Manon Marchive

Oral lichenoid lesions: Narrative Review

Faculdade de Ciências da Saúde

Universidade Fernando Pessoa

Porto, 2023

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como parte dos requisitos para a obtenção doGrau de

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Manon Marchive

RESUMO

Este trabalho tem com objetivo melhorar compreensão das lesões liquenoides orais que foram em 2020 incluídas na lista de doenças orais potencialmente malignas da Organização Mundialde Saúde (OMS), elucidando sobre o seu diagnóstico, fisiopatologia e causas. Contribuindo para mais fácil diferenciação destas lesões de outras semelhantes, conduzindo à melhoria dos cuidados prestados aos pacientes.

Foi realizada uma pesquisa bibliográfica eletrónica de artigos científicos, na base de dados PubMed. Foram encontrados 345 artigos potencialmente qualificados. Aplicando os critérios de inclusão e exclusão, apenas 1 RCT, 12 revisões sistemáticas e 7 meta-análises foram incluídos e analisados neste trabalho.

A literatura existente demonstra que embora as lesões liquenoides orais estejam associadas a um risco acrescido de malignidade, o seu diagnóstico pode ser complexo devido à sua semelhança com outras condições. É por esta razão fundamental o conhecimento de todas as suas características de forma a evitar diagnósticos tardios.

Palavras-chave: Lesões liquenoides orais, Reações liquenoides orais, Transformação maligna,Líquen plano oral

ABSTRACT

This work aims to improve understanding of oral lichenoid lesions, which in 2020 were included in the World Health Organization's (WHO) list of potentially malignant oral diseases,by elucidating their diagnosis, pathophysiology and causes. Contributing to easier differentiation of these lesions from other similar ones, leading to improved patient care.

An electronic bibliographic search of scientific articles from the online database PubMed was carried out. 345 potentially qualified articles were found. Applying the inclusionand exclusion criteria, only 1 RCT, 12 systematic reviews and 7 meta-analyses were included and analyzed in this work.

The existing literature shows that although oral lichenoid lesions are associated with an increased risk of malignancy, their diagnosis can be complex due to their similarity to other conditions. It is therefore essential to know all their characteristics in order to avoid late diagnosis.

Keywords: Oral lichenoid lesion; Oral lichenoid reactions; Malignant transformation, Oral lichen planus

DEDICATION

I would like to dedicate this thesis to the extraordinary people who have played important roles in my journey of education and personal growth. Each one of you has played a unique and essential role in this journey.

I will be eternally thankful to my parents, whose constant support even when far away, sacrifices, and love have been my pillars of strength, for your belief in my potential and the chances you have provided.

To my family - siblings, Eugénie, Fati, François, Paul, and Alex, from the very beginning, you've believed in me and celebrated every achievement.

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Finally, I am grateful for Fernando Pessoa University varied and inclusive community. Interacting with students from other origins and cultures has helped me have a better understanding of the world and diversified my viewpoint.

As I start on the next stage of my journey, I will bring with me the information, experiences, and ideals instilled in me. I am extremely happy to be a member of this institution and appreciative for the huge impact that it has had on my life.

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LIST OF ABREVIATIONS

ACE	Angiotensin-converting enzyme
BMT	Bone marrow transplantation
BMZ	Basement membrane zone
BQ	Betel quid
CD3+	Cluster of differentiation 3
CD4+	Cluster of differentiation 4
CD8+	Cluster of differentiation 8
CGVHD	Chronic graft-versus-host disease
CLA+	Cutaneous lymphocyte antigen
COVID-19	Coronavirus Disease
COX-2	Cyclooxygenase-2
CUS	Chronic ulcerative stomatitis
d	Day
DIF	Direct immunofluorescence
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
EOLP	Erosive oral lichen planus
GIT	Gastrointestinal tract
GVHD	Graft-vs-host disease

HIV	Human immunodeficiency virus
IFN	Interferon
IgM	Immunoglobulin M
IIF	Indirect immunofluorescence
IL-2	Interleukin-2
La/SSB	Sjogren's syndrome B
LCRs	Lichenoid contact responses
LDE	Lichenoid drug eruptions
LDR	Lichenoid drug reaction
LP	Lichen planus
LPP	Lichen planus pemphigoid
mg	Milligram
mg/d	Milligrams per day
mRNA LNP	Messenger RNA lipid nanoparticles
N/A	Not available
Ni	Nickel
nm	Nanometer
NSAIDs	Nonsteroidal anti-inflammatory drugs
OLCH	Oral lichenoid contact hypersensitivity,
OLCHR	Oral lichenoid contact hypersensitivity reactions
OLCL	Oral lichenoid contact lesions

OLCR	Oral lichenoid contact reaction
OLDR	Oral lichenoid drug reactions
OLL	Oral lichenoid lesion
OLL-GVHD	Oral lichenoid lesions of graft-versus-host disease
OLP	Oral lichen planus
OLR	Oral lichenoid reaction
OML	Oral malignant lesion
OMS	Organização Mundial de Saúde
OP	Oral prothese
OPMD	Oral potentially malignant disorders
OSCC	Oral squamous cell carcinoma
PMD	Potentially malignant disorders
RCT	Randomized control triad
RNP	Ribonucleoprotein
Ro/SSA	Sjogren's-syndrome-related antigen A
SCC	Squamous-cell carcinoma
TNF	Tumor necrosis factor
TNF-a	Tumor necrosis factor alpha
UK	United Kingdom
UV-A	Ultraviolet-A
wk	Week

WHO World Health Organization's

I. INTRODUCTION

For several decades, the terminology, classification, and diagnosis of oral lichenoid lesions (OLL) have been the topic of intense research, debate, and study. Various terminology for these lesions have been used interchangeably in the scientific literature over time, causing confusionand difficulty in clinical practice. This ambiguity impedes our capacity to establish precise and standardized approaches to diagnosis and management, both of which are critical for providing the best patient care (Müller, 2017).

Furthermore, the diagnostic process for oral lichenoid lesions is complex and difficult becauseof clinical and histological comorbidity with OLP. It can be difficult to distinguish between OLP and OLLs because both illnesses might have lichenoid inflammation, Wickham striae, anda similar clinical appearance. This diagnostic uncertainty can result in incorrect diagnosis, delayed therapy, and poor patient outcomes (Rotaru *et alli.*, 2020a).

To overcome these issues, attempts are being made to develop more exact and consistent terminology and classification for oral lichenoid lesions. The World Health Organization (WHO) have been working to produce uniform standards for the diagnosis and classification of oral mucosal illnesses, including OLLs. Such program seeks to increase diagnostic accuracy, standardization in reporting, and our understanding of the etiology and pathophysiology of OLLs (Kamath, Setlur and Yerlagudda, 2015).

Overall, for establishing a correct management and prognosis of lichenoid lesions, it is mandatory to establish a precise diagnosis (Yamanaka *et alli.*, 2018).

1. Materials and Methods

This narrative review was executed via bibliographic research from October 2022 to January 2023, with the help of online scientific database PubMed. The keywords "oral lichenoid lesions", "oral lichenoid reactions", "malignant transformation" and "oral lichen planus" were used Boolean connectors "AND", "OR" and "NOT" between them.

Only relevant articles with acceptable method, verified results, clear conclusions, and open access were considered for inclusion. Although some older papers were included, priority was given to those published less than ten years ago (2013-2023), and only those with references to oral lichenoid lesions were considered.

Articles that were not fully available for online consultation, did not mention oral lichenoid lesions, did not meet the pre-requisites, were irrelevant, or had unclear methodology or results were excluded as exclusion criteria. Neither the articles written in languages other than Portuguese or English.

Following the application of the inclusion and exclusion criteria, a total of 69 articles were usedto conduct this narrative evaluation.

II. DEVELOPMENT

1. Oral lichenoid lesions

i.Definition

In 1973, Pinkus provided the first microscopic description of lichenoid reactions. Finne *et alli.* introduced the term "oral lichenoid lesion" (OLL) in 1982 (Dudhia *et alli.*, 2015). Which defines oral lesions that are associated with bone marrow transplantation, drug intake, dental restorative materials, food or flavor allergies and systemic disease (autoimmune liver disease), instead the term Oral lichen planus (OLP) concerns a idiopathic lesion, which means that a trigger cannot be identified (Rotaru *et alli.*, 2020b).

In 2020, through a consensus, WHO defined oral lichenoid lesions as oral lesions with lichenoid characteristics but without the typical clinical or histological signs of OLP, namely those that exhibit asymmetry, are reactions to dental restorations, or are drug-induced lesions (Warnakulasuriya, 2020; Warnakulasuriya *et alli.*, 2021).

OLLs include (a) atypical OLP and unilateral lichenoid lesions (Van der Meij and Van der Waal, 2003; van der Meij, Mast and van der Waal, 2007), (b) those in close contact relationship to a dental restoration, frequently amalgam, known as oral lichenoid contact reactions (OLCR) (Al-Hashimi *et alli.*, 2007; McParland and Warnakulasuriya, 2012), (c) lichenoid drug reactions (LDR) (Al-Hashimi *et alli.*, 2007) (e) oral lesions following consumption of food or some substances, such as cinnamon, and (f) oral lesions of graft-versus-host disease. Furthermore, users of betel quid (BQ) have acquired lichenoid contact responses (Reichart and Warnakulasuriya, 2012; Warnakulasuriya *et alli.*, 2021).

There are four types of oral lichenoid lesions (OLL) that have been identified so far: lichenoid lesions in chronic graft-versus-host disease (cGVHD), oral lichenoid contact hypersensitivity reactions (OLCHR), oral lichenoid drug reactions (OLDR), and lichen planus-like lesions that lack one or more clinical characteristics (e.g., lichen planus pemphigoid, chronic ulcerative stomatitis) (Rotaru *et alli.*, 2020b).

ii. Epidemiology of Oral lichenoid lesions

The OLL is a common condition, with a prevalence of 2.4% in the general population. These lesions are most common in adults oral mucosa, mainly in women over the age of 53. When associated with composite restorations, the lesions are mostly found in the buccal mucosa, lateral border of the tongue, and oral mucosa of the lips. It is typically small and unilateral. This finding may be useful in distinguishing OLL from oral lichen planus (OLP) lesions, which are usually bilateral in the oral mucosa (de Mattos Camargo Grossmann, 2015).

iii. Etiology of Oral lichenoid lesions

OLL is a chronic inflammatory disease with unknown etiology or pathogenesis. OLL is most likely caused by external triggers such as dental restorative materials and systemic drugs, although it can also be caused by systemic disorders. Disparities in etiologies may have a significant impact on treatment options (Zhou *et alli.*, 2022).

Metals used in dental restorations, dental adhesives, and flavoring ingredients in oral hygiene products have all been suggested as potential triggers for contact hypersensitivity reactions andsubsequent OLL development. Some medications have been linked to the development of OLLs, particularly lichenoid drug reaction. OLLs have been associated with nonsteroidal anti- inflammatory drugs (NSAIDs), antihypertensives (e.g., ACE inhibitors), antimalarials (e.g., hydroxychloroquine), and some antibiotics (Dudhia *et alli.*, 2015).

OLL develops as an allergic reaction in patients with graft-vs-host disease (GVHD), in individuals with systemic disorders, such as chronic hepatitis C, and in patients who have been vaccinated against hepatitis B (de Mattos Camargo Grossmann, 2015).

Thyroid conditions and medications can also contribute to OLL (Olms and Remmerbach, 2017).

2. Associated factors with Oral lichenoid lesions

i.Drugs and medications

OLLs have been caused by drug and medication use, either locally or systemically (Kamath, Setlur and Yerlagudda, 2015).

Several medicines have been associated with LDE, but only a few of them have been proven as causing oral involvement. Most lichenoid reactions are caused by antibiotics, antihypertensives,gold compounds, diuretics, antimalarial medicines, and nonsteroidal anti-inflammatory drugs, Table 1. In pediatric patients, hepatitis B vaccination has been related to OLDR. Some experts believe that the so-called "Grinspan syndrome," in which OLP is associated with diabetes and arterial hypertension, is merely an example of OLR caused by the medications used to treat the latter two conditions at the same time (Dudhia *et alli.*, 2015).

OLR caused by antiretroviral medicines used to treat HIV has also been reported (Alrashdan, Cirillo and McCullough, 2016).

These lesions are clinically indistinguishable from OLP, with erythematous erosions and ulceration, as well as isolated areas of radiating striae. Depending on the medicine, OLDR lesions appear as white reticular papules or erythematous erosions and can cause substantial mouth pain. Oral LDEs can occur in locations other than the palate or lip, and unlike OLP, lesions are usually unilateral (Dudhia *et alli.*, 2015).

