MALIGNANT TRANSFORMATION IN ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS: A RETROSPECTIVE STUDY

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MALIGNANT TRANSFORMATION IN ORAL LICHEN PLANUS AND ORAL LICHENOID LESIONS: A RETROSPECTIVE STUDY

ABSTRACT

Background: Oral lichen planus (OLP) and oral lichenoid lesions (OLLs) are chronic inflammatory diseases associated with T-cell mediated immunological dysfunction and are classified as oral potentially malignant disorders (OPMDs). Studies have provided evidence of malignant potential of OLP and OLL but studies targeting Asian population is lacking. There is inconsistency in the malignant transformation (MT) rate of OLP and OLL. **Objectives**: The aim of this study was to determine the MT rate of OLP and OLL diagnosed at the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya. The specific objectives were to determine the prevalence of OLP/OLL diagnosed at the Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya. This study also sought to determine the socio-demographic, clinical features, histopathological features and MT rate of OLP and OLL in patients seeking treatment at the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya. **Methods**: A retrospective study was conducted by retrieving pathologic reports of OLP, OLL and oral epithelial dysplasia (OED) with a provisional diagnosis of OLP and OLL from the year 2008-2018. Clinical notes of the retrieved cases were reviewed to look for evidence of malignant transformation. Histopathological slides were reviewed to evaluate the histopathological features of OLP, OLL and OLP/OLL with dysplasia. **Results**: The prevalence of OLP/OLL was 5.7%. Most of the cases were OLL, followed by OLP and OLP/OLL with dysplasia. The overall MT rate for OLP was 1.89%. The specific MT rate for OLP, OLL and OLP/OLL with dysplasia was 0%, 0% and 12.5% respectively. The most common dysplastic features seen were premature keratinization in single cell and generalized premature keratinization. **Conclusions**: OLP/OLL with dysplasia showed the highest MT rate. It is

important to regularly follow-up OLP and OLL patients, particularly those with dysplastic changes.

Keywords: lichen planus, lichenoid lesions, epithelial dysplasia, malignant transformation

TRANSFORMASI MALIGNA DALAM LIKEN PLANUS ORAL DAN LESI LIKENOID ORAL: SATU KAJIAN RETROSPEKTIF

ABSTRAK

Latar Belakang: Liken planus oral (OLP) dan lesi lichenoid oral (OLL) adalah penyakit radang kronik yang dikaitkan dengan disfungsi imunologi yang dimediasi oleh sel T dan diklasifikasikan sebagai gangguan oral berpotensi malignan (OPMD). Kajian telah memberikan bukti potensi malignan OLP dan OLL tetapi kajian yang mensasarkan populasi Asia masih kurang. Terdapat ketidakseragaman dalam kadar transformasi malignan (MT) OLP dan OLL. **Objektif**: Tujuan kajian ini adalah untuk menentukan kadar MT OLP dan OLL yang didiagnosis di Klinik Perubatan Mulut, Fakulti Pergigian, Universiti Malaya. Objektif khusus adalah untuk menentukan prevalensi OLP/OLL yang didiagnosis di Unit Patologi Oral Diagnostik, Fakulti Pergigian, Universiti Malaya. Kajian ini juga bertujuan untuk menentukan ciri-ciri sosio-demografi, ciri-ciri klinikal, ciri-ciri histopatologi dan kadar MT OLP dan OLL dalam pesakit yang mendapatkan rawatan di Klinik Perubatan Mulut, Fakulti Pergigian, Universiti Malaya. **Kaedah**: Satu kajian retrospektif telah dijalankan dengan mengambil laporan patologi OLP, OLL dan displasia epitelium oral (OED) dengan diagnosis sementara OLP dan OLL dari tahun 2008-2018. Nota klinikal kes yang diambil semula dikaji untuk mencari bukti transformasi malignan. Slaid histopatologi dikaji untuk menilai ciri-ciri histopatologi OLP, OLL dan OLP/OLL dengan displasia. **Keputusan**: Prevalensi OLP/OLL adalah 5.7%. Kebanyakan kes adalah OLL, diikuti oleh OLP dan OLP/OLL dengan displasia. Kadar MT keseluruhan untuk OLP adalah 1.89%. Kadar MT khusus untuk OLP, OLL dan OLP/OLL dengan displasia masing-masing adalah 0%, 0% dan 12.5%. Ciri-ciri displasia yang paling biasa dilihat adalah keratinisasi pramatang dalam sel tunggal dan keratinisasi pramatang umum. **Kesimpulan**: OLP/OLL dengan displasia menunjukkan

kadar MT tertinggi.Adalah penting untuk membuat susulan secara berkala dengan pesakit OLP dan OLL, terutamanya mereka yang mempunyai perubahan displastik.

Kata kunci: lichen planus, lesi lichenoid, displasia epitelium, transformasi malignan

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LIST OF SYMBOLS AND ABBREVIATIONS

AAOMP : American Association of Oral and Maxillofacial Pathology

ACE : Angiotensin-converting enzyme

BQOLL : Betel-quid induced oral lichenoid lesion

C-D-R : Challenge-Dechallenge-Rechallenge

DIF : Direct immunofluorescence

DM : Diabetes mellitus

GVHD : Graft-versus-host disease

HCV : Hepatitis C virus

H&E : Haematoxylin & eosin

IIF : Indirect immunofluorescence

LOH : Loss of heterozygosity

MT : Malignant transformation

NHMS : National Health and Morbidity Survey

NSAID : Non-steroidal anti-inflammatory drugs

OED : Oral epithelial dysplasia

OLCL : Oral lichenoid contact lesions

OLD : Oral lichenoid dysplasia

OLDR : Oral lichenoid drug reactions

OLL : Oral lichenoid lesions

OLL-GVHD : Oral lichenoid lesion-Graft versus host disease

OLP : Oral lichen planus

OPMD : Oral potentially malignant disorder

OSCC : Oral squamous cell carcinoma

PAS : Periodic Acid Shiff

PVL : Proliferative verrucous leukoplakia

SPSS : Statistical Package for Social Sciences

TSH : Thyroid stimulating hormone

WHO : World Health Organization

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory disease associated with cell-mediated immunological dysfunction affecting about 1.01% of the global population (González-Moles, Warnakulasuriya, et al., 2020). OLP commonly presents as reticular white striations involving the oral mucosa and is usually asymptomatic in non-erosive form (Carrozzo et al., 2019; Cheng et al., 2016; González-Moles et al., 2021). Van der Meij and Van der Waal (2003) proposed the term "oral lichenoid lesion" (OLL) to describe a group of lesions that resemble OLP but lacking the typical clinical and histopathological features of OLP. In the 2003 modified WHO diagnostic criteria for OLP, epithelial dysplasia was quoted as an exclusion criterion, which is in consensus with Krutchkoff & Eisenberg's idea of "oral lichenoid dysplasia" (OLD) as a distinct entity. OLD represents lesions demonstrating both dysplastic and lichenoid features and having higher risk of malignant transformation (MT) compared to OLP and OLL (Shearston et al., 2019). Studies are ongoing to determine whether OLD is an OLP that has transformed into a lesion exhibiting potentially malignant features or a potentially malignant lesion with lichenoid appearances. Nevertheless, various papers have been published to study the MT in OLP, OLL and OLD. The WHO Collaborating Centre for Oral Cancer classified OLP as an oral potentially malignant disorder (OPMD) in the year 2005 and for the first time, included OLL as an OPMD in the year 2020 (Warnakulasuriya et al., 2021; Warnakulasuriya et al., 2023). Various studies have provided evidence of malignant potential of OLP and OLL (Aghbari et al., 2017; Fitzpatrick, Hirsch, et al., 2014; Giuliani et al., 2019; Guan et al., 2020; Iocca et al., 2020). However, most of the studies on MT of OLP were reported in North America and Europe (González-Moles, Ramos-García, et al., 2020; González-Moles et al., 2019; Warnakulasuriya et al., 2023), hence study concentrating on Asian population is of interest.

