named according to its clinical manifestations that are similar to those of Lichens [8,9]. In 1907, Lieberthal characterized the OLP manifestations in American Literature for the first time [10].

In 1929, lichenoid reactions were attributed to OLP [11]. Lichenoid drug eruptions (LDE) can be considered a variant of LP; many cases, associated with prophylactic antimalarial drugs, were diagnosed during World War II [12]. In 1971, drug-induced lichenoid lesions were comprehensively defined by Almeyda and Levantine [13]. In 1973, Pinkus carried out the first

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microscopic description of lichenoid reactions [8,14]. In 1982, Finne used the term OLR (oral lichenoid reaction) in the clinical description of lesions that are non-differentiable from OLP [8,15]. In 1985, Krutchkoff and Eisenberg proposed pathologic classification systems of OLP and OLL (oral lichenoid lesion) [16]. In 1986, Lind et al used the term LR (lichenoid reaction) for clinical lesions related to amalgam restorations, which clinically established the causal relationship [14].

Unlike OLP, which has a single title, lichenoid reactions have been listed with different terms in the review of articles based on various etiopathogeneses according to the frequency of repetition, as follows:

OLR (Oral Lichenoid Reaction) [5,11,14,15,17-26].

OLL (Oral Lichenoid Lesions) [6,8,15,16,22,23,25-27].

OLDR (Oral Lichenoid Drug Reaction) [5,22,23,28].

OLCR (Oral Lichenoid Contact Reaction) [22].

OLTR (Oral Lichenoid Tissue Reaction) [25,27].

LDE (Lichenoid Drug Eruption) [11,12].

OLLC (Oral Lichenoid Lesions Related to Contact) [15].

OLLD (Oral Lichenoid Lesions Related to Drug) [15].

Contact lichenoid stomatitis [25,27].

Contact lesions [15].

Contact allergy [15].

Lichenoid stomatitis [23].

Stomatitis venenata [23].

OLL-GVHD (Oral Lichenoid Lesions of Graft Versus Host Disease) [11].

The prevalence of OLP in the general population has been reported to be about 1% to 2% [9,29], and the prevalence of oral lichenoid lesions has been reported to be approximately 2.4% in the general population [25]. The prevalence of OLP in women is twice as high as that in men [9], and the mean age of the patients is 55 years old [2,30] although it has also been reported in children and in adolescents [5,31]. Similarly, oral lichenoid lesions occur in women three times more than that in men [6,15] and with the mean age of 53 years [25]. Similar to OLP, oral lichenoid reactions have also been reported in children [22,32].

The purpose of this literature review is to detect the similarities and the differences of these lesions to improve the information of colleagues in managing this group of patients.

Clinical features:

There are six forms of clinical presentation: reticular, papular, plaque-like, atrophic (erythematous), erosive, and bullous 18,31]. The erosive and bullous forms may transform into the ulcerative forms. Sometimes, different subtypes can appear in the same patient [22]. The reticular form is the most common type of OLP [33,34]. The clinical features of OLP comprise slender white lines and small papules called Wickham's striae [5,35]. Similarly, oral lichenoid lesions can clinically manifest as each of the six forms [15,23,25]. The Wickham's striae are also sometimes seen in lichenoid lesions related to drug and there is a greater tendency for the remaining hyperpigmentation [36,37]. Radiation striate is a clinical presentation for a drug-induced lichenoid reaction but not for OLP [8,21].

In OLP, the patients with reticular or plaque-like forms tend to be asymptomatic [34] although atrophic and erosive lesions cause severe symptoms [29,38,39]. The main symptoms caused by the erosive, atrophic, and bullous forms in either OLP or lichenoid lesions include pain, soreness, and bleeding; the combination of these symptoms can affect the quality of life of the patients [4,18]. Dry mouth has been reported in LP patients [40]. However, such a complication has not been reported in lichenoid lesions of the mouth; the occasional reports may be due to the side effects of medications. In the lichenoid lesions associated with amalgam restorations, metallic taste can be a significant oral complication [15,41], which is probably related to metal or amalgam corrosion [41]. OLP lesions usually develop in the form of symmetrical, bilateral, and multiple lesions [18,19,33]. In contrast, oral lichenoid lesions are mostly limited in size with a unilateral tendency [27,33,42]. In OLP lesions, the buccal mucosa, the dorsal surface of the tongue, and the gingiva are commonly affected [18,43]; the buccal mucosa is involved in 80%-90% of the cases [5,44]. The reticular form is often found on the buccal mucosa although the dorsal and the lateral surfaces of the tongue, the gingiva, the alveolar sulcus, and the