Attempting to distinguish the two disorders histologically may be problematic since, as with clinical findings, those traits considered diagnostic of an LDE can also be seen in some cases with idiopathic OLP. A deep and diffuse subepithelial mixed infiltrate of lymphocytes, plasmacells, and neutrophils with or without eosinophils; perivascular inflammation; and intraepithelial colloid bodies are histological characteristics that can be helpful in the diagnosisof OLDR. An appropriate drug history raises clinical suspicion of the presence of a lichenoid reaction, especially if the patient is taking a "high-risk" drug. A clinically unusual distributionof lesions, including involvement of uncommon and unilateral sites, and "nonclassical" (i.e., lichenoid) histology raises the level of suspicion. Indirect immunofluorescence (IIF) tests of OLDR patient sera may reveal circulating basal cell cytoplasmic autoantibodies in a "string ofpearls" pattern. IIF is negative in OLP

(Dudhia *et alli.*, 2015).

The most reliable method to recognize a lichenoid drug reaction is to observe the resolution of the reaction when the suspected inciting drug is removed, and to see if the reaction recurs when the patient receives the same drug again. This is both impractical (since such reactions might continue for months) and potentially harmful. As a result, confirming the diagnosis of OLDR remains difficult. Surprisingly, no evidence-based studies on OLDR exist (Al-Hashimi *et alli.*, 2007).

Oral lichenoid drug reactions can occur at any time, even years after the initiation of a specific drug therapy, but there appears to be a relatively clear temporal correlation between the use ofthe suspected medication and the development of oral lesions in many cases. There is currently no specific test for oral lichenoid drugs reaction (Carrozzo *et alli.*, 2019).

OLDR is treated by discontinuing the suspect medicine and replacing with another medication. Normally resolve within weeks to months of stopping the medication, but delayed responses are possible. Lesions which are milder, reticular, or erosive may persist for longer periods of time (Dudhia *et alli.*, 2015).

Table 1. Medication associated with inducing Oral lichenoid lesions (OLL)

Type of medication	Examples
Antianxiety/psychotropic agents	Benzodiazepin, lithium, tricyclic antidepressants (Müller, 2017).
Antibiotics and chemotherapeutic agents	Penicillin, tetracycline, streptomycin, pyrazinamide, sulfadoxin, ketoconazole, pyrimethamine, demeclocycline, isoniazid, rifampin (Guijarro-Guijarro and López-Sánchez, 2003; Müller, 2017).
Anticonvulsants	Carbamazepine, phenytoin, valproate (Müller, 2017).
Antidiabetic agents	Chlorpropamide, tolbutamide, insulin, glyburide, glipizide, sulfonylureas (Guijarro-Guijarro and López-Sánchez, 2003; Müller, 2017).
Antifungal	Amphotericin B, ketoconazole (Müller, 2017).
Antiepileptic agents	Carbamazepine (Guijarro-Guijarro and López-Sánchez).
Antihypertensive agents	Methyldopa, labetalol, propranolol, captopril, atenolol, chlorothiazide, enalapril, furosemide, hydroclorothiazide, metopolol (Guijarro-Guijarro and López-Sánchez, 2003; Müller, 2017).
Antimalarials	Chloroquine, quinacrine, quinidine, hydroxychloroquine (Guijarro-Guijarro and López-Sánchez, 2003; Müller, 2017).
Antimaniac drugs	Lithium salts (Guijarro-Guijarro and López-Sánchez,2003).
Antiplatelet agent	Clopidogrel (Guijarro-Guijarro and López-Sánchez, 2003).
Antirheumatic agents	Gold Salts (Guijarro-Guijarro and López-Sánchez, 2003).
Antiulcer medication	Bismuth (Guijarro-Guijarro and López-Sánchez, 2003).
Benzodiazepines	Lorazepam (Guijarro-Guijarro and López-Sánchez, 2003).
Nonsteroidal anti-inflammatorydrugs	Salicylates, indomethacin, fenelofenac, isoxicam, piroxicam, naproxen, ibuprofen, diclofenac, aspirin (Guijarro-Guijarro and López-Sánchez, 2003; Müller, 2017).
Miscellaneous	Allopurinol, bismuth, dapsone, gold salts, penicillamine, sulfasalazine (Müller, 2017).
Biologic agents	Obinutuzumab, tumor necrosis factor a, TNF-a inhibitors, infliximab, certolizumab, etanercept, abatacept (Müller, 2017).
Antiretrovirals	Zidovudine (Müller, 2017).
Statins	Fluvastatin, lovastatin, pravastatin, simvastatin (Müller, 2017).

ii.Dental restorative materials

Various materials are utilized during dental treatment that can have negative effects on patients and dental personnel, so they must be used with prudence. In 2006, Khamaysi, Bergman and Weltfriend, conducted a study of allergens in dental practice that are associated with contact reactions and discovered that patch testing of 134 patients revealed that cheilitis and perioral dermatitis were the most common oral manifestations (25.6%), followed by burning mouth syndrome (15.7%), lichenoid reaction (14%), and orofacial granulomatosis (10.7%). According to Khamaysi, Bergman and Weltfriend,

mercury allergy did not play a role in oral lichenoid reactions (Khamaysi, Bergman and Weltfriend, 2006; Syed, Chopra and Sachdev, 2015).

Dental materials are considered to be one etiologic cause of OLLs, and OLLs are considered to be either a disease or the consequence of oral prostheses (OPs). They are sometimes considered both, with OPs contributing as an aggravating factor for existing OLLs. Hypersensitivity reactions in individuals with OLLs caused by OPs normally disappear when the trigger is removed, and a persistent inflammatory state, which is typical of OLLs, is not maintained. When there are multiple OPs in the mouth, it might be difficult to determine which OP should be removed if an adverse reaction occurs and to confirm whether the lesion was caused by theOP (Ju *et alli.*, 2021).

Amalgam, base metals, and precious metals can all induce metal reactions. Intra-oral lichenoid reactions, a burning sensation, and/or swelling of the buccal mucosa are the most common symptoms. Amalgam is the dental material that generates most negative reactions in patients. The degree of severity of adverse reactions ranges from mild to moderate, indicating that, except in rare situations, adverse reactions are not life threatening (Syed, Chopra and Sachdev, 2015).

Lind introduced the term Oral lichenoid reaction (OLR) in 1986, to describe clinical lesions associated with amalgam restorations (Lind *et alli.*, 1986). Copper and tin, which are both significant corrosive components in amalgam, may potentially be a source of lichenoid mucosal modifications. Aside from amalgam, additional metals that can cause oral lichenoid mucositis include gold, palladium, nickel, chromium, and cobalt. A sensitivity response resulting in immune-mediated damage to the basal epithelium may occur as a result of oral mucosa contactwith some dental restorative materials. Aside from dental materials, a variety of topical substances including cinnamon and other flavorings, oral cosmetics, various food products and beverages, as well as additives, may cause an adverse reaction on the oral mucosa According to some authors, when the dental restotation is removed and replaced, there’s a improvement (Al-Hashimi *et alli.*, 2007; Dudhia *et alli.*, 2015). However, there is no evidence about the benefit of having your amalgam restorations changed (Alrashdan, Cirillo and McCullough, 2016).

A theory attempting to explain the pathogenesis of OLR was proposed, based on the assumption that dental materials in direct contact with the oral mucosa may directly alter

the antigenicity of basal keratinocytes through the release of mercury or other products, resulting in a type IV/delayed hypersensitivity immune reaction (Alrashdan, Cirillo and McCullough, 2016).

OLR could represent a delayed hypersensitivity reaction in which helper CD4 T lymphocytes and cytotoxic CD8 T lymphocytes function by producing cytokines (TNF- and IFN-), which stimulate pro-inflammatory cells and cause tissue damage or a delayed hypersensitivity reaction involving CD3+, CD4+, and CD8+ cells. Both lesions have CD3+CD4+, CD3+CD8+, CD4+CLA+, CD8+CLA+ cells, and E-selectin (Werneck *et alli.*, 2022).

The term "oral lichenoid contact lesion" refers to oral lesions that, are clinically and histopathologically similar to oral lichen planus (Carrozzo *et alli.*, 2019).

The duration of contact between the oral mucosa and the presumed causative substance is most likely a factor in the development of OLCL (Al-Hashimi *et alli.*, 2007).

Based only on histological criteria, it is insufficient to distinguish between idiopathic LP and lichenoid allergic contact manifestations. Histopathologic markers distinguishing OLP include the predominance of lymphoid follicles composed mainly by plasma cells and neutrophils. Although OLP lesions are often bilateral and symmetrical, those caused by sensitivity to dental restorations have an unsymmetrical and often unilateral distribution, appearing next to the restorations. The strong topographic link between the restoration and the lesion is critical clinical information required to validate the diagnosis of amalgam restoration. The lateral edges of the tongue and the buccal mucosa are common places (Dudhia *et alli.*, 2015).

OLR is often diagnosed based on the topography and location of the lesions, as OLR is clinically and histologically indistinguishable from idiopathic OLP in the majority of cases. Cutaneous patch testing may also help distinguish these lesions (Alrashdan, Cirillo and McCullough, 2016).

Patch tests are commonly used to detect individuals who may be experiencing hypersensitivity reactions; however, whether they are beneficial in treating oral lichenoid contact lesions is debatable. Skin testing is favored over mucosal testing due to its higher sensitivity and specificity, as well as the fact that the concentration of an allergen on

mucosa must be 5-12 times higher than that on skin to prevent exposing patients to the risk of a dangerous reaction (Carrozzo *et alli.*, 2019).

The value of cutaneous patch testing of a battery of dental restorative materials, which is often performed on the forearm or back of test subjects, is still debatable. There is still debate about which mercurial/amalgam compounds or salts to use in skin patch testing, how to distinguish sensitivity from irritant responses, how long test materials should be in contact with the skin (72 hours, 96 hours, 7 days, 14 days, or even longer), and the value of skin patch testing in identifying true OLCL. Furthermore, the validity of extrapolating skin reactions to mucosal responses is being debated. Nonetheless, skin patch testing may be useful to the clinician, particularly in determining appropriate substitute materials (those to which the patient has not shown a reaction) (Al-Hashimi *et alli.*, 2007).

If a patient tests positive for any component of existing dental restorations, most typically amalgam or ammoniated mercury, then the restoration in direct contact with the lesion should be removed/replaced/covered. The resolution following removal more reliably verifies the diagnosis. A positive patch test combined with a strong clinical association between oral lichenoid contact reaction lesions and amalgam restorations is a good predictor of improvement after amalgam removal (Dudhia *et alli.*, 2015).

The majority of such OLCLs disappear within several months after the presumed causal material is removed and replaced (Al-Hashimi *et alli.*, 2007).

Unfortunately, there is no clear evidence that patients with OLP or OLR would benefit from having their amalgam restorations changed on a regular basis (Alrashdan, Cirillo and McCullough, 2016).

There are numerous case reports and cases within substantive trials where "spontaneous" OLCL resolution occurred without the removal/replacement of suspect filler material (Al-Hashimi *et alli.*, 2007).

The evidence for the need and utility of a biopsy for histological confirmation of an OLCL diagnosis is inconclusive, particularly in distinguishing OLP from OLCL. Published investigation papers revealed the difficulties in identifying the two disorders based solely on histological findings (Al-Hashimi *et alli.*, 2007).

When lesions exhibit unusual clinical manifestations, there is no response, or there is suspicion for probable malignancy, a biopsy is mandatory (Dudhia *et alli.*, 2015).

OLLs linked to contact hypersensitivity, particularly to dental metals, may be a risk factor for the development of oral squamous cell carcinoma of the mouth (Dudhia *et alli.*, 2015).

iii.Graft-versus-host disease

GVHDs are most common in patients of allergic bone marrow transplantation (BMT), that is the forme of treatment used for life-threatening blood and bone marrow illnesses such as leukemia, aplastic anemia, and disseminated metastatic diseases. GVHD is a complication caused by T-cell activation in response to molecules from the major histocompatibility complex after an allogenic histocompatible BMT that can affect with high frequency skin, gastrointestinal tract, oral mucosa, eyes and liver. The T-cells from donors perceive molecules from the host tissue as foreign (Dudhia *et alli.*, 2015).

Oral lesions are often associated with GVHD and occur in 25-70% of cases. Diagnosis is mostly clinicopathological, as 85% of GVHDs exhibit clinical and histopathologic characteristics of OLP. The presence of LP-like lesions in graft-versus-host disease suggests that LP has an immunological base too (Dudhia *et alli.*, 2015).

Oral GVHD and oral LP are clinically and histologically identical. Although the antigen specificity of OLP and mucocutaneous GVHD is likely to be different, they are expected to have comparable immunological effector processes that result in T cell infiltration, epithelial basement membrane disruption, basal keratinocyte apoptosis, and clinical disease. TNF-a has been confirmed as a significant effector molecule in GVHD in a number of experimental systems. Importantly, neutralizing anti-TNF-a antibodies have been found in both mice and humans to relieve cutaneous and intestinal GVHD (Alrashdan, Cirillo and McCullough, 2016).

Histopathologic findings include epithelial maturation disturbances, with dyskeratosis, basal squamatization, subepithelial vacuolization at the stromal interface, and scanty lymphocytic infiltration in the upper lamina propria. Inflammatory cells are cuffed perivascularly (Dudhia *et alli.*, 2015).