1.2 RESEARCH QUESTIONS

1. What is the prevalence of OLP and OLL among the cases diagnosed at the Faculty of Dentistry, Universiti Malaya?
2. What are the significant sociodemographic, clinical and histopathological features associated with OLP/OLL?
3. What is the rate of malignant transformation in OLP/OLL?

1.3 AIM

To determine the MT rate of OLP and OLL diagnosed at the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya.

1.4 OBJECTIVES

1. To determine the prevalence of OLP/OLL among the cases diagnosed at the Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya.

2. To determine the sociodemographic, clinical and histopathological features of OLP/OLL among the patients seeking treatment at the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya.

3. To determine MT rate of OLP and OLL in patients seeking treatment at the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya.

1.5 Study Hypothesis

There is a difference in the MT rate between OLP and OLL

1.6 Null Hypothesis

There is no significant difference in the MT rate between OLP and OLL

CHAPTER 2: LITERATURE REVIEW

2.1 Oral Lichen Planus (OLP)

2.1.1 Background of lichen planus

Lichen planus is a chronic immune-mediated, inflammatory disease that can affect skin, mucous membranes, nails and scalp. Historically, Ferdinand Ritter von Hebra, who coined the term "lichen ruber planus" in 1860, is widely credited with providing the first clinical description of lichen planus (Cheng et al., 2016). Erasmus Wilson, a British physician, first described the condition in 1869 and simplified the name to “lichen planus”. Lichens are primitive plants made up of symbiotic algae and fungi, that typically forms a low crusty, leaflike, or branching growth on rocks, walls, and trees. The Latin term *planus* means flat. The term “lichen planus” was coined probably due to the appearance of skin lesions resembling lichen growing on rocks. The characteristic white striations in cutaneous lichen planus were described by Louis Wickham in 1895, which was referred as “Wickham’s striae”. The histological features of OLP were first highlighted by Dubreuilh in 1906, which were later described by Shklar as three main features: i) hyperkeratosis or parakeratosis of surface epithelium, ii) infiltration of the upper corium by a broad band of lymphocytes and iii) hydropic degeneration or liquefaction degeneration of the basal layer (Shklar, 1972). Clinically, lichen planus can be classified into three main subtypes: cutaneous lichen planus, mucosal lichen planus, and scalp lichen planus (lichen planopilaris) (Solimani et al., 2021). These subtypes can appear singularly or simultaneously. Cutaneous lichen planus classically presents as red to brown, violaceous, polygonal, slightly scaling, and extremely itchy flat papules, most frequently affecting the extremities. It is represented by the 6 “P” – pruritic, purple, polygonal, planar and plaques (Gorouhi et al., 2014). Mucosal lichen planus on the other hand presents as a well-defined lace-like white striae on an erythematous background. The oral cavity is the most commonly affected area, but it can also be seen in the

oesophagus and vulvovaginal area. Lichen planopilaris is a chronic inflammatory disorder of the scalp characterized by the presence of extensive whitish scarring areas in the absence of follicular orifices and tufted hair follicles.

2.1.2 Epidemiology of OLP

Global prevalence of OLP is 1.01%, with South-Central America, Africa, and Europe exhibiting a higher prevalence compared to the Asian population (González-Moles, Warnakulasuriya, et al., 2020). The prevalence of OLP was 1.74% in South-Central America, 1.43% in Africa, and 1.32% in Europe (González-Moles, Warnakulasuriya, et al., 2020). The prevalence of OLP in Asia is 0.57% (Li et al., 2020). India has a lower prevalence of OLP (0.49%) likely due to masking of OLP lesions by excess keratosis caused by tobacco products. Middle-aged adults are most commonly affected by OLP with a slight predominance in females (Carrozzo et al., 2019; Cheng et al., 2016; Li et al., 2020). Women after the age of forty show a higher risk of developing OLP, with patients under 40 years old having a prevalence of 0.62%, while patients 40 years and older have a prevalence of 1.90% (González-Moles, Warnakulasuriya, et al., 2020; Li et al., 2020). There has been no racial propensity reported.

2.1.3 Etiology of OLP

OLP is a T-cell mediated chronic inflammatory oral mucosal disease of unknown etiology. The antigen that initiates the inflammatory process is not known. Two theories have been proposed to explain the inflammatory process in OLP: i) dysregulated T-cell mediated response to exogenous trigger, and ii) dysregulated response to an autologous keratinocyte antigen, which is considered autoimmune (Kurago, 2016). There have been several suggestions for the potential triggers and contributing factors for OLP, such as: i) stress, ii) local and systemic inducers of cell-mediated hypersensitivity, iii) autoimmune

response to epithelial antigens and iv) microorganisms (Cheng et al., 2016; Kurago, 2016).

Although the cause-and-effect relationship between stress and onset of OLP has not been established, it is possible that in some patients, managing psychological disorders could also help with OLP control, as it is common to observe an exacerbation of OLP symptoms during periods of increased emotional symptoms (De Porras-Carrique et al., 2022). Aguirre-Urizar et al. (2020) showed that one third of their OLP and OLL patients presented psycho-emotional disorders, mainly depression and anxiety. According to a systematic review and meta-analysis conducted by De Porras-Carrique et al. (2022), patients with OLP experience stress, anxiety, and depression more frequently than people in the general population.

In general, hypersensitivity corresponds to lichenoid mucositis (Kurago, 2016). It is seen with local reactions to dental restorative materials (e.g. amalgam), flavouring agents (e.g. cinnamon) and drugs. However, hypersensitivity reactions usually resolve after removal of the trigger, as opposed to the chronic nature of OLP.

There are a few evidences that support autoimmunity in OLP, including disease chronicity, female predilection, adult onset, , association with other autoimmune diseases, occasional tissue-type associations, depressed immune suppressor activity in OLP patients and the presence of autocytotoxic T cell clones in OLP (Roopashree et al., 2010).

Hepatitis C virus (HCV) is the only microbe that has so far been found to have a strong correlation with OLP out of those that have been studied for their potential role in the disease, and even then, only in certain geographical areas (Kurago, 2016). According to Kurago, using antimicrobial rinses and removing calculus and plaque in OLP patients

improved their care. This suggests that bacteria may play a role in the inflammation associated with OLP.

2.1.4 Systemic association of OLP

Numerous systemic diseases, including diabetes mellitus (DM), hypertension, metabolic syndrome, thyroid disorders, psychological conditions, chronic liver disease, gastrointestinal disorders, and genetic predisposition to cancer, have been associated with OLP (Hasan et al., 2019). Grinspan et al. (1966) were the first to report an association between DM and OLP, in which they proposed a syndrome under the name of Grinspan to describe a syndromic complex consisting of a triad of hypertension, DM and OLP. Various studies have demonstrated an association between DM and OLP (Dave et al., 2021; Mallah et al., 2022; Sun et al., 2024).