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vermilion of the lower lip can also be affected [33]. OLP on the dorsal surface of the tongue usually manifests itself as a thick hyperkeratotic plaque [33,45,46]. Its appearance on the palate is unusual and it is rarely seen on the floor of the mouth [8,33,47]. In gingival involvement, OLP clinically manifests as desquamative gingivitis [33,43]. In some patients, the only manifestation of LP is the atrophic and erosive lesions of the attached gingiva, either focal or generalized. The facial gingivae are mostly affected although the palatal and lingual gingivae are also involved in severe cases [33,48,49]. The site of lichenoid lesions is generally similar to that of OLP [6,7], manifesting respectively on the buccal mucosa and the lateral border of the tongue [17,19] followed by the gingiva, the lips, the floor of the mouth, and the palate [6,22]. Lichenoid lesions have several features:

1) In the lesions related to dental restorations, there is direct or close contact with the agent, usually in the posterior buccal mucosa and the lateral border of the tongue [22,23,42].

2) In the lesions related to drug, there is a medical history of taking drug and they can appear at unusual sites such as the palate and the labial mucosa [8,27,43].

3) In patients with chronic GVHD and lichenoid lesions, the prevalent involvement of the palate has been reported [26].

4) In the lichenoid reactions related to composite restorations, the oral mucosa of the lips is often involved [25].

Etiology:

The exact etiology of OLP is unknown [2,45]. However, factors such as drugs, viral antigens, chemical components, stress, genetics, immunological factors, increased oxidative stress, and depression can contribute to the development of OLP [5,14,50]. On the other hand, OLP can be responsible for mental problems in a person [5,51].

Local conditions such as poor oral hygiene and smoking may exacerbate the risk of immune stimulation due to increased exposure [31,45]. There are reports about the association of OLP with a number of viral infections such as EBV, VZV, HSV, HPV, CMV, and HIV; the most common evidence of HCV is available [5,31,45,52].

Several chronic liver diseases such as chronic active hepatitis, primary biliary cirrhosis, and cirrhosis of unknown origin are associated with LP, which is probably due to the commonality of the characteristics of the autoimmune process [5,31]. Some believe that treatment of hepatitis C infection with Interferon alfa (IFN-α) and Ribavirin can exacerbate OLP [18,25]. IFN-α has also been reported as the causative agent of oral lichenoid lesions [25].

Unlike OLP, oral lichenoid reactions have distinct and detectable etiologies [8,11,24,53], which respectively include:

1. Dental materials: the main cause of oral lichenoid lesions is the reaction to dental materials [25,54,55], the most common of which are amalgam restorations containing mercury [22,41,56]. However, hypersensitivity to other components of amalgam, such as copper, tin or zinc can also be related to the reaction [14,25,57]. It has been reported that broken amalgam restorations or those that have undergone abrasion are more probable to develop these lesions [22]. Composites play a role in triggering hypersensitivity reactions but are less likely to develop lichenoid lesions [11,25]. The content of dental resin-based composites such as HEMA, Bis-GMA, and methacrylate resins are also mentioned as the causes of the reaction [11,14]. Dental casting alloys including nickel, gold, palladium, cobalt, chromium, and copper can also lead to oral lichenoid reactions [5,11,14], among which nickel is the most commonly used dental casting metal for oral lichenoid reactions, which plays an important role in orthodontics and prosthodontics [11]. Oral lichenoid reactions have also been reported in relation to porcelain, glass-ionomer, temporary acrylic coatings, tattoos; and oral piercings [25,58]. The contact of dental materials with the oral mucosa creates hypersensitivity reactions within a few days but clinical manifestations may take several years to appear after the onset of the contact [25,42]. Dental materials that can cause oral lichenoid reactions are listed in Table 1 in detail [11,14,18,22].

2. Systemic drugs: unlike the cutaneous type, oral lichenoid lesions related to drug rarely occur [25]. Several drugs are associated with the development of oral lichenoid reactions, which are listed in

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Table 1. Dental materials causing oral lichenoid reactions

Dental Metals
Beryllium Cobalt Copper Chromium Gold Indium Mercury Nickel Palladium Silver Tin
Dental Restorative materials
Amalgam Composite Glass ionomer Porcelain Resin-based materials
Other dental materials
Acrylate compounds Eugenol

Table 2 in detail [5,11,14,18,22,25]. Gold salts are probably the most common drugs causing lichenoid lesions [5]. Hepatitis B vaccination is considered as an oral lichenoid reaction causative agent in children [8,22]. There is a latent period of taking drug to the manifestation of symptoms depending on the type of medication [11] but its average duration is 2 to 3 months; the delay in manifestation has been reported for up to one year. Therefore, the exact history of the patient's drug regimen within 12 to 24 months should be considered [22,59].

Similar to the manifestation of the lesions, the improvement can often be seen for weeks to months after discontinuation of drug intake [5,8]. Sometimes, the synergistic effects of various drugs can increase the frequency of these lesions, e.g., the lichenoid lesions resulting from multiple drugs in Grinspan syndrome [8,11].