Clinical characteristics alone are frequently adequate for diagnosis, provided they are present in the context of a patient who has received an allogeneic haematopoietic stem-cell transplant.Histological confirmation of OLL-GVHD is suggested in the absence of signs/symptoms of involvement of other systems or organs, or when investigations of such other sites yield only negative or nonspecific results and in cases of atypical clinical presentation to rule out dysplasia/malignancy, particularly as part of clinical monitoring of patients with long-standingchronic disease (Al-Hashimi *et alli.*, 2007).

As a result, medications that have proven effective in the treatment of oral GVHD may be useful to the management of OLP. The natural history of OLL-GVHD is of great interest (Al-Hashimi*et alli.*, 2007).

Graft vs. host disease can be classified as acute or chronic based on the time it takes for symptoms to appear after a transplant (the threshold is in the range of 100 days); however, in the United States the most recent National Institutes of Health consensus criteria suggest that classification should be based on specific symptoms and signs rather than a strict temporal definition (Carrozzo *et alli.*, 2019).

Acute GVHD manifests as within the first 100 days of transplantation as dermatitis, enteritis, and hepatitis, as well as immunosuppression and cachexia (Alrashdan, Cirillo and McCullough,2016), it mostly affects three organ systems: the skin, the liver, and the gastrointestinal tract (GIT), including the oral cavity. Acute OLL-GVHD is frequently painful, erythematous, ulcerated, or characterized by prominent desquamation (Al-Hashimi *et alli.*, 2007).

While chronic GVHD occurs after day 100 and is characterized by an autoimmune-like syndrome similar to ulcerative colitis, primary biliary cirrhosis, Sjogren's syndrome, rheumatoid arthritis, and lupus-like disease with glomerulonephritis (Alrashdan, Cirillo and McCullough, 2016). Chronic GVHD (cGVHD) involves a greater number of organs, and oral involvement, particularly salivary glands involvement is more prevalent (Al-Hashimi *et alli.*, 2007). The skin is a key target, exhibiting either lichenoid eruptions or sclerodermatous alterations (Alrashdan, Cirillo and McCullough, 2016). Chronic OLL-GVHD are characterizedby keratotic white striae or plaques with erythema, erosion, or ulceration (Al-Hashimi *et alli.*, 2007).

The mouth can be affected by both acute and chronic graft vs. host disease, but the latter is

morelikely to induce lichenoid lesions (Carrozzo *et alli.*, 2019). Oral involvement occurs in 33 to 75% of acute GVHD patients and up to 80% of chronic GVHD patients (Alrashdan, Cirillo and McCullough, 2016), which are made up of three unique illness types that can coexist: Oral lichenoid lesions, including reticulation, ulcerations, and mucosal atrophy; salivary gland malfunction, including chronic dry mouth and hyposalivation symptoms; and orofacial fibrosiswith limited mouth opening (Carrozzo *et alli.*, 2019).

Since GVHD tends to be a multiorgan illness, systemic therapy is recommended. Few, if any, studies have directly examined the effect, if any, on oral GVHD. High-dose systemic corticosteroids are still an essential component of GVHD treatment. This is typically combinedwith one of the calcineurin inhibitors, most commonly cyclosporine. Recent studies utilizing systemic tacrolimus or sirolimus, on the other hand, have been described (Al-Hashimi *et alli.*, 2007).

Topical medicines, primarily corticosteroids, are used in local treatments for oral cGVHD. Topical budesonide, dexamethasone mouthrinse, cyclosporine, and azathioprine have all been shown to be effective. Topical tacrolimus shows the most promise, although there are concerns about its oncogenic potential, which may limit its future use. Because of the carcinogenic potential of ultraviolet light, local phototherapy with UV-A light combined with the use of topical or systemic leukocyte-sensitizing psoralen is of concern. Anecdotal evidence suggests that low-level laser therapy is effective (Al-Hashimi *et alli.*, 2007).

Considering that GVHD frequently involves several systems or organs, treatment for OLL-GVHD is often included as part of the systematic management. Treatment is appropriate as a complement to systemic therapy for OLL-GVHD, especially if escalating systemic immunosuppressive therapy may be avoided. Unfortunately, there have been few well- controlled studies of systemic therapy for GVHD that have clearly investigated the effect or benefits on OLL-GVHD, and even fewer have assessed medicines, either local (topical) or systemic, specifically for OLL-GVHD (Al-Hashimi *et alli.*, 2007).

In basic terms, the information about OLP therapies is applicable to OLL-GVHD, with the exception that there have been no reports of the use of retinoids (systemic or topical) for OLL-GVHD and only a small number of case reports about the use of retinoids in

cutaneous and ocular GVHD. Several studies have found that patients with OLL-GVHD had a statistically higher chance of acquiring OSCC than the general population. As a result, long-term monitoring of OLL-GVHD is recommended. Surveillance for opportunistic infections in the oral cavity is also recommended for patients receiving active immunosuppressive medication for GVHD (Al-Hashimi *et alli.*, 2007).

Previous research suggests that GVHD and immunosuppressive therapy may raise the incidence of solid malignancies, particularly oral cavity and skin squamous-cell carcinomas (SCCs). Thiswould imply that, like OLP, OLL-GVHD is a condition linked with the risk of malignant transformation (Al-Hashimi *et alli.*, 2007).

OLL-GVHD causes morbidity in and of itself, but it may also be a sign of active GVHD involvement in important organs such as the GIT, liver, and lung (Al-Hashimi *et alli.*, 2007).

iv.Others factors

OLL can be caused by a variety of factors (Müller, 2017). A few case studies have noted the presence of OLLs in patients with no indication of relationship with any of the factors listed above. Factors such as dental tartar and plaque accumulation have been mentioned in these individuals. A curious case report of OLL in a patient with a triad of dental tartar, hyposialia, and mouth breathing is presented. There were no other factors related with the patient. The authors believe that the OLL was caused by pathogen accumulation in tartar and a lack of salivary antibody defense due to hyposialia (Bäckman and Jontell, 2007). Similar reports have corroborated the existence of this phenomenon, resulting in recognized it as a possible role in the etiology of OLLs (Kamath, Setlur and Yerlagudda, 2015).

OLL severity seems to be associated with increased anxiety, higher scores on the oral health impact profile, and a lower quality of life (Zucoloto *et alli.*, 2019).

The development of OLL is a rare adverse reaction to vaccinations (Hertel *et alli.*, 2022). They have been seen in COVID19 patients (Toader *et alli.*, 2022). Previously, lichenoid drug eruptions were described as relatively unusual adverse reactions to vaccination, particularly in relation tothe hepatitis B vaccine (Hertel *et alli.*, 2022).

Accordingly, OLL/OLP appears to be a potential adverse drug reaction to COVID-19 vaccines, particularly those targeting mRNA LNP. However, the given study discovered cases of newly diagnosed OLL/OLP in which adenovirus vectors were supplied as well. In the case of OLL, aspecific cause is required to trigger a type IV hypersensitivity reaction, which could be an element in the formulation. Despite the fact that both OLL and OLP might cause symptoms such as erosion, ulceration, or the formation of bullae, they are classed as premalignant lesions with an increased chance of developing into oral squamous cell carcinoma (OSCC). The results suggest a possible danger of substantial secondary consequential morbidity. However, spontaneous remission is possible, at least in the case of OLL, therefore the chance of OSCC formation might be conservatively evaluated as extremely low. Along with the retrospective nature of the study, come certain limitations, which further studies may address, as outlined in the introduction, OLL and OLP cannot be distinguished, neither from the clinical presentation nor from histopathology. Thus, it remains uncertain if the recorded cases were OLL or OLP. OLL might be diagnosed with relative certainty if clinical follow-up revealed a spontaneous remission over time. Prospective clinical trials may investigate distinguishing between the two entities. So far, it may be presumed that the bulk of the lesions were OLL, as it has been linked to the usage of several medications (Hertel *et alli.*, 2022).

The findings from real-world data indicate that the onset of OLL/OLP is a rare adverse drugs reaction to COVID-19 vaccinations, particularly mRNA LNP. However, in the case of OLL, spontaneous remission may be predicted over time. As a result, the current study's findings should not limit the use of COVID-19 vaccinations in broad levels of the population (Hertel *et alli.*, 2022).

OLL can also be triggered by a habit of consuming cinnamon-containing foods or oral hygiene products (e.g., toothpaste, mouthwashes; oral lichenoid contact hypersensitivity, OLCH).(Rotaru *et alli.*, 2020a). Similarly to the OLCR to amalgam, discontinuing the cinnamon product causes the mucosal lesions disappear fast (Müller, 2017).

A lichenoid reaction occurs in tobacco chewers at the location of quid or gutka placement. Betel quid chewing has been discovered to be strongly related with this lesion, which arises at the site of quid placement (Choudhary *et alli.*, 2022).

Metal ions, particularly nickel (Ni), can be increased in saliva by OPs, exacerbating OLL.

As a result, replacing Ni-releasing OPs with other types of OPs is strongly advised in patients with refractory OLL, especially if the OPs are suspected of being aggravating factors. Contact allergic reactions between the oral mucosa and the OP might produce patient complaints of burning mouth syndrome, recurrent aphthous stomatitis, and gingivitis. These allergic reactions are thought to be the cause of OLLs, a chronic inflammatory condition caused by T cells. Although T cells are clearly involved in OLL pathogenesis, it is unknown which antigens trigger an immunological response mediated by CD4+ and CD8+ T cells (Ju *et alli.*, 2021).

3. Pathophysiology and clinical-pathological features

OLL is assumed to be induced by specific triggers or systemic diseases, and it has a more extensive and deeper inflammatory infiltration of lymphocytes, as well as a higher number of eosinophils, plasma cells, and granulocytes than OLP (Zhou *et alli.*, 2022).

i.Distribution

Oral lichenoid lesions and Oral lichen planus have reticular appearances very similar, Table 2. A close association to a restoration may suggest the latter diagnosis (Warnakulasuriya, 2020).

Table 2. Distribution of oral lichenoid lesions (OLL) and oral lichen planus (OLP)

	Oral lichenoid lesions	**Oral lichen planus**
Distribution	Usually unilateral (Kamath, Setlur and Yerlagudda, 2015). Atypical places (ex. palate) and frequently in topographic relationship to causing agent (Kamath, Setlur and Yerlagudda, 2015; Rotaru *et alli.*, 2020a).	Bilateral and symmetrical (Kamath, Setlur and Yerlagudda, 2015; Rotaru *et alli.*, 2020a).
	• graft versus host disease: any oral mucosal locations (Rotaru *et alli.*, 2020a).	• reticular: posterior buccal mucosa bilaterally (typically), spreading almost to the commissures; may involve lateral and dorsal surface of the tongue, gingiva, and vermilion border (Rotaru *et alli.*, 2020a).
	• oral lichenoid contact hypersensitivity reaction: when in contact with a dental restoration at the level of the buccal mucosa and/or the lateral border of the tongue (Rotaru *et alli.*, 2020a). • oral lichenoid drug reaction: single oral lesion (as opposed to bilateral, symmetric, and multifocal OLP lesions) (Rotaru *et alli.*, 2020a).	• papular: buccal mucosa (Rotaru *et alli.*, 2020a).
		• plaque-like: dorsal surface of tongue (often) or bilateral posterior buccal mucosa (Rotaru *et alli.*, 2020a).
		• atrophic/erosive: frequently bilateral and symmetric. Desquamative gingivitis occurs when EOLP affects the gingival mucosa (Rotaru *et alli.*, 2020a).
	• lichen planus pemphigoides: buccal mucosa and gingiva (Rotaru *et alli.*, 2020a). • chronic ulcerative stomatitis: gingiva (may look like desquamative gingivitis), tongue, and buccal mucosa (Rotaru *et alli.*, 2020a).	• Classical white striae (Wickham's striae) (Kamath, Setlur and Yerlagudda, 2015).
		• Idiopathic (Kamath, Setlur and Yerlagudda, 2015).
	• lupus erythematosus: hard palate, buccal mucosa, and/or gengiva (Rotaru *et alli.*, 2020a).	

EOLP: Erosive oral lichen planus

ii.Clinical patterns

The clinical presentation of Oral lichenoid lesion (OLL) is similar to that of Oral lichen planus(OLP), Table 3 (Mendes *et alli.*, 2018). Clinically, oral lichenoid lesions can have a variety of symptoms, from asymptomatic white reticular striae and plaques to severe erythematous, eroded, or ulcerated lesions (Al-Hashimi *et alli.*, 2007). Most occurrences include exposure to a triggering cause, such as drugs or dental materials. Single or unilateral lesions, as well as a deep perivascular or mixed infiltrate of inflammatory cells, are common in OLL patients, but not always present. The distinction between OLP and OLL is frequently a source of consternation for doctors and pathologists. Furthermore, the specific etiopathogenesis of OLP and OLL is uncertain (Mendes *et alli.*, 2018).

The clinical appearance of OLDR is unknown in comparison to other oral lichenoid lesions, although the unilateral location may aid in identification (Carrozzo *et alli.*, 2019).