Several authors have reported that the prevalence of HCV infection in patients with OLP varies from 0.5% to 35% for specific geographic areas (Hasan et al., 2019). A systematic review and meta-analysis conducted by González-Moles et al. (2023) showed that patients with OLP had a significantly greater prevalence of hepatic diseases, such as Hepatitis B, Hepatitis C, hepatic steatosis, cirrhosis and non-specific liver diseases.

De Porras-Carrique et al. (2023) showed that patients with OLP have a global prevalence of thyroid disease of 7.96%. The chance of OLP patients getting thyroid disease is about twice that of the general population without OLP. Hashimoto's thyroiditis and hypothyroidism are the most common thyroid diseases among OLP patients. Periodic thyroid stimulating hormone (TSH) determination in OLP patients is advisable to discover any undiagnosed thyroid disease.

2.1.5 Clinical features of OLP

The World Health Organization (WHO) defined OLP as "A chronic inflammatory disorder of unknown aetiology with characteristic relapses and remissions, displaying white reticular lesions, accompanied or not by atrophic, erosive, and ulcerative and/or plaque type areas. Lesions are frequently bilaterally symmetrical. Desquamative gingivitis may be a feature." (Warnakulasuriya et al., 2021). As stated in the definition, OLP characteristically presents as multiple, bilateral, almost symmetrical, well defined intersecting white striae arranged in a background of mild to severe erythema (Aguirre-Urizar et al., 2020; Cheng et al., 2016). The characteristic clinical feature of OLP is the presence of minute white papules that often coalesce to form either a reticular, annular or plaque like pattern, known as Wickham's striae. There are six subtypes of OLP: reticular, papular, plaque-like, erosive, atrophic and bullous. When the lesion appears on the gingiva, it gives a feature of desquamative gingivitis. Reticular form is the most frequent presentation among the subtypes, characterised by the presence of intersecting white lines forming lacelike pattern in an erythematous background. The erosive form is the next most common presentation and the most severe subtype exhibiting erythematous ulcerative lesions with white striae at the periphery. Pseudomembrane may occasionally cover the related ulcers. Papular OLP usually presents as small pinpoint papules. These asymptomatic papules are occasionally too small to be seen with the naked eye, making them easy to miss. These pinpoint papules may represent the initial and transient phase of OLP (Gorouhi et al., 2014). The plaque form appears as a homogenous white patch and can be confused with oral leukoplakia. The plaque form is more common in smokers. The atrophic subtype is similar to erosive subtype, but with a more prominent thin lesion on an erythematous background and radiating white lines at the periphery. Bullous form of OLP is relatively rare. A patient may have more than one of these forms coexisting together. Buccal mucosa is the most common site affected by OLP, followed by the

tongue (González-Moles, Warnakulasuriya, et al., 2020). It can also affect the gingiva, floor of the mouth, lips, hard and soft palate (Carrozzo et al., 2019). The reticular form of OLP is usually asymptomatic whereas patients with ulcerative-atrophic forms will complain of burning sensation or discomfort especially when eating spicy or acidic food. The condition can be extremely painful, affecting the patient's quality of life. Some patients will describe a sense of mucosal roughness, reduced mucosal flexibility, and reduced mouth opening (Cheng et al., 2016). However, OLP is a dynamic disorder that frequently exhibits an erratic clinical course, consisting of "silent periods" and "active periods"(Aguirre-Urizar et al., 2020). The "silent periods" are generally related to the presence of white lesions in the form of plaques and papules, whereas "active periods" are represented by the presence of red lesions in the form of erosive-atrophic ulcers. Extra-oral manifestations of OLP can affect the skin, the vulvar and vaginal mucosa, the glans penis, the scalp (which can cause alopecia), and the nails (Al-Hashimi et al., 2007). Approximately 15% of OLP patients demonstrate cutaneous lesions (Carrozzo et al., 2019). On the other hand, about 60% of cutaneous lichen planus cases will exhibit oral manifestations (Cheng et al., 2016).

2.1.6 Histopathological features of OLP

Histopathologically, OLP characteristically exhibits a well-defined band like lymphocytic inflammatory infiltrate confined to the superficial part of lamina propria, basal cell liquefactive degeneration and lymphocytic exocytosis (Cheng et al., 2016). T lymphocytes make up the great majority of inflammatory cells in OLP; most of these T cells are activated CD8+ T cells. These cells are thought to have a major role in the pathophysiology of OLP by inducing apoptosis in keratinocytes in reaction to an unknown keratinocyte antigen (Idrees et al., 2021). A mixed inflammatory infiltrate may be seen in atrophic form of OLP (Warnakulasuriya et al., 2021). In addition, the epithelium can also show presence of civatte bodies, atrophy, acanthosis,

hyperparakeratosis, hyperorthokeratosis, a homogeneous eosinophilic deposit at the epithelium-connective tissue junction, and ulceration. Saw tooth rete ridges are less common in oral lesions (Cheng et al., 2016; Kramer et al., 1978). In dark-skinned individuals, melanin incontinence may be seen. Diagnosis of OLP must always include both clinical and histological features of the lesion (Aguirre-Urizar et al., 2020; Cheng et al., 2016; Van der Meij & Van der Waal, 2003; Warnakulasuriya et al., 2021). Although diagnosis of OLP can be achieved based on the clinical and histopathological features, direct immunofluorescence (DIF) testing can aid as an adjuvant to differentiate OLP from other autoimmune erosive diseases such as lupus erythematosus. DIF of OLP produces shaggy fibrinogen deposits at the epithelial basement membrane zone in the absence of immunoglobulins and complement (Carrozzo et al., 2019; Cheng et al., 2016).

2.2 Oral Lichenoid Lesions (OLL)

2.2.1 Background of OLL

The term “OLL” was first proposed by Van der Meij and Van der Waal (2003) to describe lesions that were clinically or histopathologically resembling OLP. They further classified OLL into: i) amalgam restoration, topographically associated OLL, ii) drug related OLL, iii) OLL in chronic graft versus host disease and iv) OLL, unclassified (van der Waal, 2009).

The WHO Collaborating Centre for Oral Cancer 2020 defined OLL as “Oral lesions with lichenoid features but lacking the typical clinical or histopathological appearances of OLP i.e. may show asymmetry or are reactions to dental restorations or are drug-induced.” (Warnakulasuriya et al., 2021). OLL presents as unilateral, asymmetrical white and red lesions with features resembling OLP in the presence of a "recognizable causal factor" which includes dental restorations, food and medications. The removal of the causative agent results in resolution of the lesions (Aguirre-Urizar et al., 2020). OLL can

be divided into 3 subgroups: i) oral lichenoid contact lesions (OLCL), ii) oral lichenoid drug reaction (OLDR), iii) oral lichenoid lesion- graft versus host disease (OLL-GVHD) (Warnakulasuriya, 2018).