3. GVHD: this is a condition that can occur after allogeneic bone marrow transplantation [18,60]. The lichenoid changes are common in the chronic type of GVHD, and lichenoid reactions have the highest positive predictive value for chronic GVHD [25].

4. Other factors: OLP-like lesions at the site of betel nut chewing have been named as betel quid oral lichenoid lesions [61-63].

Bäckman and Jontell [64] investigated the lichenoid lesions in contact with calculus; they introduced calculi as a possible new etiologic agent [14,64]. In some studies, dental plaque has also been considered as the cause of these reactions [11,64]. Flavoring agents in foods and toothpastes, such as cinnamon, may stimulate lichenoid reactions [8,14,65]. Other reported causative agents of oral lichenoid reactions are listed in Table 3 [14,22,61,64,65].

Pathogenesis:

The pathogenesis of OLP is still a matter of debate. Several types of cells, extracellular matrix proteins, and chemokines participate in the onset of OLP by activating different pathways [66]. The presence of cells involved in the migration and activation of T

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Table 2. Systemic drugs causing oral lichenoid reactions

Antibiotics
• Demeclocycline • Penicillin • Tetracycline
Anticonvulsants
• Carbamazepine • Oxcarbazepine • Phenytoin • Valproate sodium
Antidiabetics
• Insulin • Sulfonylureas Chlorpropamide Glipizide Tolazamide Tolbutamide
Antidiarrheal
• Bismuth
Antifungals
• Amphotericin B • Ketoconazole
Antihypertensives
• Alpha-2 adrenergic receptor agonists Methyldopa • Angiotensin-converting enzyme inhibitors Captopril Enalapril • Beta blockers Atenolol Labetalol Metoprolol Oxprenolol Practolol Propranolol • Calcium channel blockers Amlodipine • Diuretics Furosemide Hydrochlorothiazide • Vasodilators Diazoxide

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Antimalarials
•Chloroquine •Hydroxychloroquine •Pyrimethamine
•Sulfadoxine •Quinacrine •Quinidine •Quinine
Antimycobacterials
•Aminosalicylate sodium •Ethambutol •Isoniazide •Pyrazinamide •Rifampin •Streptomycin
Antiplatelets
•Clopidogrel
Antiretrovirals
•Ziduvodine
Benzodizepines
•Lorazepam
Chemotherapeutics
•Dactinomycine •Fludarabine •Hydroxyurea •Imatinib
Corticosteroids
•Prednisolon
NSAIDS
•Aspirin •Diflunisal •Fenclofenac •Ibuprofen •Indomethacin •Isoxicam •Naproxen •Phenylbutazone •Piroxicam •Rofecoxib •Salsalate •Sulindac
Others
•Hepatitis B vaccine •Pyridoxine (Vitamin B6)

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Table 3. Other agents causing oral lichenoid reactions

Flavorings
• Balsam of Peru • Cinnamic aldehyde • Cinnamon • Menthol oil • Peppermint • Vanillin
Others
• Chewing tobacco (Betel quid) • Dental calculus

cells and killing the keratinocytes provides a cell-mediated immunity although the function of the matrix metalloproteinase, chemokines, and mast cells is a non-specific immune response [66,67]. Finally, circulating anti-desmoglein 1 and 3 autoantibodies, immunoglobulin M (IgM), and IgA suggest the role of humoral immunity in developing OLP [66].

The roles of various immune compartments involved in the development and progression of OLP are described below:

1) The innate immune system: the exact LP antigen is unknown so far [18] although some consider the overexpression of heat shock proteins on the surface of keratinocytes due to external stimuli such as drugs, viral infections, bacterial products, mechanical trauma, and also internal factors such as stress [8,18]. The role of different dendritic cells in the development of OLP has been expressed by inflammatory responses [66]. The antigenic variations on the surface of keratinocytes are initially detected by oral mucosal Langerhans' cells [18,66,68]. The increase in the count and activity of these cells in the connective tissue and epithelium causes a local immune response [18], and the mast cell degranulation and activation of the macrophages release tumor necrosis factor (TNF) and Kinase cytokines, inducing the expression of $ICAM_1$ (intercellular adhesion molecule 1) , $ELAM_1$ (endothelial cell leukocyte adhesion molecule 1), and $VCAM_1$ (vascular cell adhesion molecule 1) to facilitate the migration of T lymphocytes [18,21]. Recent articles recognize the increased count of mast cells in OLP lesions as a certain finding [21]. M1 macrophages may aggravate the emergence of OLP by producing pro-inflammatory agents such as TNF-α and interleukin 1 beta (IL1-β). In addition, TNF-α production by macrophages can initiate basal keratinocyte apoptosis and indirectly increase the rate of basement membrane rupture because of matrix metallopeptidase 9 (MMP9) produced by T cells [66]. Many studies have reported the role of various MMPs in the immigration of T cells to extravascular tissues, their migration through the basement membrane, and also the degradation of the basal membrane [18,66,69,70]. Chemokines, such as RANTES (Regulated Upon Activation Normal T cell Express Sequence), are a family of small cytokines that are secreted by keratinocytes and mastocytes, recruiting further T lymphocytes, resulting in the development of OLP [66].