Clinical symptoms of oral lichenoid contact lesions have rarely been adequately reported. Although there is not much evidence to support this statement, oral lichenoid contact lesions are thought to be less symmetrical and more usually unilateral than oral lichen planus. Similarly, lesions with amalgam restorations are commonly but not always observed to be near to one another. It is possible that oral lichenoid contact lesions do not have the usual reticular appearance of oral lichen planus, but instead show as patches or atrophic lesions. They usually are on the tongue's edges and the posterior buccal mucosa (Carrozzo *et alli.*, 2019).

Table 3. Clinical presentation of Oral lichenoid lesions (OLL) and Oral lichen planus (OLP)

	Clinical presentation
Oral lichen planus	• reticular: most common; lacy white streaks (Wickham striae) with well-defined erythematous borders; lesions canproduce roughness and reduced mucosal flexibility (Rotaru*et alli.*, 2020a). • papular: tiny white pinpoint papules that may join together(Rotaru *et alli.*, 2020a). • plaque-like: massive, homogeneous white patches. • erosive: atrophic or erythematous ulcerations, mucosa erosions, and mild radiating white striae (Rotaru *et alli.*, 2020a). • atrophic: atrophic lesions are surrounded by erythema withradiating white striae. When gingiva is implicated, it manifests as 'desquamative gingivitis' (Rotaru *et alli.*, 2020a). • bullous: fluid-filled lesions (Rotaru *et alli.*, 2020a). When compared to erosive OLP (EOLP, the other three lesions), non-erosive OLP lesions (reticular, papular, andplaque-like) are typically asymptomatic (Rotaru *et alli.*, 2020a).
Oral lichenoid lesions	Occur in multiple forms similar to OLP (Rotaru *et alli.*,2020a). • erythematous (Rotaru *et alli.*, 2020a). • reticular: chronic graft vs. host disease, oral lichenoid drugreaction (Rotaru *et alli.*, 2020a). • plaque-like: chronic graft vs. host disease (Rotaru *et alli.*,2020a). • atrophic: oral lichenoid drug reaction (Rotaru *et alli.*,2020a). • erosive: chronic graft vs. host disease, oral lichenoid drugreaction (Rotaru *et alli.*, 2020a).
Oral lichenoid drug reaction	Similar to OLP, if not identical (Carrozzo *et alli.*, 2019). • single lesion, which is more common than OLP (Müller,2017). • temporal association with new drug intake, the start of OLDR might range from weeks to years (Müller, 2017).
Oral lichenoid contact reaction	• Unilateral or bilateral (Carrozzo *et alli.*, 2019). • Topographic association with amalgam fillings is common(Al-Hashimi *et alli.*, 2007) • Gingiva is unusually affected (Carrozzo *et alli.*, 2019). • OLCR-amalgam: Direct contact with dental amalgam caused a unilateral lesion (Müller, 2017). • OLCR-cinnamon: White plaques or erythema in the area of contact and resolve if the product is discontinued (Müller,2017).
Graft vs host disease	• CGVHD (presents >6 months after an allogeneic BMT)similar, if not identical, to OLP (Müller, 2017). • Common scarring lesions (Carrozzo *et alli.*, 2019). • Sometimes leukoplakia-like (Carrozzo *et alli.*, 2019).

CGVHD: Chronic Graft vs host disease ; EOLP: Erosive oral lichen planus; OLCR: Oral lichenoid contact reaction; OLDR: Oral lichenoid drug reaction ; OLP: Oral lichen planus

iii.Signs, symptoms and clinical behavior

OLL manifests as dotted grey-white streaks, reticulated and plaque-like keratotic papules, Table 4, and also causes mucosal congestion, erosion, ulceration, atrophy, and blistering (Zhou *et alli.*, 2022). A symptom of OLR could be an asymmetrical appearance or interaction with filler materials such as amalgam or (very rarely) gold and composites (Schmidt-Westhausen, 2020).

Table 4. Signs and symptoms of Oral lichen planus (OLP) and Oral lichenoid lesions (OLL)

	Signs and symptoms
Oral lichen planus (OLP)	• Keratotic striae or a white plaque are the most common (Warnakulasuriya, 2020). • Asymptomatic (Warnakulasuriya, 2020; Warnakulasuriya*et alli.*, 2021). • The ulcerative/erosive variety is sore and painful (Warnakulasuriya, 2020; Warnakulasuriya *et alli.*, 2021).
Oral lichenoid lesions (OLL)	• Keratotic striae or a white plaque are the most frequent (Warnakulasuriya, 2020). • Red and atrophic spots may be painful (Warnakulasuriya*et alli.*, 2021). • Asymptomatic (Warnakulasuriya, 2020; Warnakulasuriya *et alli.*, 2021).
Oral Graft versus host disease (OGVHD)	• Atrophic and red regions may be painful (Warnakulasuriya *et alli.*, 2021).

4. Diagnosis

It has been challenging to make a clear diagnosis of OLP and OLL due to both the dynamic nature of the lesions and the comparable clinical and histologic appearances in varied situations.OLP and OLL are complex to distinguished clinically or histologically (Schmidt-Westhausen, 2020). To obtain a correct diagnosis, is essential to have a complete understand of the clinical and pathological variants of OLL and OLP, as well as a thorough comprehension of the patient's medical history and meticulous intra oral examination (Rotaru *et alli.*, 2020a).

Clinical and histopathologic similarities across diseases might impede diagnosis, as seen

in oral lichen planus (OLP) and oral lichenoid lesion (OLL). Despite having similar clinicopathological manifestations, the etiology, diagnosis, and prognosis of OLL and OLP differ, necessitating the separation of OLL and OLP. As a result, the oral physician and oral pathologist must be familiar with variations in clinicopathological aspects of both, as well as acquire a detailed history and do a complete mucocutaneous examination in addition to specific diagnostic testing. The challenges in differentiating between these two illnesses have been extensively researched in the literature, but no definitive result has been reached (Dudhia *et alli.*,2015).

OLL, unlike OLP, is a type IV hypersensitivity reaction to noxious agents such as corrosion products or medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), beta- blockers, and angiotensin-converting enzyme (ACE) inhibitors. As a result, OLL is also known as lichenoid drug eruption. OLP and OLL cannot be separated safely based on clinical or histological criteria. Both OLP and OLL efflorescences range from whitish lesions, such as striae, plaques, and papules, to reddish modifications that correspond to atrophy, erosion/ulceration, or bullae. These lesions may appear alone or in any combination. The usual histology of OLP and OLL is defined by an immunologic reaction dominated by CD8+ cytotoxic T cells, which directs against the basal layer of keratinocytes. As a result, apoptotic cells (known as Civatte bodies) can be discovered inside the oral squamous epithelium (Hertel*et alli.*, 2022).

Furthermore, there is a range of oral lichenoid lesions (OLL) that can throw the differential diagnosis off. These include lichenoid contact lesions, lichenoid lesions of graft versus host disease. and lichenoid drug reactions (nonsteroidal antiinflammatory medicines, some antihypertensives, and oral hypoglycemics, for example), can all contribute to the development of oral lichenoid reactions (OLR). A variety of dental restorative materials, including amalgam, gold, and nickel, have been associated with localized OLR in a number of patients. Several dermatoses (e.g., lupus erythematosus, erythema multiforme) may have some lichenoid characteristics, either clinically or histologically (Alrashdan, Cirillo and McCullough, 2016).

The term oral OLP now refers to lesions that have no identifiable trigger and are consequently "idiopathic," where as OLL refers to all other oral lesions that are associated with drug intake, systemic disease (such as chronic liver disease), food or flavor allergies, hypertension, and diabetes mellitus. Because many disorders have common clinical and

histological aspects, identical therapy may be employed in all of them. However, unlike OLP, OLL resolves after the causal agent is removed (Dudhia *et alli.*, 2015).

OLL and OLP are distinguished by two factors: (1) the relationship with drug administration, contact with a metal or food item, or systemic disease, and (2) the resolution when the offending agent is removed. However, the distinction is not always obvious (Dudhia *et alli.*, 2015). A close contact with a restoration, as well as the unilateral nature, point to OLL rather than OLP. Patch testing is suggested as a supplement to confirm lichenoid reactions to dental restorative materials (Warnakulasuriya, 2020). The presence of precipitating factors distinguishes oral lichenoid lesion (OLL) from OLP (Mendes *et alli.*, 2018).

The clinical (history and presentation), histopathologic, immunofluorescence, biomarker, reflectance confocal microscopy, fluorescence spectroscopy, and/or treatment trial aspects support the diagnosis of OLP and OLL (Rotaru *et alli.*, 2020a).

A specific oral lichenoid lesion can sometimes be detected visually without the need for furthertesting, but this is unusual. Oral lichenoid lesions can be difficult to diagnose because their clinical and histological characteristics frequently overlap. A complete history and clinical evaluation by a multidisciplinary team of specialists may be required to investigate oral involvement (Carrozzo *et alli.*, 2019).

The clinical features of idiopathic OLP are shared by oral lesions connected to chronic GVHD, chronic ulcerative stomatitis, lichenoid medication responses, and even lichenoid contact hypersensitivity. Also, the anatomic placements of lesions, the clinical kind, and prior treatments all influence the histopathologic characteristics. Consequently, biopsy specimens must be accompanied with clinical information (anatomic site,clinical history, and lesion meticulous description) (Rotaru *et alli.*, 2020).

For a clear and reliable conclusive diagnosis, a complete history and clinical features of lesions should be correlated with complicated tests such as histology, DIF, IIF, and cutaneous patch testing, Table 6 (Rotaru *et alli.*, 2020a). It is also crucial to note that the diagnostic process for OLP and OLL necessitates ongoing monitoring and, if necessary, further biopsies for histological evaluation and immunofluorescence tests (Rotaru *et alli.*, 2020b).

Because many lichenoid lesions have overlapping clinicopathological symptoms, using adjunct tests to confirm conclusive diagnosis is essential for proper therapy and prognosis of the lesions. Direct immunofluorescence (DIF) can be useful in this scenario. Although clinical and histopathological features are sufficient for diagnosing most patients with OLP and OLL, DIF is a key tool in differentiating some lichenoid lesions and may improve OLP and OLL diagnosis, particularly in lesions with typical clinical and histological features of OLP.

Even though not specific for OLP, direct immunofluorescence (DIF) may be necessary to distinguish OLP from other lichenoid diseases such as erythematous lupus, chronic ulcerative stomatitis (CUS), and lichen planus pemphigoid (LPP), especially when clinicopathological features coincide. Given the large number of oral lesions with a clinicopathological lichenoid pattern, additional tests to confirm conclusive diagnosis of lichenoid lesions are advised for proper management and prognosis of the lesions. DIF is an important technique for distinguishing some rare lichenoid lesions, such as LPP and CUS, and it has a better sensitivity when analyzing lesions with characteristic clinical and histological OLP features (Yamanaka *et alli.*, 2018).

If OLLs (OLCH, OLDR) disappear after the trigger has been identified and eliminated (in months or even years), it may indicate a successful diagnosis (therapeutic probation) (Rotaru *et alli.*, 2020a).

Table 5. Distinguishing Oral lichenoid lesions (OLL) from Oral lichen planus (OLP) adapted from (Müller, 2017).

Disease	Immunopathology
Oral lichen planus	• DIF: usually negative but may see shaggy depositsof fibrin and/or complement (C3) at BMZ and IgM-positive colloid bodies. • IIF: usually negative
Oral lichenoid drug reaction	• DIF: shaggy deposits of fibrin at BMZ and IgMpositive colloid bodies similar to OLP. • IIF: occasionally, it is possible to identify circulatingantibodies directed to the basal cells by their annular fluorescent distribution termed ‘string of pearls’ pattern
OLCR—amalgam and OLCR—cinnamon	• DIF: similar to OLP • IIF: usually negative
Chronic graft vs host disease	• DIF: similar to OLP • IIF: negative

BMZ: Basement membrane zone ; DIF: Direct immunofluorescence; IgM: Immunoglobulin M ; IIF: Indirect immunofluorescence; OLCR: Oral lichenoid contact reaction ; OLP: Oral lichen planus

i.Histopathology

Oral lichenoid lesions are frequently characterized histopathologically by a lichenoid tissue reaction with two main features: (1) a bandlike lymphohistiocytic infiltrate that fills the lamina propria; and (2) liquefactive degeneration of basal keratinocytes. These reactions could be the result of a variety of different causes, but they all have a common pathologic process: immune-mediated destruction to the oral epithelium basal cells (Al-Hashimi *et alli.,* 2007).

The histopathologic characteristics of oral lesions in lupus erythematosus are similar to those of OLP, OLDR, and OLCHR. In terms of mast cell number OLP has higher mast cells than oral lichenoid reactions (Rotaru *et alli.*, 2020a).

The oral mucosa can also show LP-like lesions as hyperkeratotic, white, thickened, inflammatory reactions known as "lichenoid." This reaction has been described using several terms, including OLL, oral lichenoid reaction (OLR), oral lichenoid tissue reaction, lichenoid contact stomatitis, and LP-like lesions (Dudhia *et alli.*, 2015).