2.2.2 Oral Lichenoid Contact Lesions

The term "OLCL" refers to oral lesions that, although clinically and histopathologically resembling OLP, are believed to be the result of a localized (contact) hypersensitivity reaction to dental restorative materials, primarily amalgam (McParland & Warnakulasuriya, 2012). Skin patch testing for identifying true OLCL is controversial but could be beneficial for the clinician, especially when determining what kind of replacement material is appropriate (Al-Hashimi et al., 2007). OLCL presents unilaterally, located in the posterior areas of the buccal mucosa and on the lateral margins of the tongue and is strongly associated with amalgam restorations. OLCL has also been linked to flavourings like peppermint, menthol, cinnamon, and eugenol, which cause lesions at the point of contact, usually on the buccal mucosa or lateral border of the tongue (Cheng et al., 2016). OLCL may not have the reticular appearance of OLP and instead seem patchy or atrophic (Carrozzo et al., 2019; González-Moles & Ramos-García, 2022). Most of these OLCLs resolve in a few months with the removal and replacement of the suspected causative material (Al-Hashimi et al., 2007).

2.2.3 Oral Lichenoid Drug Reaction

OLDR is the appearance of the lichenoid oral mucosa in temporal association with the use of specific medications (Al-Hashimi et al., 2007). Examples of drugs associated with OLDR include beta blockers, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, dapsone, diuretics, oral hypoglycaemic agents, gold salts, and penicillamine. In terms of clinical manifestations, OLDRs resemble OLP-like lesions, which are reticular or plaque-like, erosive, and erythematous

lesions that typically occur unilaterally following drug use (González-Moles & Ramos-García, 2022). However, it is difficult to clinically diagnose OLDR as the lesions may occur anytime, even years after the introduction of the drug and resolution does not occur immediately after withdrawal of the medication. Challenge-dechallenge-rechallenge (C-D-R) protocol which includes withdrawal of the causative medication resulting in resolution of the lesion and reintroduction of the medication resulting in reappearance of the lesion can be applied to confirm the diagnosis of OLDR (González-Moles & Ramos-García, 2022).

2.2.4 Oral Lichenoid Lesion – Graft Versus Host Disease

OLL-GVHD is a common and serious complication of hematopoietic stem cell transplant recipient (González-Moles & Ramos-García, 2022). In acute form, it is a fatal condition, usually affects the skin, gastrointestinal tract and liver. On the other hand, the chronic form commonly affects the oral cavity. Acute OLL-GVHD manifests as erythematous, ulcerated lesions, or with significant desquamation. It is frequently uncomfortable. The most common presentation of chronic OLL-GVHD is keratotic white striae or plaques with regions of ulceration, erosion, or erythema (Al-Hashimi et al., 2007). A history of hematopoietic stem cell transplantation and a clinical presentation resembling OLP are adequate for the diagnosis.

2.2.5 Histopathological features of OLL

Microscopically, features of OLL overlap with that of OLP, and it is difficult to differentiate them. Nevertheless, the epithelium in OLDR may include more apoptotic keratinocytes, often known as colloid or civatte bodies (Cheng et al., 2016; González-Moles & Ramos-García, 2022). Unlike the superficial band-like infiltration typical of OLP, the inflammatory infiltrate frequently extends deep into the lamina propria. In OLDR, perivascular chronic inflammatory cell infiltrates are commonly observed (Cheng

et al., 2016). A predominance of eosinophils and plasma cells in the inflammatory infiltrate may be seen in OLDR (González-Moles & Ramos-García, 2022). On the other hand, lymphoid follicles in the submucosa may be observed in OLCL (Cheng et al., 2016; González-Moles & Ramos-García, 2022). Besides that, marked epithelial acanthosis with elongated rete ridges, interface mucositis, deep perivascular infiltrates and a mixed inflammatory infiltrate comprising histiocytes, lymphocytes, plasma cells, and eosinophils are observed in OLCR (Cheng et al., 2016). A study conducted by Lodolo et al. (2023) has shown significantly higher number of eosinophils and plasma cells in OLL.

In contrast to OLP, indirect immunofluorescence (IIF) testing can help diagnose OLDR by identifying circulating antibodies that target basal cells with an annular fluorescent distribution, also known as a "string of pearls" pattern (Cheng et al., 2016). DIF of OLCL is similar to OLP and IIF testing is usually negative.

2.3 Diagnostic Criteria

The WHO first formulated a diagnostic criterion for OLP in 1978. The histopathological criteria include orthokeratotic and parakeratotic epithelium with varying epithelium thickness, sometimes saw-tooth rete ridges, civatte bodies in the basal layer of the epithelium or superficial lamina propria, a narrow band of eosinophilic material in the basement membrane zone, well-defined band-like zone of cellular infiltration that is confined to the superficial lamina propria, consisting mainly of lymphocytes and liquefaction degeneration in the basal cell layer. Due to high inter- and intra-observer variability and lack of clinicopathologic correlation in the diagnosis of OLP, van der Meij and van der Waal suggested a modification to the WHO diagnostic criteria to achieve a more consistent diagnosis of OLP. They suggested including both clinical and histopathological criteria in diagnosing OLP and OLL (Van der Meij & Van der Waal, 2003). Based on the 2003 modified WHO diagnostic criteria, a diagnosis of

OLP is made only when the lesion meets all the clinical and histopathological criteria. Lesions that resemble OLP clinically but do not fulfil all the clinical criteria are termed as “clinically compatible with” OLP. Similarly, lesions which showed less obvious histopathological features are termed “histopathologically compatible with” OLP. The term OLL will be used if the lesion was clinically typical of OLP but histopathologically only “compatible with” OLP, histopathologically typical of OLP but clinically only “compatible with” OLP, clinically “compatible with” OLP and histopathologically “compatible with” OLP.

Epithelial dysplasia is regarded as an exclusion criterion in the modified WHO criteria. This is to avoid confusion with the term “OLD” which was coined by Krutchkoff & Eisenberg to describe a lesion histopathologically displaying lichenoid features with dysplastic features within the epithelium. In year 2016, the American Association of Oral and Maxillofacial Pathology (AAOMP) introduced a set of diagnostic criteria in an attempt to exclude OLL which was proven to be premalignant. In addition to the 2003 modified WHO diagnostic criteria, the AAOMP diagnostic criteria suggested that verrucous epithelial architecture must be absent to diagnose OLP. This is due to proliferative verrucous leukoplakia (PVL) which may exhibit histopathologic and clinical characteristics that are comparable to OLP. A proposed checklist was developed to help in diagnosing OLL. It should be noted that the AAOMP diagnostic criteria also precludes epithelial dysplasia in diagnosing OLP. In an ambispective study conducted by Aguirre-Urizar et al. (2020), OLL showed 4.6 times increased risk of MT compared to OLP and hence the authors proposed a new diagnostic criteria to differentiate OLP and OLL. Interestingly, the authors included epithelial dysplasia in the diagnosis of OLP and OLL. In the clinical criteria proposed by Aguirre-Urizar et al. (2020), presence of white papules (reticular) in the oral mucosa is an essential criterion to diagnose OLP or OLL. Presence of multiple lesions, bilateral and occasionally symmetric will favour the diagnosis of