2) Cell-mediated immune system: this is considered as the main pathogenesis of OLP [5,18]. T lymphocytes are the main components of inflammatory infiltration; the CD4 T cell count in the lamina propria and the CD8 T cell count adjacent to the epithelial basal membrane are significantly high. The CD8 accumulation ratio increases with the progression of the lesions [21,71]. These two types of T cells produce a spectrum of cytokines and inflammatory mediators and subsequently react to them. The difference in the clinical presentation of OLP may be due to differences in these cytokines that are effective in cell proliferation and apoptosis [21]. Inflammatory cytokines associated with CD4 cells are produced from the three subtypes of TH_1, TH_2, and TH_{17}. Today, the role of the inflammatory cytokine of TH_{17} has been highlighted in the pathogenesis of OLP [66]. The chemokines produced by active keratinocytes mentioned in the innate immune system induce the recruitment of CD8 cells and the detection of altered antigen of keratinocytes by CD8 cells, resulting in the degeneration of the basal layer due to apoptosis [18,66].

The mechanisms involved in the basal keratinocyte apoptosis are listed below:

1. TNF-α release from CD8 T cells,
2. CD95L on the T cell surface binding with CD95 on the keratinocyte surface,
3. The release of granzyme B and perforin by natural killer cells (NKC) and T cells [5,18,6].

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One of the most studied chemokines is RANTES, which is secreted by active T-lymphocytes, keratinocytes, and mastocytes [66]. The secretion of RANTES from T cells selectively the monocytes, eosinophils, and lymphocytes. On the other hand, the attraction and activation of basophils and mast cells by RANTES will re-attract the T cells [21].

In explaining the role of stress in the development of OLP mentioned in etiology, the suggestion is the change in the ratio of TH_1 to TH_2 cytokines and the increase in TH_2 response [66].

3) The humoral immune system: it is suggested that this immune system is effective in the OLP pathogenesis due to the production of circulating anti-desmoglein 1 and 3 autoantibodies. In addition, the production of circulating IgA and IgM in patients with OLP suggests the role of humoral immunity [18,66].

The main causes of the chronic nature of OLP are as follows:

1. Complex interactions between mast cells and T cells and the effects of the produced cytokines [21],
2. Interactions between cytokines produced from keratinocytes and lymphocytes or other immune cells,
3. Localized interferon gamma (IFNγ) production, maintaining major histocompatibility complex (MHC) class II expression through keratinocytes [66],
4. Active T cells and TH1 cytokines; the increased production of intercellular adhesion molecules on the surface of macrophages and Langerhans' cells results in increased adhesion cycles and lymphocyte migration [22].

According to the literature, biomarkers such as CD275, circulating anti-desmoglein 1 and 3 autoantibodies in the serum, urinary prekallikrein, and PLUNC (Palate/Lung And Nasal Epithelium Associated Protein) have been proposed to predict the onset and severity of OLP lesions [18]. Chart 1 shows a brief review of OLP etiopathogenesis.

The pathogenesis of oral lichenoid reactions is explained below according to the etiological factor:

Lichenoid reactions related to dental restorations:

The contact between the oral mucosa and special restorative materials of dentistry such as amalgam or the products resulting from their corrosion may induce sensitivity response, causing immune-mediated damage in the keratinocytes of the basal layer of the epithelium [15]. Most of these reactions occur due to the type IV hypersensitivity reaction (often called delayed type hypersensitivity). These reactions include cellular mediated immune reaction, primarily macrophages and T lymphocytes which have been sensitized to antigens (haptens). In most cases, haptens are responsible for inducing contact sensitivity. A hapten is a low molecular weight (typically less than 500 Dalton) incomplete antigen, which is bonded to proteins in order to generate a complete antigen. Penetration of hapten to the skin or mucosa is essential for absorption by Langerhans cells and binding with MHC class II, so that the antigen would be presented to lymphocytes. In the lymph nodes, Langerhans cells along with antigenic peptide get into contact with intact HLA-DR molecules of lymphocytes, causing induction of a set of metabolic and morphological changes in the last cells (lymphocytes). This, in turn, results in the production of different cytokines with the ability to modify and intensify the corresponding immune response. The type I hypersensitivity reactions (IgE-mediated) are far less prevalent and are led by antibodies [11].