Histopathologically, oral lichenoid drugs reactions reveal a subepithelial inflammatory infiltration with evident eosinophils and/or plasma cells. This infiltration is more diffuse and deeper than oral lichen planus, and it may seem perivascular. None of these characteristics have been reliably recorded, and other oral lichenoid conditions, such as discoid lupus erythematosus, may have similar histological abnormalities (Carrozzo *et alli.*, 2019). Histopathology may aid in the diagnosis of OLCL if it demonstrates a mixed cell subepithelial infiltration and a deeper diffuse distribution in the lamina propria (Carrozzo *et alli.*, 2019).

However, oral lichenoid contact lesions are usually difficult to distinguish from other oral lichenoid lesions and oral lichen planus after histopathological evaluation, Table 5 (Carrozzo *et alli.*, 2019). With the exception of eosinophilic infiltration and significant parakeratosis, lichenoid drug eruptions histologically resemble lichen planus (Rasul *et alli.*, 2022).

Histopathologic aspects vary depending on anatomic site, clinical type, stage of disease activity; microscopic diagnosis of OLP; and other considerations. As referred before, uniform oral lesion requires only one tissue sample; atypical oral lesions require samples from various different regions with varied mucosal clinical characteristics (Rotaru *et alli.*, 2020a). A biopsy would be a suitable clinical practice in the vast majority of cases, if not all, of patients. Histopathology, on the opposing side, can be subjective and nonspecific, and it is unlikely to differentiate between the different types of oral lichenoid lesions. Additional testing, such as direct and salt-split skin indirect immunofluorescence and ELISA tests, may be performed if a bullous disease, lichen planus pemphigoides, or chronic ulcerative stomatitis is suspected. In cases of recalcitrant and atypical mucocutaneous symptoms, additional study is required, including a PET-scan for total body cancer screening if paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome is suspected. Immunoblotting, immunoprecipitation, and ELISAs can also help with the diagnosis. When a medical history, clinical features, and immunological findings (e.g., positive antinuclear antibody test) suggest systemic lupus erythematosus, testing for anti-DNA antibodies as well as other autoantibodies such as anti-Sm, anti-RNP, anti-Ro/SSA and La/SSB, antiantiphospholipid and anticardiolipin should be considered (Carrozzo *et alli.*, 2019).

When examining oral biopsies with lichenoid features, it is critical to correlate the clinical

presentation with the histologic features for an assertive diagnosis (Müller, 2017).

Table 6. Differentiating histological features between Oral lichenoid lesions (OLL) and Orallichen planus (OLP) adapted from (Müller, 2017).

	Histology
Oral lichen planus	• Hyperparakeratosis, but orthokeratosis can occur. • Atrophic, acanthotic, or "sawtooth" epithelium. • Basal cell degeneration with leukocytic exocytosis and thepresence of Civatte bodies. • A band-like or patchy lymphocytic infiltration next to thebasal cells. • Limited to lamina propria. • Subepithelial clefting can occur in erosive OLP. • Plasmacells, in addition to lymphocytes, can be seen in gingival biopsies. • There is no evidence of epithelial dysplasia or verrucous architectural alteration.
Oral lichenoid lesions	• Strict lymphohistocytic infiltrate. • Diffuse and deeper distribution in lamina propria andsuperficial submucosa. • Focal parakeratosis, focal interruption of granular layerl cytoid bodies in keratinized and granular layers.
Oral lichenoid drugreaction	• Similar to OLP, but with more apoptotic keratinocytes. • The inflammation may be diffuse rather than band-like,with plasma cells and eosinophils involved. • Perivascular chronic inflammation is common.
Oral lichenoid contactreaction	• OLCR-amalgam: Histology is similar with OLP; however,tertiary lymphoid follicles can be detected. • OLCR-cinnamon: Epithelial acanthosis with elongated reteridges, interface mucositis, diffuse mixed inflammation with deep perivascular infiltrates.
Graft vs host disease	• Similar to OLP in that it includes basal cell degenerationand colloid bodies. • Chronic inflammatory infiltration can be sparser and mixed at times.

OLCR: Oral lichenoid contact reaction ; OLP: Oral lichen planus

5. Classifications

OLP and OLL diagnosis is a diagnostic challenge for clinicians. WHO introduced the OLP diagnostic criteria in 1978 and van der Meij and van der Waal modified it in 2003 (Van der Meij and Van der Waal, 2003; Rotaru *et alli.*, 2020b).

Van der Meij and Van der Waal suggested a revised set of OLP and OLL diagnostic criteria in2003, including clinical and histological characteristics. This new classification showed decreased inter- and intra-observer variability, allowing pathologists/researchers to make more reproducible diagnoses while reducing individual diagnostic variation. Furthermore, such information could contribute to improved clinical, pathological, and etiological definition of these lesions, eradicating certain biases associated with inaccurate nomenclature of these conditions. Such classification, however, has significant limitations because the proposed criteria are not universally present in all OLP and/or OLL patients (Mendes *et alli.*, 2018).

To differentiate OLL from OLP, a thorough history and complete mucocutaneous examination are required, as well as specific diagnostic testing (i.e. DIF, IIF, cutaneous patch testing) for confirmation of lesion and cause, because the best way to treat OLL is to identify the causing drug or material and replace it with another drug or material. If the causative agent cannot be stopped or if residual lesions exist following elimination of cause therapy for OLP, i.e. topical corticosteroids, topical corticosteroids can be used with unclear success for OLL depending on the degree and severity of residual disease. Above important, more universal diagnostic criteriawith treatment guidelines are essential for OLP and OLL in order to avoid misdiagnosis and subsequent malignant transformation mistakes (Dudhia *et alli.*, 2015).

Despite being histopathologically indicative of OLP, unilateral lesions typical of OLP would fall within the category of OLL based on the modified WHO criteria. Furthermore, despite the fact that OLP is a recognized precancerous condition/potentially malignant disorder, clinically typical OLP lesions with dysplasia will fall under the category of OLL. This modification of the older criteria for the diagnosis of OLP and OLL has resulted in a group of lesions that require careful consideration before devising a treatment plan; the treatment of OLP and OLL is completely different despite clinical and histopathological similarities. Furthermore, the malignant transformation rate of this entity will falsely

change in the literature over time as many OLP lesions diagnosed as OLL using the modified WHO criteria will show malignant transformation, resulting in a decrease in the malignant transformation of OLP and an increase in the malignant transformation of OLL (Dudhia *et alli.*, 2015).

OLP and OLL cannot be distinguished clinically or histologically. OLLs share clinical and histological characteristics. Despite documented variations between idiopathic LP and LDE, the WHO "gold standard" LP criteria do not differentiate between the two diseases (Dudhia *et alli.*, 2015).

According to the WHO, there are no clinical or histologic criteria for either OLP or OLL (Rotaru *et alli.*, 2020a).

Clinical and histological diagnostic criteria for oral lichen planus and lichenoid lesions are currently insufficient (Carrozzo *et alli.*, 2019).

In 2005, Issa *et alli.*, suggested site and association-based listing. Interestingly, the concept of topographical linkage is mentioned in both Waal's (2009) and Issa *et alli.*, (2005) classifications,Table 7. Both authors believe that intimate topographical linkage of OLLs with amalgam and other materials implies a cause-and-effect relationship and should be used for lesion naming. Van der Meij (2009) proposed a separate category for such lesions, referring to them as lichenoid contact responses (LCRs), and noted the absence of mention in the WHO monograph (Issa *et alli.*, 2005; Waal, 2009; Kamath, Setlur and Yerlagudda, 2015).

The WHO classification (van der Meij, Mast and van der Waal, 2007) provides a comprehensive enumeration of OLP and OLL traits, with the latter being diagnosed through exclusion rather than exclusion (Kamath, Setlur and Yerlagudda, 2015).

In 2009, Van der Waal established a causative classification based on the condition's etiological variables. The absence of distinguishing histological criteria is, of course, one of the classification's shortcomings (Kamath, Setlur and Yerlagudda, 2015).

Table 7. Different classifications proposed for Oral lichenoid lesions (OLL) over time.

<table>
<tr><th colspan="3">**Issa *et alli.*, 2005** (Issa *et alli.*, 2005)</th></tr>
<tr><th>Classified clinically into three groups</th><th>Classified according to their relationship with restorations</th><th>Classified according to their oral location</th></tr>
<tr><td>• White patches, striated, plaque, or reticular lesions
• Erosive or atrophic lesions
• Ulcerative lesions</td><td>• OLLs only in contact with restorations
• OLLs in clinical contact, and at least one addicional site without clinical contact with restorations
• OLLs without clinical contact with restorations</td><td>• OLLs located on the buccal mucosa (unilateral or bilateral)
• OLLs present on the lateral or dorsal surface ofthe tongue
• Gingival lichenoid lesions
• Other structures of oral mucosa ; lips, floor of the mouth, and palate</td></tr>
<tr><th colspan="3">**Modified WHO diagnostic criteria of oral lichen planus and oral lichenoid lesion (2007)**
(van der Meij, Mast and van der Waal, 2007)</th></tr>
<tr><th colspan="3">**Clinical and histopathologic criteria should be used to make a final diagnosis:**</th></tr>
<tr><td colspan="3">OLL: The term OLL will be used in the situations that follow:
• Clinically similar of OLP but histopathologically only compatible with OLP
• Histopathologically typical of OLP but clinically only compatible with OLP
• Clinically compatible with OLP and histopathologically similar to OLP</td></tr>
<tr><th colspan="3">**Van der Waal (2009)** (Waal, 2009)</th></tr>
<tr><th colspan="2">Clinical criteria</th><th>Histopathologic criteria</th></tr>
<tr><td colspan="2">• Amalgam restoration topographically-associated OLL
• Drug-related OLL
• OLL in chronic graft-versus- host disease
• OLL, unclassified (e.g., erythematous changes limited to the gingiva with no evidence of “classic” OLP else where in the oral cavity, or lesions having a lichen planus appearance, but that lack one or more characteristic clinical features, such as bilateral presentation)</td><td>N/A</td></tr>
<tr><th colspan="3">**Modified WHO diagnostic criteria of oral lichenoid lesion (2020)**
(Warnakulasuriya *et alli.*, 2021)</th></tr>
<tr><th colspan="2">Clinical presentation</th><th>Symptoms</th></tr>
<tr><td colspan="2">• Asymetrical
• White lines (reticular: lace-like, linear, or annular), papular, and sometimes plaque-like.
• Red and erosive, with white striae.</td><td>• Asymptomatic
• Red and atrophic spots may be painful</td></tr>
</table>

N/A: not available; OLL: Oral lichenoid lesion; OLLs: Oral lichenoid lesions; OLP: Oral lichen planus

6. Management and Treatment

A gradual strategy should be used in management and treatment of this conditions. The first stage is to establish a diagnosis based on history, clinical examination, and complex testing such as histopathology examination, direct immunofluorescence (DIF), indirect immunofluorescence (IIF), and cutaneous patch testing, as previously stated (Alrashdan, Cirilloand McCullough, 2016; Rotaru *et alli.*, 2020a).

The most important objective of any treatment for oral lichen planus/oral lichenoid lesions is symptom control; individuals with reticular and other asymptomatic lesions usually do not require active treatment (Carrozzo *et alli.*, 2019). In general, treatment should focus on curing atrophic and erosive/ulcerative lesions, reducing associated symptoms, and lowering the risk ofmalignant transformation (Alrashdan, Cirillo and McCullough, 2016).

Eliminating potential precipitating or inciting factors is an important initial step in treating symptomatic oral lichen planus/oral lichenoid lesions. Sharp or broken teeth, poorly fitting dentures, alcohol consumption, and smoking are all triggering factors and irritants that should be avoided or minimized (Carrozzo *et alli.*, 2019).

In patients with gingival disease, an effective oral hygiene regimen should be implemented (Alrashdan, Cirillo and McCullough, 2016). Plaque reduction may improve the lesions, consequently good oral hygiene and the use of chlorhexidine-containing mouthwash should bepromoted (Carrozzo *et alli.*, 2019).

A medication history should be collected in order to discover reversible causes of lichenoid eruptions, as removal of the offending medicine can be curative when achievable (Alrashdan, Cirillo and McCullough, 2016).

In many cases of oral lichen planus/oral lichenoid lesions are chronic, the patient's medical history, psychological condition, treatment compliance, and potential drug interactions must all be considered when determining the cost-effectiveness of any treatment process. Due the lack of a permanent cure, a variety of treatment methods for decreasing and treating the uncomfortable symptoms of oral lichen planus/oral lichenoid lesions have been established. Unexpectedly, a number of commonly used treatments are thought to produce lichenoid lesions.Topical therapies are typically utilized as the first

line of therapy considering they have few negative side effects, (Table 8). Systemic treatment, on the contrary, may be required if the lesions are widespread and affect the skin or other mucosae, or if the disease is recalcitrant. Most drugs used to treat oral lichen planus/oral lichenoid lesions are immunosuppressive, and few were created specifically for oral illness. As a result, adequate studies determining their efficacy are lacking. Furthermore, some features of the therapy, such as the ideal dose, treatment duration, safety, and real efficacy, are mostly unclear. Off-label usage of drugs used to treat oral lichen planus/oral lichenoid lesions should be reported to patients (Carrozzo *et alli.*, 2019).