OLP, whereas presence of unique lesions, unilateral and/or asymmetric will favour the diagnosis of OLL. Unique or multiple lesions, bilateral or not, symmetric or not, but with a recognized etiopathogenic factor will favour the diagnosis of OLL. Presence of band-like chronic lymphocytic inflammatory infiltrate in the lamina propria and liquefactive degeneration of the basal cells of the mucosal epithelium were compatible or suggestive of OLP and OLL. There are no pathognomonic diagnostic histopathological criteria suggested for OLP or OLL. Warnakulasuriya et al. (2021) in a workshop convened by WHO Collaborating Centre for Oral Cancers proposed a diagnostic criteria for OLP based on the previous proposals mentioned above (Aguirre-Urizar et al., 2020; Cheng et al., 2016; Van der Meij & Van der Waal, 2003). The clinical criteria for OLP includes: i) presence of bilateral, more or less symmetrical white lesions affecting buccal mucosa, and/or tongue, and/or lip, and/or gingiva, ii) white papular lesions and lace-like network of slightly raised white lines (reticular, annular or linear pattern) with or without erosions and ulcerations iii) sometimes presents as desquamative gingivitis. Histopathological criteria for OLP includes: i) presence of a well-defined band-like predominantly lymphocytic infiltrate that is confined to the superficial part of the connective tissue, ii) signs of vacuolar degeneration of the basal and/or supra basal cell layers with keratinocyte apoptosis, iii) in the atrophic type there is epithelial thinning and sometimes ulceration caused by failure of epithelial regeneration as a result of basal cell destruction. A mixed inflammatory infiltrate may be found. Warnakulasuriya et al. (2021) did not preclude epithelial dysplasia in the diagnosis of OLP. Studies showed an improvement in inter- and intra-observers' agreement in diagnosing OLP when applying the 2003 modified WHO diagnostic criteria and the AAOMP diagnostic criteria (Idrees et al., 2021; Rad et al., 2009).

2.4 Oral Lichenoid Dysplasia

Krutchkoff and Eisenberg (1985) first coined the term "OLD" to describe lichenoid lesions demonstrating dysplastic features and the author believed that OLD is a distinct entity that showed risk of MT. Van der Meij et al. adapted this idea and excluded epithelial dysplasia in the diagnosis of OLP. The presence of dysplasia plays an important role in determining MT of OLP. Given that the clinical features of OLD resemble those of OLP and OLL group more so than oral epithelial dysplasia (OED), Czerninski et al. (2015) suggested that OLD belongs to the spectrum of lichen planus disorders rather than being considered as a distinct entity. Farah et al. (2021) conducted a study assessing the comparative molecular profile and pathways of OLP, OLL and OED. The molecular evidence suggested that OLD is not a unique disease entity. While different from OED, its transcriptome and immunophenotypic profile is comparable to that of OLP (Farah et al., 2021). González-Moles and Ramos-García (2024) strongly suggested that the presence of epithelial dysplasia should not be used as a diagnostic exclusion criterion for OLP, given that there is no evidence indicating that OLP cannot develop epithelial dysplasia during its progression to malignancy, as occurring in the other OPMDs. The assessment of epithelial dysplasia in OLP is complicated primarily due to the similarity between some characteristics of epithelial dysplasia and the key histological facts of OLP (vacuolizing degeneration of the basal layer of the epithelium). This similarity can be particularly noticeable when diagnosing mild and moderate dysplasia, where the lower layers of epithelium exhibit histopathological alterations.

The debate about whether dysplastic features seen in OLP warrants it as a distinct entity on its own, or is it a continuum from OLP to malignancy, or is it a malignant lesion with lichenoid features is ongoing. González-Moles et al. (2021) suggested future research focusing on OLP where dysplasia was not present in the initial biopsy to examine whether epithelial dysplasia may develop in OLP.

2.5 Malignant potential of OLP and OLL

Despite the fact that OLP was first discussed in the year 1860, controversy regarding its etiopathology, diagnostic criteria and MT are still subjects to be debated. The first case of OLP that transformed into malignancy was reported by Hallopeau in year 1910. Since then, numerous studies have been conducted to study the MT of OLP and OLL. The overall MT rate of OLP is reported as 1.4% with an annual MT rate of 0.28%. On the other hand, OLL have a higher MT rate compared to OLP with an overall MT rate of 3.8% and annual MT rate of 0.57% (Iocca et al., 2020).

In a prospective study conducted by Van der Meij et.al in 2006 which included 67 OLP patients and 125 OLL patients fulfilling the 2003 modified WHO diagnostic criteria, four patients from the OLL group developed oral squamous cell carcinoma (OSCC) during the follow up period. MT was not reported in the OLP group (van der Meij et al., 2007).

Fitzpatrick et al. published a systematic review on MT of OLP and OLL which included 7,806 patients with OLP and 125 patients with OLL. 85 OLP patients developed OSCC. Among 125 patients with OLL, four developed OSCC, with a MT rate of 1.09% in OLP and 3.2% in OLL. Cases with epithelial dysplasia on initial biopsy were excluded from the study. (Fitzpatrick, Hirsch, et al., 2014)

In 2019, Shearston et al. conducted a retrospective study observing the malignant potential of OLP, OLL and OLD. Patients diagnosed with OLP, OLL, OLD between the year 2006 and 2014 were cross-matched with cancer registry data for OSCC. The study showed that OLP and OLL patients have a low risk of MT (0.49% in OLP, 0% in OLL) while OLD patients had a MT rate of 6.8%. However, the authors were unable to determine if the OLD lesions described in the study represented a transitional phase through which OLP progressed into OSCC (Shearston et al., 2019).

A 14-year longitudinal retrospective cohort study of 829 OLP patients in New Zealand conducted by Guan et al. reported a MT rate of 2.8% in OLP with a mean duration of MT being 4.3±2.2 years. The atrophic/ulcerative forms were 25.8 times more likely to progress to OSCC compared with the hyperplastic types. It was also reported that as the age increases by 1 year, there is a 5% increased risk of MT. The study excluded lesions histologically demonstrating dysplasia as the true entity of OLD was not clear (Guan et al., 2020).

Aguirre-Urizar et al. (2020) proposed a diagnostic criteria to differentiate OLP and OLL. They observed that OLL have 4.6 times higher risk of MT with a meantime of carcinoma diagnosis in 4.3years. The authors suggested that OLL should be differentiated from OLP as OLL have a higher malignant potential. The authors also highlighted that epithelial dysplasia should not be excluded as it is the gold standard feature to indicate the prognosis of oral lesions.

A retrospective study by Tsushima et al. (2021) studying MT of OLP in Japanese population showed a MT rate of 0.7%, with predominantly the red type OLP undergoing MT. Cai et al. (2022) criticised that there might be an overestimation of MT of OLP. From the retrospective study by Cai et al., it was observed that five out of ten cases that transformed into carcinoma were oral leukoplakia. The overestimation of MT of OLP may be contributed by inclusion of epithelial dysplasia while diagnosing OLP. Secondly, OLP patients may have developed oral leukoplakia with dysplasia during the disease course, which may have eventually transformed into OSCC. Thirdly, the early stage of proliferative verrucous leukoplakia would have been misdiagnosed as OLP (Cai et al., 2022).

A number of systematic reviews and meta-analyses have been conducted over a decade. Most of the studies showed a higher MT rate in the OLL group ranging from 1.8% to 3.8% (Aghbari et al., 2017; Giuliani et al., 2019; Iocca et al., 2020; Ramos-García et al., 2021). The tongue, predominantly the lateral border, is the most common site for MT (Giuliani et al., 2019). It is interesting to note that, in a systematic review conducted by Giuliani et al.,2019, the author found that 27 OLP patients who developed OSCC had previously received systemic and topical steroid therapy for their OLP.