The hypersensitivity reaction to composites is not common because the level of free monomers is less than 1% of all monomers. This value is lower in cases with dual polymerization, while it is higher for self-cure cases. Reaction to HEMA, Bis-GMA, and methacrylate resins that are present in composites has been reported. However, after light-curing, finding free molecules in composites is uncommon and this can justify the lower prevalence of lichenoid reactions to composites in comparison with amalgam [15].

Lichenoid reactions related to systemic drugs:

The exact mechanism of these reactions is still unknown. Patch test of the patients indicates that most of them are indeed allergic to the precursor components of the medication [11]. However, due to contradictory findings, determining whether this disease can be categorized as an allergic reaction or not is difficult [18].

Medications can have local activity in the tissue, causing degranulation of mast cells or local release of neuropeptides, which directly affect the mast

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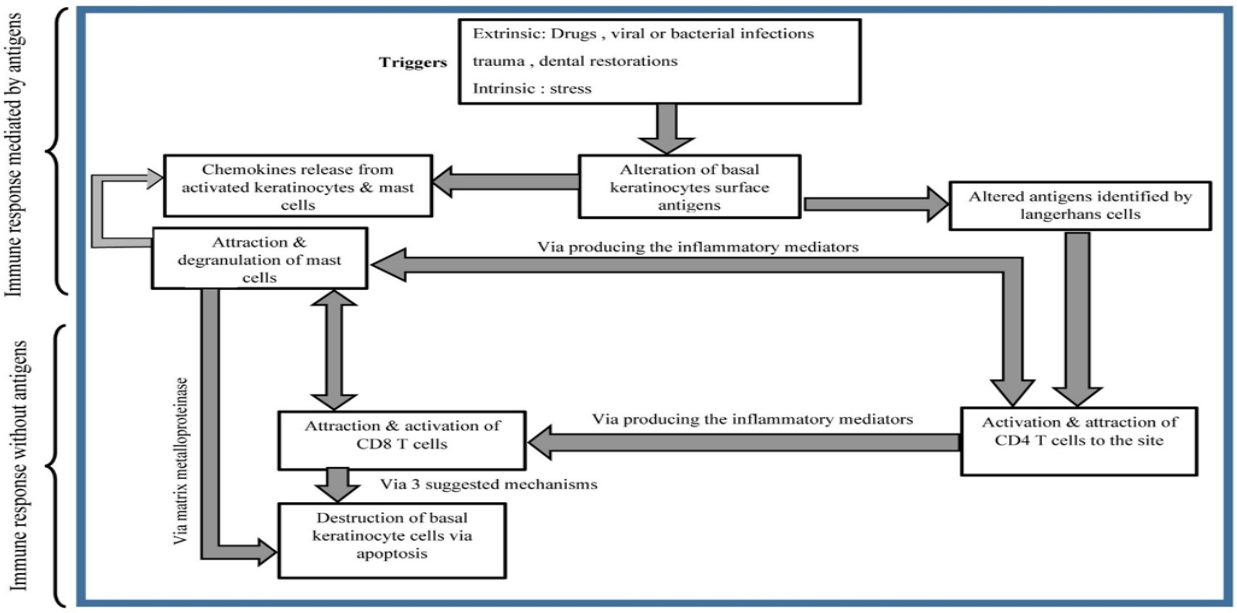

Chart 1. A brief review on oral lichen planus (OLP) etiopathogenesis

cells. Furthermore, with their presence in regional lymph nodes and peripheral blood, medications can have a direct effect on B lymphocytes [11].

In lichenoid drug reactions, expression of antigen in MHC class II is lower compared to OLP, and expression of CD_{25} (the possible marker of cellular activation) has not been observed. It has also been shown that Langerhans cells have a lower HLA-DR expression level in lichenoid drug reactions compared to OLP, which is compatible with diminished cellular activation [12].

Lichenoid drug reactions induced by Zidovudine are possibly developed by $CD^{+}{}_{8}T$ cells which have been previously provoked by antigens. These cells are entrapped and remain on the mucosa, causing mucosal damage through cross-reaction with the medication [28].

Penicillamines alter the superficial antigen, while the sulfhydryl groups in Captopril transform the enzymatic systems. These changes develop an immune response to keratinocyte antigens, which result in lichenoid reactions [11].

Histopathological features:

The histopathological features of OLP are similar to those of cutaneous LP [12,18].

The most accepted OLP features to date are the following three criteria that should be present at same time:

1. The presence of a band-like area, well-distinguished from the cellular infiltration and limited to the surface of the connective tissue, which is predominantly composed of lymphocytes.
2. The presence of hydropic degeneration of the basal cell layer.
3. The absence of dysplasia in the epithelial layer [16,18,23,27].