Immunomodulating medications, such as topical and systemic corticosteroids, are often used to reduce inflammation and restore comfort in OLP and OLL patients. There is still controversy about whether such medicines should be used in OLP and OLL because they may suppress local cellmediated immunity and so increase the course of malignant growth. Corticosteroid medication has been suggested to not only speed the development of a tumor, but also to lessen symptoms. As a result, the chances of the problem progressing to an advanced stage before it is finally detected and treated increases (Van der Meij and Van der Waal, 2003).

Some oral lichenoid lesions, such as oral lichen planus, oral lichenoid contact lesions, oral lichenoid contact reactions, discoid lupus erythematosus, and chronic ulcerative stomatitis, respond better to topical therapy than others, which require systemic medications and multidisciplinary management (Carrozzo *et alli.*, 2019).

Patients with oral lichenoid contact lesions may benefit from targeted amalgam replacement, but also possible that simple restoration polishing and better oral hygiene could reduce plaque buildup and frictional trauma to the mucosa, improving the condition of the oral lichenoid contact lesion. Patients should, always, be informed about the benefits and risks of amalgam removal. It is also important to note the condition's cyclical nature, which is characterized by periods of spontaneous remission and exacerbation, the paucity of data in favor of amalgam replacement, and the unpredictability of the amalgam removal process. A number of risks should be fully disclosed, including the possibility of iatrogenic dental damage, the possibilityof lesions worsening immediately after amalgam replacement (especially if a rubber dam is not used), the shorter lifespan of some alternative materials, and the possibility of developing further allergic reactions involving

any of the recently added restoration materials (Carrozzo *et alli.*, 2019).

Withdrawal and replacement may necessitate medical consultation in cases of drug associations. It has frequently been found that, despite removal, lesions do not exhibit quick remission. This has been attributed to the offending drug molecule sensitizing the oral mucosal tissues, which continues as an independent cause long after removal (Baganbagan, Thongprasom and Scully, 2004).

i.Topical corticosteroids

Topical drug treatment is preferable since it has fewer side effects (Alrashdan, Cirillo and McCullough, 2016). Topical corticosteroids have become widely recognized as the first-line therapy for symptomatic oral lichen planus/oral lichenoid lesions. However, it is uncertain which steroid potential, formulation, concentration, or dose regimen is considered "standard of care". Ointments and suspensions are commonly used, although creams can have a harsh flavor and do not melt well with adhesive pastes, and gels almost always include alcohol and sting. Sprays, which are typically used to treat nasal allergies and asthma, can also be utilized intra- orally. In 30%-100% of treated patients, mid-potency corticosteroids such as triamcinolone acetonide 0.1% and betamethasone, potent fluorinated corticosteroids such as fluocinolone acetonide 0.1% and fluocinonide 0.05%, and super potent halogenated corticosteroids such as clobetasol propionate 0.05%, reduced painful symptoms (Carrozzo *et alli.*, 2019). Clobetasol ointment (0.05%) is applied on the painful areas, 3-4 times in 24 hours (Rotaru *et alli.*, 2020b). Adhesive pastes such as sodium carboxymethyl cellulose (Orabase, ConvaTec Ltd, Reading, UK) and hydroxyethyl cellulose, as well as specific drug delivery methods such as lipid-loaded microspheres, can improve adherence to the oral mucosa for an extended period of time. Iatrogenic Cushing's syndrome has been rarely documented with the use of topical corticosteroids, with acute pseudomembranous candidiasis being the most common severe side effect. This can be avoided by using antifungals (miconazole gel) or chlorhexidine mouthwash.Topical steroids may be best delivered using custom-made trays when lesions of oral lichen planus/oral lichenoid lesions are restricted to the gingivae (Carrozzo *et alli.*, 2019).

Empirical evidence suggests that mouth rinses are beneficial in patients with extensive

symptomatic OLP where the lesions are inaccessible for the application of ointments or gels. Higher potency corticosteroids, such as clobetasol, appear to be more effective, according to the research. Topical corticosteroids have few significant side effects since they are generally well tolerated. Secondary candidosis; nausea; oral use not tolerated; refractory response; mucosal atrophy; oral dryness; sore throat; unpleasant taste; and delayed healing have all been documented as side effects (Alrashdan, Cirillo and McCullough, 2016).

ii.Other topical agents

Other topical immunosuppressive or immunomodulatory agents, such as calcineurin inhibitors (cyclosporine, tacrolimus, or pimecrolimus) or retinoids, have been shown to be beneficial for symptomatic oral lichen planus/oral lichenoid lesions, particularly if the lesions are resistant to corticosteroids. Cyclosporine has been used as a mouthrinse (50-1,500 mg/d) or in adhesive bases (26-48 mg/d), however it is costly, not always efficacious, and less successful in causing clinical improvement than topical clobetasol. Tacrolimus is 10-100 times more powerful than cyclosporine and has a higher percutaneous absorption rate. Several uncontrolled, non- randomized investigations have shown that this drug is effective and safe in the treatment of refractory erosive oral lichenoid lesions at doses ranging from 0.03% to 0.1%. Burning on application is a typical adverse effect that affects <20% of people. Tacrolimus circulating therapeutic levels can be demonstrated after topical administration, and they can occasionally produce systemic adverse effects (Carrozzo *et alli.*, 2019). Topical tacrolimus can be applied twice daily (Protopic 0.1%) and tends to be effective in minimizing symptoms and healing lesions (Rotaru *et alli.*, 2020b). Pimecrolimus is the most recently approved calcineurin inhibitor for the treatment of oral lichen planus/oral lichenoid lesions. It is expected to have less immunosuppressive potency than cyclosporine and tacrolimus, and it has less penetration through the skin than topical steroids or topical tacrolimus. Nonetheless, a recent randomized controlled trial comparing pimecrolimus 1% vs. tacrolimus 0.1% in adhesive ointment in the treatment of symptomatic oral lichen planus/oral lichenoid lesions found no clinical difference.(Carrozzo *et alli.*, 2019).

Because of a probable increased risk of malignancy development (squamous cell

carcinoma and lymphoma) in patients using topical tacrolimus/pimecrolimus for cutaneous disorders, the US Food and Drug Administration issued a 'Black Box' warning on the use of tacrolimus and pimecrolimus. The decision was highly criticized in the medical community because it was based on case reports and animal data. A new 'deductive meta-analysis' showed no evidence ofan elevated risk of skin cancer with topical corticosteroids use. Two different articles described the development of oral squamous cell carcinoma in two patients with oral lichen planus/oral lichenoid lesions and a history of topical tacrolimus 0.1% therapy (Carrozzo *et alli.*, 2019).

Topical rapamycin (sirolimus), which reduces the response to interleukin-2 (IL-2) and limits T and B cell activation, has recently been proposed as an effective alternative therapy in refractory erosive oral lichen planus. Notably, rapamycin has both immunosuppressive and tumor inhibitor qualities, so it might theoretically manage unpleasant sensations while also lowering the chance of developing cancer in people with oral lichen planus/oral lichenoid lesions (Carrozzo *et alli.*, 2019).

Topical retinoids such as tretinoin, isotretinoin, fenretinide, and tezarotene are less effective and more prone to induce side effects than topical corticosteroids (Carrozzo *et alli.*, 2019).

iii.Systemic Therapy

Systemic corticosteroids are suggested for patients with severe painful oral lichen planus/oral lichenoid lesions that have not responded to topical therapy or who have widespread oral lichen planus/oral lichenoid lesions involving skin, genitals, esophagus, or scalp. Prednisolone, at a starting dose of 40-80 mg daily for 1-4 weeks, is usually enough to produce a noticeable reaction, which is often followed by a gradual reduction in dosage. The usual adult dose is 40 mg of prednisolone per day for the first 5 days and then the dose is reduced to 10-20 mg of prednisolone daily for the next 7-10 days. However, recurrences are prevalent, and systemic corticosteroids do not constitute a viable therapeutic option in chronic oral lichen planus/oral lichenoid lesions due to the toxicity profile associated with long-term therapy. Long-term therapy typically includes corticosteroid-sparing substances and other immunosuppressants such as azathioprine and mycophenolate mofetil, although there has been little rigorous researchof their efficacy in

the oral lichen planus/oral lichenoid lesions population. Hydroxychloroquine sulfate is first-line systemic therapy for severe discoid lupus erythematosus, although it may also be useful for chronic ulcerative stomatitis (Carrozzo *et alli.*, 2019).

Additionally, biologic agents such as Basiliximab, Etanercept, Efalizumab, and Alefacept have recently been proposed for the treatment of oral lichen planus/oral lichenoid lesions, particularly in patients with severe manifestations or those who have failed traditional first- and second-line therapy such as topical corticosteroids/topical calcineurin inhibitors (Carrozzo *et alli.*, 2019).

Phototherapy, surgery, and laser treatment (with carbon dioxide and low-dose excimer 308-nm laser) have been proposed as nonpharmacological treatments, although their efficacy has yet tobe established. It is worth noting that surgical intervention has been shown to aggravate oral lichen planus/oral lichenoid lesions (Carrozzo *et alli.*, 2019).

iv.Novel Treatments

New therapeutic techniques for OLP are being investigated, including topical aloe vera, biologics, low intensity laser, and oral curcuminoids (Alrashdan, Cirillo and McCullough, 2016).

Topical aloe vera and oral curcuminoids have been proposed as viable treatments for oral lichen planus/oral lichenoid lesions. However, various distinct aloe vera formulations have been recorded to date, and the amount of active product can vary substantially depending on the plant's age, growth and harvesting conditions, plant sections, and extraction procedures utilized. Furthermore, in up to 40% of patients, oral curcuminoids may cause significant side effects such as liver damage. Amlexanox and topical thalidomide have also been studied and found tobe more effective in controlling painful symptoms of oral lichen planus/oral lichenoid lesions than weak topical corticosteroids, which are no longer commonly used in the treatment of oral lichen planus/oral lichenoid lesions (Carrozzo *et alli.*, 2019).

Table 8. Therapy for Oral lichenoid lesions (OLL).

	Drug	Dose	Treatment duration	Author
Topical	**Corticosteroids**			
	Clobetasol ointment 0.05%	3/4 d	N/A	Carrozzo *et alli.*, 2019
	Clobetasol propionate 0.05%	N/A	N/A	Carrozzo *et alli.*, 2019
	Triamcinolone acetonide 0.1%	N/A	N/A	Carrozzo *et alli.*, 2019
	Betamethasone	N/A	N/A	Carrozzo *et alli.*, 2019
	Fluocinolone acetonide 0.1%	N/A	N/A	Carrozzo *et alli.*, 2019
	Fluocinonide 0.05%	N/A	N/A	Carrozzo *et alli.*, 2019
	Immunosuppressive/ Immunomodulatory agents			
	Cyclosporine mouthrinse	50-1.500mg/d	N/A	Carrozzo *et alli.*, 2019
	Cyclosporine adhesive bases	26-48mg/d	N/A	Carrozzo *et alli.*, 2019
	Tacrolimus 0.1%	2/d	N/A	Carrozzo *et alli.*, 2019; Rotaru *et alli.*, 2020
	Pimecrolimus 1%	N/A	N/A	Carrozzo *et alli.*, 2019
	Rapamycin (sirolimus)	N/A	N/A	Carrozzo *et alli.*, 2019
	Retinoids			
	Tretioin	N/A	N/A	Carrozzo *et alli.*, 2019
	Isotretinoin	N/A	N/A	Carrozzo *et alli.*, 2019
	Tezarotene	N/A	N/A	Carrozzo *et alli.*, 2019
Systemic	**Corticosteroids**			
	Prednisolone	40-80 mg/d	1-4 wk	Carrozzo *et alli.*, 2019
	Immunosuppresants			
	Azathioprine	N/A	N/A	Carrozzo *et alli.*, 2019
	Mycophenolate mofetil	N/A	N/A	Carrozzo *et alli.*, 2019
	Biologic agents			
	Basiliximab	N/A	N/A	Carrozzo *et alli.*, 2019
	Etanercept	N/A	N/A	Carrozzo *et alli.*,2019
	Efalizumab	N/A	N/A	Carrozzo *et alli.*, 2019
	Alefacept	N/A	N/A	Carrozzo *et alli.*, 2019
Other	**Low intensity laser**	N/A	N/A	Alrashdan *et alli.*, 2016
	Topical aloe vera	N/A	N/A	Alrashdan *et alli.*, 2016; Carrozzo *et alli.*, 2019
	Oral curcuminoids	N/A	N/A	Alrashdan *et alli.*, 2016; Carrozzo *et alli.*, 2019
	Amlexanox	N/A	N/A	Carrozzo *et alli.*, 2019
	Topical thalidomide	N/A	N/A	Carrozzo *et alli.*, 2019

D: day; mg/d: milligram per day; N/A: not available; wk: week; %: percent

7. Follow-up

It is indisputable that, due to the high malignant transformation rates of OLLs, regular follow-ups and biopsies are required to monitor the lesion's progression if signs and symptoms change overtime. Follow-up protocols that vary every three months following treatments during the first year can be accepted as part of long-term care for OLL patients, largely to detect changes that may indicate malignant transformation. Biannually biopsies are recommended for the next two years. If changes are observed in a lesion, recurrences or spreads, biopsies should be repeated (Kamath, Setlur and Yerlagudda, 2015).