By applying strict clinicopathological inclusion criteria, Idrees et al. (2020) conducted a systematic review and meta-analysis to more accurately estimate the MT rate of OLP and the associated risk factors. Their requirements included: (a) the documentation of an OLP diagnosis confirmed by a clinician; (b) the proper documentation of cancer development occurring at the same location as the OLP lesion; and (c) a minimum follow-up of six months before cancer development. The study reported that 0.44% of OLP patients transformed into carcinoma. Smokers, alcoholics and those with seropositivity for HCV have a higher risk of MT.

Another systematic review by González-Moles, Ramos-García, et al. (2020) which included 10 highest quality studies showed a MT rate of 2.28% in OLP and 2.11% in OLL. There was no significant difference between the MT of OLP and OLL. González-Moles emphasized that epithelial dysplasia should not be excluded in diagnosing OLP.

A meta-analysis by González-Moles et al. (2021) showed that OLP with dysplasia has a higher tendency for malignancy (6.22%) whereas 0.44%-2.28% of non-dysplastic OLP may progress into carcinoma. The authors believed that presence of dysplasia is a risk predictor for MT and should not be excluded from diagnosing OLP. Histopathological features of OLP with dysplasia include irregular stratification, cellular and nuclear

pleomorphism, loss of basal cell polarity, and basal cell hyperplasia with a basaloid appearance. However, the term "OLD" was suggested not to be used to avoid confusion.

A recent systematic review and meta-analysis published by González-Moles and Ramos-García (2024), by including the most recent primary-level studies, have demonstrated a higher MT ratio in OLP compared to their previous report in year 2019 (González-Moles et al., 2019). The study concluded that OLP with dysplasia had significantly higher MT rate than OLP. The reported MT rates for OLP, OLL, lichenoid reactions, and OLP with dysplasia are 1.43%, 1.38%, 1.20%, and 5.13%, respectively. The presence of epithelial dysplasia, a higher methodological quality, tobacco and alcohol consumption, the location of lesions on the tongue, the presence of atrophic and erosive lesions, and HCV infection were all significant risk factors for malignant transformation.

Based on high-quality longitudinal follow-up studies conducted over the past 20 years by several authors, primarily from North America and Europe, a percentage of OLP cases may eventually progress to cancer. Presence of epithelial dysplasia, red type of lesions, lesions on the tongue, long follow-up period, smoking, alcohol consumption, and seropositivity for HCV showed an increased risk of malignancy (González-Moles et al., 2021). Given that OLP is an OPMD, dysplasia could be a normal stage in the progression to OSCC. The majority of papers reporting primary research on OLP patients with long-term follow-up and MT evaluation are from North America and Europe,Warnakulasuriya et al. (2023) expressed interest on whether MT rates in different populations are comparable. In a systematic review which included the ten high-quality studies reporting MT of OLP, six studies were from the Europe, two from Oceania, one from North America and one from Asia. The MT of OLP from the Europe population ranged from 0.98% to 2.84%, whereas the study from Asia showed MT rate of 5.85% (González-Moles, Ramos-García, et al., 2020). Given that Asia is the largest continent containing

the highest population with diverse ethnicity, study focusing in this region could give different insights on the MT of OLP. A considerable influence on the MT of OLP and OLL can come from the various genetic, cultural, and environmental elements brought about by Asia's ethnic diversity. Hence it is worthwhile to study the risk of MT in OLP and OLL patients from this region.

CHAPTER 3: METHODOLOGY

3.1 Study design:

This was a retrospective study to determine the MT rate of OLP and OLL among the patients seeking treatment at the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya. Clinical folders and histopathological reports of OLP, OLL and OED with a provisional diagnosis of OLP/OLL diagnosed at the Oral Medicine Clinic and Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya were retrieved and checked prospectively from the day of diagnosis for any evidence of dysplastic changes or MT. Clinical and histopathological information were collected by reviewing the clinical folders and histopathological slides respectively. The clinical and histopathological data collected were entered into Microsoft Excel and analysed using statistical methods.

This study was approved by the Medical Ethics Committee at the Faculty of Dentistry, Universiti Malaya with Ethics Committee/ IRB reference number of DF OS2320/0096 (P).

3.2 Sample selection:

All the OLP/OLL and OED cases with a provisional diagnosis of OLP/OLL diagnosed during the period 2008-2018 that fulfilled the inclusion and exclusion criteria were selected.

The inclusion criteria were:

1. Cases with a clinical diagnosis of OLP/OLL
2. Cases with a histopathological diagnosis of OLP/OLL
3. Cases with a minimum follow up of 3 years
4. OED cases with a provisional diagnosis of OLP/OLL

The exclusion criteria were:

1. History of previous head and neck malignancies
2. Use of systemic immunosuppressive medications for at least 2 years at the time of OSCC diagnosis
3. Cases with a verrucous morphology on clinical or histopathological examination
4. Cases with incomplete clinical and histopathological records
5. OED cases with superimposed candidiasis

3.3 Materials and Methods:

3.3.1 Search strategy

3.3.1.1 OLP/OLL:

Diagnostic reports of OLP/OLL were retrieved from Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya database using search terms: OLP, OLL, oral lichenoid reactions. Clinical folders of the retrieved cases of OLP/OLL were obtained from the Oral Medicine clinic, Faculty of Dentistry, Universiti Malaya. Histopathological slides and paraffin tissue block of the OLP/OLL cases were retrieved.

3.3.1.2 OED:

Diagnostic reports of OED were retrieved from the Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya database using search term: dysplasia/OED. Clinical folders of the retrieved cases of OED with a provisional diagnosis of OLP/OLL were obtained from Oral Medicine clinic, Faculty of Dentistry, Universiti Malaya. Histopathological slides and paraffin tissue block were retrieved from the Diagnostic Oral Pathology Unit.

3.3.2 Methods

3.3.2.1 Clinical data extraction

Sociodemographic and clinical data were extracted from the clinical folders. The data extracted included:

- Gender, race, age at initial diagnosis and age at oral malignancy diagnosis
- Medical and drug history
- Habits
- Clinical presentation, cutaneous involvement, site of the lesions, clinical symptoms, treatment with topical/systemic steroid
- Presence of dental restorations adjacent to the lesion
- Correlation of the initiation of the lesion with medication use
- Signs of MT

3.3.2.2 Histopathological data extraction

Histopathological slides of all the OLP, OLL and OED cases were reviewed to confirm the presence of the histopathological features of OLP and OLL. New sections from the paraffin tissue block were obtained and stained with Haematoxylin and Eosin (H&E) if necessary.

1. The histopathological features of OLP included:
   - Presence of band-like, predominantly lymphocytic infiltrate in the lamina propria confined to the epithelium-lamina propria interface
   - Basal cell liquefactive (hydropic) degeneration
   - Lymphocytic exocytosis

2. The histopathological features of OLL included:
    - Inflammatory infiltrate extending deep into lamina propria
    - Perivascular inflammatory cell infiltrate
    - A mixed lichenoid inflammatory infiltrate consisting of eosinophils and plasma cells
3. Presence of epithelial dysplasia (Appendix A)

New sections from the paraffin tissue blocks were stained with Periodic Acid Schiff (PAS) for all the OED cases with a provisional diagnosis of OLP/OLL. OED cases with the presence of candida were excluded. Histopathological slides of OED cases with a provisional diagnosis of OLP/OLL were further re-evaluated for the presence of dysplastic features and graded again using the WHO 2022 grading criteria (Appendix A) as well as the binary grading (Appendix B).