In studies that have examined the histopathological differentiation of lichenoid lesions from OLP, the most accepted results include:

The histopathological features of oral lichenoid reactions with various etiologic agents are as follows:

Lichenoid lesions related to dental restorations:

In a study, the epithelial layer changes included: 1) Layer classification should be normal. 2) The hydropic degeneration of the basal cell layer may or may not be present. 3) The absence of atypia in the epithelial layer and in the underlying layers: Lymphoid follicles should be considered in combination with mixed inflammatory cells such as plasma cells and neutrophils. In other studies, there were changes in the sub-epithelial layer, which included superficial inflammatory infiltration, focal perivascular inflammatory

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infiltration, and the presence of plasma cells, eosinophils, and neutrophils in the connective tissue [27].

In another study, it has been argued that the hydropic degeneration of the basal cell layer may be absent or low, and the formation of lymphoid follicles mainly consist of neutrophils and plasma cells in the underlying epithelial layer [23,27].

In another article, the histopathological features of contact-related OLP and lichenoid lesions were reported to be very similar [22].

Lichenoid lesions related to systemic drugs:

A study has described epithelial changes as follows: extensive degeneration in the lower prickle cell layer, spongiotic vesicle formation, the presence of hydropic degeneration of the basal cell layer, the absence of atypia, colloid body formation, the presence of apoptotic body in the subepithelial layer, non-band-like infiltrate that extends to the deeper stromal inflammatory cells predominated by plasma cells and eosinophils, and prevascular cuffing of inflammatory cells [27]. In another study, the histological characteristics of OLP and lichenoid drug reactions have been considered to be very similar [11]. It has been stated that the histological characteristics in favor of diagnosing lichenoid drug reactions include mixed infiltration of lymphocytes, plasma cells, and neutrophils with or without eosinophils, which extends to the sub-epithelial layers. Prevascular inflammation and the colloid intra-epithelial bodies have also been mentioned but are not considered for lichenoid drug reactions; however, they may be seen in discoid lupus erythematosus (DLE) [22]. In a study, the following characteristics have been mentioned: cellular infiltration in the suprabasal layer, extensive degradation in the lower prickle layer, the formation of spongiotic vesicles, apoptosis and formation of the colloid body, no clear disruption in the basal cell layer, and deep prevascular infiltration [23]. In another study, the proposed features for lichenoid drug reactions have been as follows: more diffuse subepithelial infiltration that is less band-like, and the inflammatory cells are mixed and include eosinophils and plasma cells. Prevascular infiltration, parakeratosis, and colloid bodies are observed in the epithelium [8,12].

Lichenoid lesions related to GVHD:

A study has mentioned maturation disturbance alongside dyskeratosis, basal squamatization, and prevascular cuffing of inflammatory cells which simulate burnout representation in LP [23]. In a study, in addition to the points in the previous study, sub-epithelial vacuolization was observed between the stromal and sporadic lymphocyte infiltration in the upper lamina propria [8].

Lichenoid lesions related to cinnamon:

It has been reported that infiltration is mostly in the form of plasmacytic components. Hyper-orthokeratinized or hyper-parakeratinized epithelium has been mentioned. Furthermore, epithelial hyperplasia with a psoriasiform pattern has been observed. In severe cases, neutrophilic Munro's microabscess has been suggested [23].

Other distinguishing points, irrespective of the etiological factor of lichenoid reactions, include:

The epithelium thickness is larger in oral lichenoid lesions compared to OLP, which is due to the release of inflammatory mediators that result from infiltration of different cells, causing proliferation of basal keratinocytes. Furthermore, the number of mast cells, neutrophils, and macrophages has been evaluated to be significantly higher in OLP [25]. In another study, an increased number of granulated mast cells in the basal membrane degeneration regions, hyper-vascularization, and increased thickness of the Periodic acid-Schiff (PAS) positive basal membrane have been cited [26,72].

Although some researchers still believe that OLP and oral lichenoid lesions are histopathologically non-differentiable, their distinguishing characteristics have been stated to be very clear [11,14,17,21,25].

By investigating all of the proposed differentiating characteristics, the following points are stated as the features that histopathologically differentiate OLP lesions and oral lichenoid reactions:

1. Mixed inflammatory infiltration including plasma cells, neutrophils, and eosinophils in oral lichenoid reactions, while lymphocytic infiltration is predominant in OLP.
2. A more diffuse and sporadic pattern of infiltration from the surface to the depth of the connective tissue in oral lichenoid reactions, while the infiltration is band-like in the basal layer in OLP.

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3. Focal prevascular infiltration is present in oral lichenoid reactions.
4. More civatte bodies are present in the epithelium of oral lichenoid reactions compared to the epithelium in OLP.

Malignant transformation:

The prevalence of malignancy in OLP varies from 0.1% to 5.3% in different articles [11] although the results of different studies are not comparable in terms of the prevalence because the OLP diagnostic criteria have been clinically or histopathologically different. Another issue is the failure to record the factors affecting the development of malignancy, such as tobacco consumption [18,73]. In addition, several malignancies have been reported in areas far from lichenoid lesions [21].