Proper dental hygiene, removal of accumulated plaque, tartar, and films on restoration surfaces,and use of prophylactic mouth rinses can all help to remove the promoting factors (Kamath, Setlur and Yerlagudda, 2015).

8. Risk of Malignant Transformation

According to the World Health Organization's (WHO), OLL is one of the potentially malignant diseases (PMD) (Reibel *et alli.*, 2017). OLL has been identified as a distinct disease entity in oral potential malignant disorders (OPMDs), with a higher probability of malignant transformationthan OLP (Zhou *et alli.*, 2022). Patients who have OLL have a 3.2% higher probability of transformation due to contact or medication than individuals with OLP (Meij, Schepman and Waal, 2003).

New evidence suggests that oral lichenoid lesions (OLL) to restorative materials can develop to cancer (Warnakulasuriya, 2020). A total of 3.8% of OLRs have been proven to develop into malignancy (Oivio *et alli.*, 2020).

Oral lichenoid lesions of graft-versus-host disease (OLL-GVHD) and amalgam-associated lichenoid reaction are recognized to have an association with malignancy (Dudhia *et alli.*, 2015). Local therapy for OLL-GVHD rests in topical agents, predominantly corticosteroids (Al- Hashimi *et alli.*, 2007).

There is still no agreement on the potential changes in clinical behavior of the diseases in the group of lichenoid lesions and oral lichen planus in relation to the development of cancer (Carrozzo *et alli.*, 2019). The World Health Organization has recommended the

development of diagnostic criteria to differentiate between OLP and OLL in its latest volume on the Pathologyand Genetics of Head and Neck Tumors, but both lesions should be considered at risk of malignant transformation until such criteria are available (Alrashdan, Cirillo and McCullough,2016).

The management of OPMDs includes determining the accurate diagnosis, assessing the risk, counseling on risk factors, and selecting an appropriate plan of treatment. Most cases necessitate regular follow-up by an oral health specialist. Risk assessment can be done on two levels: identifying a high risk subject based on lifestyle and estimating the risk of the condition based on clinicopathological findings (Warnakulasuriya, 2020). Also assess the potential risk based on factors that have been found to increase the probability of malignant transformation of an OPMD. Advanced age, female sex, inability to quit risk factors, presence of red areas in white and red patches, leukoplakia bigger than 200 mm2, presence of lichenoid features, and the grade of dysplasia in the pathology report remain important determinants when determining the malignant potential of OL (Warnakulasuriya *et alli.*, 2011). The prevalence of OMLs rises with age, partly due to physiological changes in the oral cavity, but also to the long-term impactof risk behaviors. Reduced saliva flow and the long-term effects of local and systemic factors such as alcohol intake, smoking, snuf, and drug use predispose individuals to various lesions that do not exist in children, in contrast to some normal mucosal variations that do exist in youth, such as geographic tongue (Oivio *et alli.*, 2020). The atrophic, erosive, and ulcerative forms are believed to expose the mucosa to damage from carcinogenic agents (Meij, Schepmanand Waal, 2003).

Recently, an algorithm has been created to assist clinicians in identifying high-risk lesions that require appropriate interventions (Speight, Khurram and Kujan, 2018). All patients with OPMD should be counseled for individual risk factors identified in their social history. Their objectiveis to reduce their future risk of cancer by quitting smoking, drinking in moderation, and, in thecase of Asian patients, quitting betel quid (areca nut) consumption (Warnakulasuriya, 2020). There are solid learning resources and guidelines for smoking cessation, and the practitioner should develop skills in providing brief interventions in clinical practice (Fiore and Baker, 2011). There is enough data to emphasize the need of quitting smoking to aid in the reversal of oral leukoplakia (Warnakulasuriya, 2020). Clinical trials are being conducted to investigate techniques for promoting the cessation of areca nut use (Moss *et alli.*, 2015). Chemoprevention trials on

oral leukoplakia have had a number of methodological limitations and adverse effects, and no solid evidence of effectiveness has been produced (Chau *et alli.*, 2017; Lodi *et alli.*, 2017).

However, dietary and nutrition guidelines for at least 5-portions of antioxidant-rich fruits and vegetables each day may help reduce chances (Warnakulasuriya, 2020). According to a meta- analysis of interventional studies, excision of oral leukoplakias may minimize the incidence of transformation (Mehanna *et alli.*, 2009). Based on these findings, it is currently advised that high risk lesions with moderate or severe dysplasia, such as erythroplakias, erythroleukoplakias, or leukoplakias, be excised in the absence of any surgical contraindications. There are no medical treatments for oral submucous fibrosis that are supported by evidence (Kerr *et alli.*, 2011; Warnakulasuriya and Kerr, 2016). Zinc supplements have been reported to alleviate symptomsof burning mouth. Clinical trials are being done using curcumin (Al-Maweri, 2019). Because cancer might develop throughout the natural course of an OPMD, it is important that patients be followed up on at regular intervals. The intervals between follow-ups should be determined based on the individual risk assessment and patient compliance (Warnakulasuriya, 2020).

An OPMD may be a risk factor for the development of oral cancer. The most significant feature is consequently secondary prevention, particularly patient education. Avoiding dangerous lifestyle choices may help to slow the development of an OPMD. There are currently no effective chemo preventive methods; nevertheless, clinical trials are ongoing, and removal of high-risk lesions is advised. Any patient diagnosed with an OPMD should have regular accessto health care facilities (Warnakulasuriya, 2020). Patients with OLL are more likely to develop a cancer and this risk increases if the patient is a smoker, alcoholic, or has hepatitis C. Despitethe fact that the risk of malignant transformation between individuals with OLP and OLL is lower than in individuals with other potentially malignant illnesses, all patients must be actively followed up on (Rotaru *et alli.*, 2020a).

In the future, molecular markers that aid in the diagnosis or prediction of possible malignant transformation of oral lichen planus and lichenoid disorders may become available (Al-Hashimi*et alli.*, 2007).

III. DISCUSSION

The words "oral lichen planus" and " oral lichenoid lesions" have long been the source of debate and controversy. The latter term is widely used to characterize oral lesions that mimic oral lichen planus both clinically and histopathologically but do not provide a cancer risk, or to suggest an unclear diagnosis of oral lichen planus (Carrozzo *et alli.*, 2019; Warnakulasuriya, 2020; Warnakulasuriya *et alli.*, 2021; Lehner, Agbo-Godeau and Bertolus, 2022). The oral lichen planus and lichenoid lesions group was proposed to be divided into four different conditions atthe 2006 World Workshop in Oral Medicine IV: oral lichen planus, oral lichenoid drug reactions caused by systemic drug exposure, oral lichenoid contact lesions caused by localized hypersensitivity to dental materials, and oral lichenoid lesions of graft-versus-host disease. Despite being a step forward, this classification did not provide acceptable clinical and histological criteria for distinguishing these three types of lichenoid disorders from oral lichen planus. Furthermore, a number of other disease entities with clinical and/or histological similarities to lichenoid tissue reaction/interface dermatitis were excluded. Other authors, Cortés-Ramírez *et alli.*, Ismail *et alli.*, Van Der Meij and Van Der Waal, have proposed alternative classifications (van der Meij *et alli.*, 1999; Ismail, Kumar and Zain, 2007; Cortés-Ramírez *et alli.*, 2009). Overall, there is still debate over the classification, diagnostic criteria, clinical features,and therapy of oral lichenoid disorders (Carrozzo *et alli.*, 2019; Rotaru *et alli.*, 2020a). More research with larger case studies is needed to validate these findings on a larger scale. As previously mentioned, several clinical, histological, immunological, and genetic criteria have been proposed in the literature to differentiate OLP and OLL; nevertheless, there is currently no clear cut off for facilitating their segregation. Furthermore, because the majority of the presented information is based on observational research, such data must be interpreted with caution due to inherent biases. Because there have been few research including indicators that aid in the differentiation of OLP and OLL cases, prospective studies with higher evidence levels are still required to better understand the pathophysiology and reliable segregational markers of these lesions (Mendes *et alli.*, 2018).

A search of the scientific literature carried out by González-Moles *et alli.*, resulted in 113 publications that use the term OLL in 6 distinct definitions (that were suggested by Van der Meij and Van de Waal (Van der Meij and Van der Waal, 2003), taking into account OLLs as lichenoid reactions caused by amalgam contact, as lichenoid reactions to drugs, such as oral lesions in the context of CGVHD, considering OLP/lichenoid reactions

jointly as any of the above, and finally there is a group of papers that do not define what they include under the term OLL (González-Moles *et alli.*, 2019). Given this context, it is clear that the lack of a definition of OLL causes significant confusion among the clinicians and researchers involved in the subject. The higher importance of the OLL term comes from the fact that Van der Meij and Vander Waal believed them to be the exclusive depositories of risk of development to oral cancer, which other authors claim is not the case with OLP (Van der Meij and Van der Waal, 2003). The claim that was proposed by both authors, has been widely utilized in later articles, with a snowball effect, despite the lack of evidence-based scientific support of such an important aspect. Many authors concluded that this was a modification proposed by the WHO based on how it was presented by Van Der Meij and Van Der Waal, 2003, although this was not the case (González-Moles *et alli.*, 2019 ; Ramos-García *et alli.*, 2021).

The diagnostic situation for OLP and OLL has changed as a result of the revised WHO criteria(2003). It is difficult to say if this is an evolution of our understanding for clinical entities based on accumulated knowledge through time, or a revolution leading to the conclusion that past studies and literature on these two entities contained significant inconsistencies. Despite this, regarding diagnosis authors referrer that distinguishing between OLP and OLL can be challenging (Dudhia *et alli.*, 2015; Schmidt-Westhausen, 2020; Lu and Zhou, 2021), most agreed that for a clear and reliable conclusive diagnosis, a complete medical and dental history and oral clinical exam of lesions should be correlated with the biopsy results tests (such as histology,DIF, IIF) and cutaneous patch testing if necessary. It is also crucial to note that the diagnostic process for OLP and OLL necessitates ongoing monitoring and, if necessary, further biopsies for histological evaluation and immunofluorescence tests because of the risk of malignant transformation (Alrashdan, Cirillo and McCullough, 2016; Rotaru *et alli.*, 2020b; Hertel *et alli.*, 2022).

In order to facilitate such segregation, a group of authors proposed that histopathological features such as strict band-like infiltration, atrophic epithelium, saw toothed rete ridges, and Max Joseph space were more common in OLP than OLL. Lip involvement, deep connective tissue infiltration, and hyperparakeratosis, on the other hand, have been described as valid markers for the diagnosis of OLL (Al-Hashimi *et alli.*, 2007; Casparis *et alli.*, 2015). In 2014, Arreaza, Rivera and Correnti discovered that OLP had higher COX-2 expression than OLL (Arreaza, Rivera and Correnti, 2014). Following that, (Batu *et alli.*, 2016) discovered higher prolidase activity, oxidative stress, and an imbalance in

the antioxidant defense system in bodily fluids of OLP- and OLL-affected individuals as compared to healthy people. However, prolidase activity and oxidative stress levels were practically same in OLP and OLL patients (Arreaza, Rivera and Correnti, 2014; Batu *et alli.*, 2016; Mendes *et alli.*, 2018).

Some oral lichenoid lesions, oral lichenoid drugs reactions, and oral lichenoid contact lesions, do not have acceptable diagnostic tests, necessitating additional research on this topic (Carrozzo*et alli.*, 2019).

Less is known about lichenoid reactions caused by silver amalgam contact, lichenoid reactions caused by medications, lesions that arise in the context of CGVHD, and other types of lichenoid lesions for which there is insufficient scientific evidence. OLL, as suggested by Van Der Meij and Van Der Waal, represents atypical variants of OLP that are less classical in appearance, both clinically and histologically, and should be classified as "atypical OLP lesions" within the OLP subgroup. The term "oral mucosal reactions to restorative materials, drugs, or tissue grafts"then applies to these reactions (González-Moles, Ramos-García and Warnakulasuriya, 2021). OLR has been associated with a variety of medications and dental materials, however only a few have been empirically proven (Alrashdan, Cirillo and McCullough, 2016). The appearanceof lesions has nothing to do with the start of a medicine or the usage of cinnamon-containing items (D. Rotaru *et alli.*, 2020). Oral lichenoid contact lesions to amalgams are assumed to be an example of delayed hypersensitivity to low-level mercury exposure (Coombs and Gell classification: type IV) (Carrozzo *et alli.*, 2019). Hypersensitivity reactions on the oral mucosa can be caused by resin-based composite, gold, and amalgam and their components (Grossmann,2015).