3.3.3 Grouping

Cases of OLP/OLL and OED with a provisional diagnosis of OLP/OLL were classified using a criteria derived from the 2003 modified WHO diagnostic criteria, AAOMP diagnostic criteria and 2020 WHO Collaborating Centre for Oral Cancers diagnostic criteria. By applying the criteria (Table 3.1), cases were grouped as:

- OLP,
- OLL,
- OLP/OLL with dysplasia,

Table 3.1: Diagnostic criteria for OLP

Clinical criteria: 1. Bilateral, almost symmetrical multifocal distribution 2. White and red lesions exhibiting one or more of following forms: i. -Reticular/annular ii. -Atrophic iii. -Erosive iv. -Plaque v. -Bullous 3. Lesions are not localized exclusively to the sites of smokeless tobacco placement 4. Lesions are not localized exclusively adjacent to and in contact with dental restorations 5. Lesion onset does not correlate with the start of a medication 6. Lesion onset does not correlate with the use of cinnamon-containing products 7. Sometimes present as desquamative gingivitis
Histopathologic criteria: 1. Band-like or patchy, predominantly lymphocytic infiltrate in the lamina propria confined to the epithelium-lamina propria interface 2. Basal cell liquefactive (hydropic) degeneration 3. Lymphocytic exocytosis (optional)

Cases that were clinically and histopathologically typical of OLP were categorized as OLP. Whereas cases that were clinically and/or histopathologically "compatible with OLP" (i.e. clinically typical of OLP but demonstrating histopathological features suggestive of OLL stated in Table 3.2 or clinically not typical of OLP but histopathologically typical of OLP or clinically and histopathologically not typical of OLP) were categorized under OLL. Cases with an identifiable causative agent were also categorized as OLL.

Table 3.2: Histopathological criteria for OLL

Inflammatory infiltrate extending deep into the lamina propria
Perivascular chronic inflammatory cell infiltrate
A mixed lichenoid inflammatory infiltrate consisting of eosinophils and plasma cells

Source: (Cheng et al., 2016; Lodolo et al., 2023)

OLL cases were subdivided into OLCL, OLDR and OLL of unknown cause according to a derived criteria from Al-Hashimi et al. (2007) stated in Table 3.3.

Table 3.3: Clinical criteria for OLL

OLCL	A direct topographic relationship between the suspected causative restorative material and the lesion
OLDR	Resolution of the reaction after the suspected inciting drug is withdrawn and reappearance when the same drug is reintroduced Temporal relationship between a medication use and the onset of the lesions
OLL-unknown cause	Cases that were clinically or histopathologically "compatible with OLP" and a causative agent could not be identified

OED cases with a provisional diagnosis of OLP/OLL and histologically having lichenoid features were reviewed by two pathologists. The final diagnosis and grading of dysplasia were reached through consensus between the two pathologists and classified as OLP/OLL with dysplasia.

The lichenoid features included presence of either a well-defined band like zone of cellular infiltration consisting of lymphocytes or a mixture of lymphocytes and plasma cells that is confined to the superficial part of the connective tissue or presence of a diffuse cellular infiltration that is extending to the deeper part of the connective tissue (Patil et al., 2015).

Cases of OLP/OLL with dysplasia were further subclassified into OLP with dysplasia and OLL with dysplasia by applying the same criteria as OLP and OLL.

3.3.4 MT of OLP/OLL

Cases that showed MT and meeting the criteria for MT of OLP were identified. The criteria for MT of OLP is stated in Table 3.4.

Table 3.4: Criteria for MT of OLP

The oral carcinoma must have developed at the same site as the previously diagnosed OLP
Must have had follow-up of at least 6 months before MT
Patient must not be using any systemic immunosuppressive medication for at least 2 years at the time of diagnosis
No history of previous head and neck malignancy
No history of organ transplantation or chronic graft-versus-host disease
Patient's demographics and medical history details should be clearly documented

Source: (Idrees et al., 2020)

3.4 Statistical analysis:

Data was analysed using Statistical Package for Social Sciences (SPSS) for Windows, Version 25.0. Released 2017(Armonk, NY: IBM Corp.). The sociodemographic, clinical and histopathological features of OLP and OLL among patients seeking treatment at the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya were analysed using descriptive statistics, where categorical variables were expressed by frequency and percentages and continuous variables expressed by mean ± standard deviation. Pearson's Chi-square test was used to determine the association between the categorical variables and different groups. Means/medians across different groups (e.g., gender, race) were compared using t-tests or ANOVA for continuous variables. The rate of malignant transformation was calculated by dividing the number of cases transformed with total number of cases in the group. A p-value of <0.05 was considered as statistically significant.

CHAPTER 4: RESULTS

4.1 Socio-demographic data

A total of 7580 biopsy cases were received at the Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya from the year 2008 – 2018. Of that, 436 cases were reported as OLP/OLL. Hence, the prevalence of OLP/OLL diagnosed in the Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya is 5.75%.

204 cases of OLP/OLL were under follow up in the Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya. After excluding patients that did not meet the inclusion and exclusion criteria, a total of 53 cases were included in this study. Majority of the patients were female (66%) with a female to male ratio of 1.9:1. The highest incidence was reported in Chinese (43.4%). The mean patient age at diagnosis for OLP/OLL was 53.2±12.0 years with a follow up of 8.4±4.4 years. Table 4.1 demonstrates the distribution of patients according to age, gender and ethnicity.

Table 4.1: Distribution of socio-demographic data

Characteristics	**Frequency, n (%)** **n=53**
Age (years) Mean ± standard deviation	53.2±12.0
Gender Male Female	 18 (34.0) 35 (66.0)
Ethnicity Malay Chinese Indian Others	 8 (15.1) 23 (43.4) 21 (39.6) 1 (1.9)

n=Frequency

4.2 Grouping

Among the 53 cases included in the study, 32 cases were classified as OLL, 13 cases as OLP and 8 cases as OLP/OLL with dysplasia. All OLP cases showed clinical and histopathological features typical of OLP. Among 32 cases of OLL, 20 cases (62.5%) exhibited clinical features typical of OLP and were histologically "compatible with" OLP. Four cases showed histopathological features consistent with OLP but clinically not typical of OLP while eight cases were both clinically and histopathologically atypical of OLP. OLL cases were further classified according to the causative agents into OLCL (15.6%), OLDR (3.1%) and OLL of unknown cause (81.2%). Besides that, further classification of OLP/OLL with dysplasia was done. One case (12.5%) was grouped into OLP with dysplasia while the other 7 cases (87.5%) were OLL with dysplasia. Table 4.2 demonstrates the clinical distribution of OLP, OLL and OLP/OLL with dysplasia cases. The relationship between the oral lesion with dental restoration and medication use were shown in Table 4.3.