Regardless of the incidence of malignant transformation, the World Health Organization (WHO) has defined OLP as a potentially precancerous condition, representing a generalized state associated with a significantly increased risk of oral cancer [74,75]. The highest prevalence of malignant transformation has been reported in erosive and ulcerative subtypes [11,76].

It is presumed that these lesions predispose the mucosa to destruction by carcinogenic agents [21,29,77]. The first evidence of the relationship between inflammation and cancer was introduced in the 19th century. Based on the observations, tumors were generated from the sites of chronic inflammation, and inflammatory cells were present in the tumor tissues [11]. In 1910, Hallopeau reported the first case of oral carcinoma originated from LP, and later, other cases were also reported [21,29]. In 1985, Krutchkoff and Eisenberg introduced the term lichenoid dysplasia; the lesion had the histopathological features of OLP and intraepithelial dysplastic lesions [16].

According to the clinical recommendations, the routine follow-up of patients with LP should be performed three times a year. OLP patients with dysplasia should be screened every 2-3 months. However, asymptomatic patients, especially those affected by the reticular type, may be examined annually. Possible symptoms indicating malignant transformation, such as the extent of symptoms and the lack of homogeneity, should be evaluated thoroughly at each appointment. Whenever there are signs of a change in the clinical presentation, the follow-up period should be shortened and an additional biopsy should be performed [18,74].

One study pointed out that the risk of malignant transformation in the lateral border of the tongue and the midline dorsum of the tongue is higher, and the likelihood of malignant transformation in LP lesions is higher at unusual sites [78]. Various mechanisms have been proposed for OLP malignancy, including:

1. Increased inflammatory cytokines and growth factors that can facilitate carcinogenesis [11].
2. Chronic inflammation causes oxidative damage to DNA through the products derived from inflammatory-induced enzymes, such as inducible nitric oxide synthase (iNOS) or cyclooxygenase-2 (COX-2), inhibiting the keratinocyte apoptosis and causing malignancy [76,79].
3. Some have suggested Candida albicans (C. albicans) as an external agent in the development of malignancy (C. albicans is capable of catalyzing the formation of N- nitrosobenzylmethylamine carcinogens.
4. The use of immunomodulators in the treatment of LP promotes malignant changes due to localized cellular immune suppression. Because of the potent anti-inflammatory effects of these factors, the development of malignancy will increase by reducing the symptoms [21,29].
5. Induction of lipid peroxidation by reactive oxygen due to inflammation is considered a cause of malignancy [80].

In a study, salivary MDA (malondialdehyde) was introduced as an indicator of increased lipid peroxidation, which is important as one of the possible mechanisms for malignant transformation [81,82].

On the other hand, human carcinoma cells have more components of 8-OHdG, which is a sign of oxidative damage to DNA [81]. Agha-Hosseini et al [80] showed P53 deficiency in the saliva among OLP patients with squamous cell carcinoma (SCC).

The prevalence of malignant transformation in lichenoid reactions is more than that in OLP and is reported to be about 0.5% to 6.5% [17]. The process of malignant transformation of oral lichenoid reactions is attributed to the phenomenon of field cancerization, in which all related events expose these patients to a higher risk of multiple

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primary malignancies in the oral cavity [11,76].

The new classification by Kalele et al [11] considers this lesion as one of the potentially malignant disorders under Group 2b, i.e., the carcinogenic group due to chronic inflammation by external factors. There is insufficient data on whether all types of oral lichenoid reactions have the potential for malignant transformation; it seems that this malignant transformation exists in the lichenoid reactions related to restorations and GVHD but not in the lichenoid reactions related to drug [23,26].

Management:

As mentioned earlier, because of the similarity in the clinical presentations of OLP and oral lichenoid reactions, the definitive diagnosis of these lesions according to histopathological presentations is necessary because the therapeutic approaches are different due to various etiologies.

To date, there is no cure for OLP [83,84], and the main goals of the treatment include controlling or reducing the symptoms as well as monitoring the dysplastic changes [21,83,85].

Small reticular or plaque-like areas of LP are rarely treated unless they spread or progress or become symptomatic. Perfect oral hygiene can alleviate the symptoms. Mechanical trauma as well as friction caused by rough dental restorations, sharp-pointed cusps, and dental prostheses with poor adaptation can exacerbate the lesions. All these aggravating factors must be eliminated or controlled [18].

In the symptomatic type of OLP, such as erosive and atrophic forms, various medications including corticosteroids, griseofulvin, topical retinoids, cyclosporine, clobetasol, tacrolimus, sulodexide, pimecrolimus, oxpentifylline, photochemotherapy, photodynamic therapy (PDT), and low-level laser therapy have been successfully tested [18,86-89].