According to Lygre *et alli.*, the main cause of OLL was an allergic reaction to dental materials, with amalgam fillings causing 84% of cases. About 2% of the population has OLL caused by amalgam restorations. Although uncommon, the composite resin can be associated with OLL (Lygre *et alli.*, 2003; de Mattos Camargo Grossmann, 2015). The ability of amalgam fillings to cause oral lichenoid contact lesions has yet to be proven in an animal model. Another study bySeno *et alli.*, found that non-toxic mercury can develop lupus-like oral mucosal lesions in the same animal model (Brown Norway rats) but with different exposure modalities (Seno *et alli.*, 2013; Carrozzo *et alli.*, 2019). Thornhill *et alli.* discovered that patch tests for amalgam or mercury were positive in 70% of amalgam

contact hypersensitivity lesions (presented as lichenoid reactions), but only 3.9% of OLP cases (Alrashdan, Cirillo and McCullough, 2016). Accordingto some authors, when the dental restoration is removed and replaced, there's a improvement (Al-Hashimi *et alli.*, 2007; Dudhia *et alli.*, 2015). Unfortunately, there is no clear evidence that patients with OLP or OLR would benefit from having their amalgam restorations updated on a regular basis. A theory attempting to explain the pathogenesis of OLR was proposed, based on the assumption that dental materials in direct contact with the oral mucosa may directly alter the antigenicity of basal keratinocytes through the release of mercury or other products, resulting in a type IV/delayed hypersensitivity immune response (Alrashdan, Cirillo and McCullough, 2016). The most reliable way for diagnosing and managing lichenoid drug reactions is to observe if the reaction disappears after the offending drug is removed, and whether it returns when the patient is challenged again. However, because this is both impractical and potentially dangerous, empiric withdrawal of a potentially offending medicine and replacement with another agent may not be required (Alrashdan, Cirillo and McCullough,2016).

Although some authors have reported that 90% of lesions improved after amalgam replacement in people with positive patch tests and lichenoid lesions in close contact with amalgam fillings,there is insufficient evidence to support routine removal of all amalgam restorations in patients with oral lichen planus or oral lichenoid contact lesions (Carrozzo *et alli.*, 2019).

According to Al-Hashimi *et alli.*, oral lichenoid drug reactions (OLDR) are infrequent in comparison to cutaneous lichenoid drug reactions. Recently, the literature has been filled with case reports and a few small studies of oral lichenoid medication responses to ACE inhibitors and nonsteroidal anti-inflammatory medicines (NSAIDs). Oral hypoglycemic medications, penicillamine, and gold, on the other hand, have been regularly implicated. There are no obvious clinical or histological signs that distinguish OLDR from oral lichen planus or other lichenoid disorders (Al-Hashimi *et alli.*, 2007). Another study from Dudhia *et alli.*, 2015, the prevalence of oral lichenoid drug reactions (OLDR) appears to be increasing, maybe due to theunderstanding that the entity has a source other than idiopathic LP. The increased prevalence may also be due to the advent of various new classes of drugs that have a higher proclivity forlichenoid responses as a side effect. drug eruptions (LDEs) can be considered a variant of LP (Dudhia *et alli.*, 2015). A lichenoid reaction similar to lichen planus develops in tobacco chewersat the location of quid or

gutka placement. Betel quid chewing has been discovered to be strongly related with this lesion, which arises at the site of quid placement. Patil *et alli.* detected lesions in only 1.5% of their patients in their study (Choudhary *et alli.*, 2022).

OLL/OLP have been referred as a possible adverse drug reaction to COVID-19 vaccinations, particularly against mRNA LNP. The findings from real-world data indicate that the development of OLL/OLP is an uncommon adverse medication reaction to COVID-19 vaccinations, particularly mRNA LNP. However, in the case of OLL, spontaneous remission may be predicted over time. As a result, the current research indicated that not limit the use of COVID-19 vaccinations in large proportions of the population, because of this possible adverse reaction. As a result, it should be presumed with precaution that the presentation of the viral spike protein to the host immune system may play a role in the pathogenic mechanism generating OLL/OLP after COVID-19 vaccinations. Despite this information, it is unknown which specific component of the vaccines is responsible for OLL/OLP. Furthermore, additional research is needed to uncover the underlying pathogenic mechanisms (Hertel *et alli.*, 2022).

Treatment options vary from topical application to systemic therapies depending on signs and symptoms of the patient. Published papers stated that treatment should be started from topical to systemic if need (Alrashdan, Cirillo and McCullough, 2016). Eliminating potential precipitating or inciting factors is an important initial step, like amalgam removal but in case of OLL associated with medication, it is more complex, because sometimes maybe complicated to change the drug, nevertheless it is important to discuss the case with the prescribing Doctor,to see if other option is possible. Ointments and sprays with corticosteroid are the usually first line of topical treatment, on detriment of creams (no intra oral adhesion). Carrozzo *et alli.*, 2019, proposed the use of mild-potency corticosteroids such as triamcinolone acetonide 0.1% and betamethasone, potent fluorinated corticosteroids such as fluocinolone acetonide 0.1% and fluocinonide 0.05%, and super potent halogenated corticosteroids such as clobetasol propionate0.05%, reduced painful symptoms. On the other hand Rotatu *et alli.* 2020, used clobetasol ointment (0.05%) is applied on the painful areas, 3-4 times in 24 hours with good results. These options treatments still have to be validated with studies with more patients. Systemic therapies should be save for more aggressive diseases or widespread oral lesions associated skin or other mucosae involvement, or if the disease is recalcitrant. It is worth mentioning, however, that scientific evidence on the use of systemic medicines in the

treatment of OLP is primarily limited to non-randomized clinical trials and is often equivocal (Alrashdan, Cirillo and McCullough, 2016). Other topical immunosuppressive or immunomodulatory agents, such as calcineurin inhibitors (cyclosporine, tacrolimus-twice a day (Carrozzo *et alli.*, 2019; Rotaru *et alli.*, 2020b), or pimecrolimus) Cyclosporine has been used as a mouthrinse (50-1,500 mg/d) or in adhesive bases (26-48 mg/d), Carrozzo *et alli.*, 2019. Evidence seams to point out that topical retinois, immunosuppressive or immunomodulatory drugs are prone to induce more side effects and be less effective when compared with topical steroids (Carrozzo *et alli.*, 2019). Systemic treatment with corticosteroids should be no longer that 4 weeks, usual treatment is 40mg predenisolone for 5 days reducing dose to 10-20mg/day for 10 days, on ideal conditions will be enough to have good results Other proposed agents are the same as used in OLP, corticosteroid-sparing substances and other immunosuppressants such as azathioprine and mycophenolate mofetil, although there has been little rigorous research of their efficacy. Novel biologic agents as Basiliximab, Etanercept, Efalizumab, and Alefacept have been proposed for causes where traditional treatment options have failed but still little research has been published (Carrozzo *et alli.*, 2019). Alrashdan, Cirillo and McCullough in 2016 suggested that topical aloe vera and curcuminoids or low intensity laser may improve OLL, with evidence based proven yet (Alrashdan, Cirillo and McCullough, 2016).

Regarding the risk of malignant transformation associated with OLL, it is noted that Lu and Zhou declare, "More importantly, recent systemic reviews revealed that OLL has a higher rate of malignant transformation than OLP, further justifying the need to differentiate the two disorders from each other". Furthermore, recent research published in Oral Diseases indicates that when investigations on OLP or OLL malignancy are conducted under strict methodologicalquality requirements, OLP malignancy figures are greater than OLL (2.28% vs 2.11%) without significant differences (p = 0.880) (González-Moles, Ramos-García and Warnakulasuriya, 2021; Lu and Zhou, 2021). Another recent study on this topic, found that the percentage of malignant transformation attributed to OLL are based on 6 systematic reviews, (Fitzpatrick, Hirsch and Gordon, 2014; Aghbari *et alli.*, 2017; Giuliani *et alli.*, 2019; González-Moles *et alli.*, 2019; Iocca *et alli.*, 2020; González-Moles, Ramos-García and Warnakulasuriya, 2021), all of which refer to a small number of primary-level studies, which usually have errors in methodology. Based on the notion of Van Der Meij and Van Der Waal, we assume that OLLs,like OLP, behave as

potentially malignant oral illnesses, however it has yet to be proved whether their malignant rate is higher than OLP (Warnakulasuriya *et alli.*, 2021). Some studies,on the other hand, demonstrate that OLLs (as defined by Van der Meij and Van der Waal) do not have a significantly higher risk of developing oral cancer than OLP (González-Moles *et alli.*,2019; González-Moles, Ramos-García and Warnakulasuriya, 2021).The World Health Organization has recommended the development of diagnostic criteria to differentiate between OLP and OLL in its latest volume on the Pathology and Genetics of Head and Neck Tumors, but both lesions should be considered at risk of malignant transformation until such criteria are available (Alrashdan, Cirillo and McCullough, 2016; Speight and Takata, 2018). In 2003, Meij, Schepman and Waal, and later, in 2008, Gonzalez-Moles *et alli.*, suggested that OLL, rather than OLP, are more likely to transform into cancer (Meij, Schepman and Waal, 2003; Van der Meijand Van der Waal, 2003; Gonzalez-Moles, Scully and Gil-Montoya, 2008). The effect of OLP therapies, most often immunosuppressive drugs, on OLP malignant transformation is unknown. Immunosuppressive drugs influence the severity and course of OLP, but they may potentially cause malignant transformation also (Alrashdan, Cirillo and McCullough, 2016). Immunomodulating treatments, such as topical and systemic corticosteroids, are often used to reduce inflammation and restore comfort in OLP and OLL patients. There is still controversy about whether such medicines should be used in OLP and OLL because they may suppress local cell-mediated immunity and change the course of malignant transformation. Oral painful lesions of oral lichen planus/oral lichenoid lesions are commonly managed with topical corticosteroids and immunosuppressants, although severe recalcitrant oral disease and extra-oral manifestations typically require systemic immunosuppression (Carrozzo *et alli.*, 2019). Corticosteroid medication has been suggested to not only accelerate the development of a malignancy, but also alleviate symptoms. As a result, the risk of the problem progressing to an advanced stage before it is finally detected and treated increases with prolong treatments (Meij,Schepman and Waal, 2003). Some of the disorders in the oral lichen planus/oral lichenoid lesions group are associated with an increased risk of oral cancer development and should be carefully and regularly monitored (Carrozzo *et alli.*, 2019). Some new treatment modalities have been recently introduced; however, the clinical evidence for their use is still inconclusive. In the light of the ongoing debate regarding the potentially malignant nature of OLP and OLL, a long-term follow-up protocol is essential (Alrashdan, Cirillo and McCullough, 2016). Plaque reduction can improve lesions; hence an excellent oral hygiene regimen

should be encouraged. Several approaches for distinguishing OLL from OLP have been presented (Eisen, 2002; Ismail,Kumar and Zain, 2007). According to Jahanshahi, Maleki and Ghalayani, the number of degranulated mast cells and epithelial thickness were higher in OLL than in OLP (Jahanshahi,Maleki and Ghalayani, 2012). When compared to OLP, Reddy *et alli.* and Mendes *et alli.*, found a higher number of degranulated mast cells in OLL (Mendes *et alli.*, 2018). Furthermore, they reported an increase in the number of eosinophils and capillaries in OLL compared to OLP andnormal mucosa, this may be linked to the higher risk of malignant transformation, but more research on the topic is mandatory (Batu *et alli.*, 2016).

IV. CONCLUSIONS

Oral lichenoid lesions (OLLs) are a group of oral mucosal disorders that have lichenoid characteristics but does not match the diagnostic criteria for Oral Lichen Planus (OLP). They represent a diagnostic challenge due to their similarities with OLP in terms of clinical and histological features. However, OLLs have distinct characteristics that distinguish them, such as asymmetry, absence of typical OLP manifestations, and different etiological factors.

The underlying causes of OLLs are not fully understood, but they are thought to cause by external triggers and also systematic disorders.

Accurate diagnosis of OLLs is essential to ensure appropriate management and treatment. Medical and dental history, supplemented by histopathological evaluation, plays a crucial role in distinguishing OLL. Histologically, OLLs display lichenoid inflammation and characteristic epithelial changes.

Treatment of OLLs focuses on alleviating symptoms, reducing inflammation, and lowering the risk of malignant transformation. Treatment options include topical or systemic corticosteroids, immunomodulatory agents, and identification and elimination of potential triggering factors. Long-term monitoring and regular follow-up with specialized healthcare professionals are essential to ensure proper management and evaluate treatment response and to monitor changes in the lesion clinical presentation, as the risk of malignant transformation is still not fulling understood.

Continued research efforts are necessary to deepen our understanding of OLLs, improve diagnostic methods, refine treatment strategies, and enhance the overall care and outcomes for individuals affected.

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