Corticosteroids are the most widely used therapeutic agents for OLP because they are effective in suppressing cell-mediated immune activity and can be used topically, intralesionally, and systemically [18]. The mechanisms of their actions include reduction of lymphocytic infiltration, maintenance of cell membrane integrity, inhibition of phagocytes, and fixation of the lysosomal membrane [14].

Triamcinolone acetonide, Fluocinolone acetonide, and Betamethasone valerate are used as topical corticosteroids [87]. Fluocinolone acetonide is the first recommended therapeutic option since it has no permanent suppressive effect on the adrenal cortex and is more effective than triamcinolone acetonide. Tissue atrophy, adrenal suppression, and secondary oral candidiasis have been reported as side effects of topical steroids [18,88]. Extensive erosive gingival lesions can be treated using occlusal splints carrying corticosteroids, which have shown little systemic absorption in clinical studies. In case of resistance against topical treatment, intralesional steroid injections, such as triamcinolone injection, are effective in combination with local anesthetics [21].

Systemic corticosteroids, such as prednisolone, are commonly used for severe and large lesions as well as hard lesions that do not respond to short-term topical treatment [18,21]; many complications have been reported in this regard. Adrenal cortex suppression is common even after short periods of drug consumption [18]. The combination of topical and systemic treatments has a good clinical effect [21].

Tacrolimus is a strong immunosuppressant used in organ transplant patients; it is also used for the treatment of ulcerative-erosive OLP that is resistant to corticosteroid therapy [18,90]. The complications of tacrolimus include local irritation, the probability of SCC induction through mitogen activated protein kinase (MAPK) and P53 pathways, gene mutation, infertility, and mucosal pigmentation [18,21,91].

Topical retinoids are used for the treatment of persistent or widespread plaque-like and reticular lesions, which may cause dryness of the mucosa. If systemic retinoids are consumed, complications such as hair loss, liver dysfunction, and teratogenicity will be observed [14,21].

The use of cyclosporins is limited due to hydrophobicity, high cost, bad taste, malignant transformation, and contribution to viral replication [21]. Antiviral drugs, such as interferon and levamisole, have been successfully used in clinical trials [14,92]. According to Agha-Hosseini et al [92], Purslane and Portulaca herbal remedies have been successfully used for the treatment of OLP lesions.

OLP lesions have been treated by PUVA (Psoralen plus long-wave ultraviolet-A) in 80% of the cases

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although complications such as nausea, dizziness, paresthesia, and pain have been seen in most patients, and there has been a possibility of cancer development with long-term use [18].

Agha-Hosseini et al [38] have reported that the use of methylene blue-mediated PDT (MBPDT) is effective for the treatment of OLP. Use of cryosurgery and carbon dioxide (CO_2) laser are not justifiable in the treatment of OLP as the first line of treatment due to recurrence [18,93].

The treatment of oral lichenoid reactions is different than that of OLP due to their distinguishing etiologic factors, and recovery is achieved in each case by eliminating the cause of the lesions. In the contact-related cases, the removal and replacement of the supposed restorative materials lead to the recovery of the lesions within a few weeks to several months [11]. The topographic relationship between restorative materials and oral lichenoid lesions suggests the therapy's prognosis, but not the definitive outcome. The lesions in close contact with the restoration show a great recovery, whereas those far from the restoration show a relatively minor improvement. Regarding the lichenoid lesions related to amalgam, composite replacement causes improvement in many cases although composite itself is also an etiologic agent for lichenoid reactions [56-41].

After replacing the amalgam, 3-, 6-, 8-, and 12-month recall visits are recommended [94]. Regarding the lichenoid reactions related to drug, it is important to determine the probable causative agent. In the next step, with the advice of a physician, the possibility of replacing the drug is investigated; the lesions will improve within a few weeks to several months if the advice of the physician is that the drug cannot be replaced [18,36].

In chronic oral GVHD cases, topical treatment often includes corticosteroid therapy [95]; other agents include topical budesonide, cyclosporine, azathioprine, and topical tacrolimus. Since GVHD often involves several organs or systems, OLL-GVHD treatment is usually a part of systemic therapy. A distinctive specific treatment for OLL-GVHD has an indication when it comes to preventing excessive immunosuppressive therapy. According to the literature, limited studies have examined the benefits of systemic GVHD therapy over OLL-GVHD therapy [11].

Conclusion

OLP and oral lichenoid reaction are two separate diseases, which in spite of their great similarities in clinical manifestations and some histopathological aspects, are different in etiological factors and in terms of management. The WHO has considered these lesions as potentially premalignant conditions. Based on the investigation conducted in this research, the final differentiation between OLP lesions and oral lichenoid reactions are based on both clinical and histopathological features according to the modified WHO criteria, which probably result in proper management.

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