Table 4.2: Clinical distribution of OLP, OLL and OLP/OLL with dysplasia cases

Distribution	**OLP n=13**	**OLL n=32**	**OLP/OLL with dysplasia n=8**
Bilateral, n (%) Unilateral, n (%)	13 (100) 0 (0)	20 (62.5) 12 (37.5)	7 (87.5) 1 (12.5)
Almost symmetrical, n (%) Non-symmetrical, n (%)	13 (100) 0 (0)	20 (62.5) 12 (37.5)	7 (87.5) 1 (12.5)
Multifocal, n (%) Isolated, n (%)	13 (100) 0 (0)	26 (81.2) 6 (18.8)	8 (100) 0 (0)

n=Frequency

Table 4.3: Relationship of the lesions with dental restorations and the use of medication

Characteristics	OLL n=32	OLP/OLL with dysplasia n=8
Associated with dental restorations, n (%)	5 (15.6)	1 (12.5)
Associated with the use of medication, n (%)	1 (3.1)	0 (0)

n=Frequency

4.3 Clinical data

In the 53 cases included in this study, 25 patients (47.2%) had more than one systemic disease, included combination of hypertension, DM and/or hypercholesteremia, whereas 12 patients (22.6%) reported no associated comorbidities. 45.3% of the patients were taking anti-hypertensive medications (ACE inhibitors or beta-blockers) and/or oral hypoglycaemic agent (i.e. metformin). Most of the patients (88.7%) denied any risky oral habits. One patient from the OLP/OLL with dysplasia group was an alcoholic and betel quid chewer. Most of the patients (54.2%) presented with involvement of multiple oral sites. The most common site of involvement was buccal mucosa (90.6%) while floor of the mouth (1.9%) was the least common site involved by OLP/OLL. Clinically, the most common clinical subtype observed was reticular form (98.1%) with 52.8% of the patients showed a combination of the clinical subtypes. Burning sensation was the most common symptom reported (41.5%) while 9.4% of cases reported no symptoms. Additionally, 1.9% of patients reported more than one symptom. Majority of the patients (88.7%) were treated with topical steroids. The clinical findings are tabulated in Table 4.4.

Table 4.4: Distribution of clinical data

Characteristics	Frequency, n(%) n=53
Comorbidities	
None	12 (22.6)
Hypertension	19 (35.8)
Diabetes mellitus	15 (28.3)
Hypercholesterolemia	16 (30.2)
Other diseases	24 (45.3)
More than one disease	25 (47.2)
Medication	
Taking antihypertensive and/or oral hypoglycaemic agent	24 (45.3)
Not taking antihypertensive and/or oral hypoglycaemic agent	29 (54.7)
Habits	
No habits	47 (88.7)
Smoking	3 (5.7)
Alcohol drinking	1 (1.9)
Betel quid chewing	1 (1.9)
More than one risky habit	1 (1.9)
Skin lesions	
Present	7 (13.2)
Absent	46 (86.8)
Site of involvement	
Buccal mucosa	48 (90.6)
Tongue	11 (20.8)
Palate	2 (3.8)
Gingiva	22 (41.5)
Alveolar ridge	3 (5.7)
Lips/labial mucosa	3 (5.7)
Floor of mouth	1 (1.9)
Retromolar trigone	5 (9.4)
Multiple sites	34 (64.2)
Clinical presentation	
Reticular	52 (98.1)
Papular	1 (1.9)
Plaque	3 (5.7)
Erosive	16 (30.2)
Atrophic	0 (0)
Bullous	0 (0)
Ulcerative	7 (13.2)
Desquamative gingivitis	10 (18.9)
Combined	28 (52.8)

Table 4.4, continued

Characteristics	Frequency, n(%) n=53
Symptoms	
No symptom	5 (9.4)
Pain/discomfort	19 (35.8)
Burning sensation	22 (41.5)
Mucosal roughness	1 (1.9)
Ulcers	9 (17.0)
Multiple symptoms	1 (1.9)
Treatment	
Topical steroids	47 (88.7)
Systemic steroids	0 (0)
Combined topical and systemic steroids	0 (0)
No treatment	6 (11.3)

4.4 Histopathological data

The majority of the cases exhibited histological features characteristic of OLP. The most frequent histopathological features of OLL seen was the presence of mixed inflammatory cells infiltrate. The distribution of histopathological features of OLP and OLL are shown in Table 4.5 and Table 4.6 respectively. Histopathological features of OLP are illustrated in Figure 4.1.

Table 4.5: Distribution of histopathological features of OLP

Histopathological features	Frequency, n (%) n=53
Band-like inflammatory infiltrate confined to the epithelium-lamina propria interface	52 (98.1)
Basal cell liquefactive degeneration	51 (96.2)
Lymphocytic exocytosis	50 (94.3)
Inflammatory cells: -Predominantly lymphocytes	24 (45.3)

Table 4.6: Distribution of histopathological features of OLL

Histopathological features	Frequency, n (%) n=53
Inflammatory cells: -Mixed inflammatory infiltrates including plasma cells and eosinophils	29 (54.7)
Inflammatory cells extending deep into the connective tissue	22 (41.5)
Perivascular inflammation	16 (30.2)

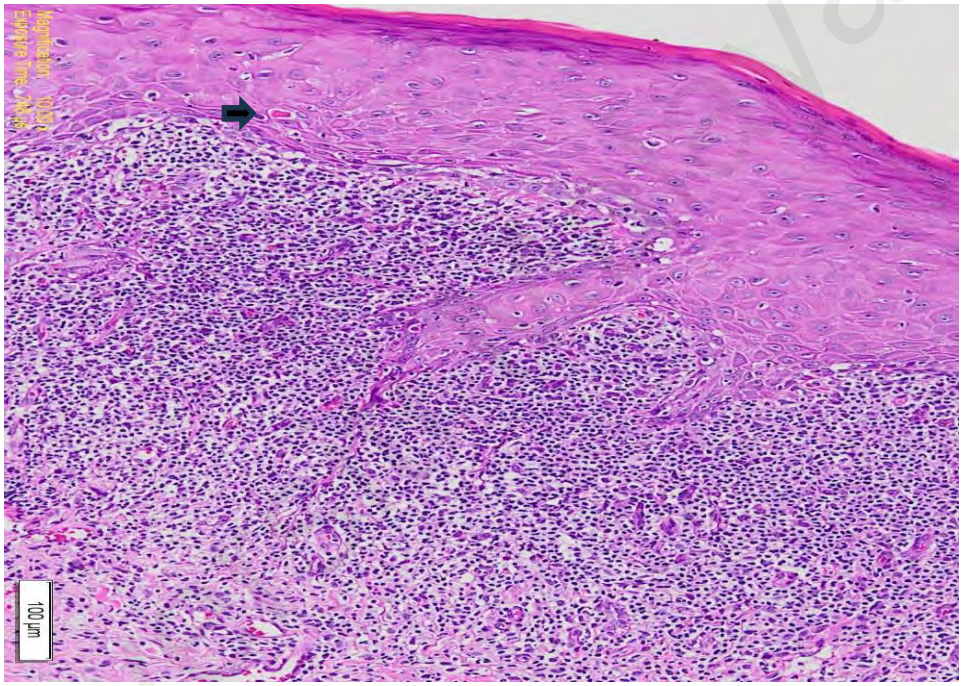

Figure 4.1: Photomicrograph showing liquefactive degeneration of the basal layer and a band-like, predominantly lymphocytic infiltration within the lamina propria. A Civatte body is present (arrow)

Among 32 cases of OLL, 28 cases exhibited histopathological features characteristic of OLL. Within the OLL subgroup, OLDR showed all the histopathological features of OLL. Conversely, 73.1% of OLL cases with an unknown cause and all cases of OLCL demonstrated a mixed inflammatory infiltrate. Histopathological features of OLL are illustrated in Figure 4.2.

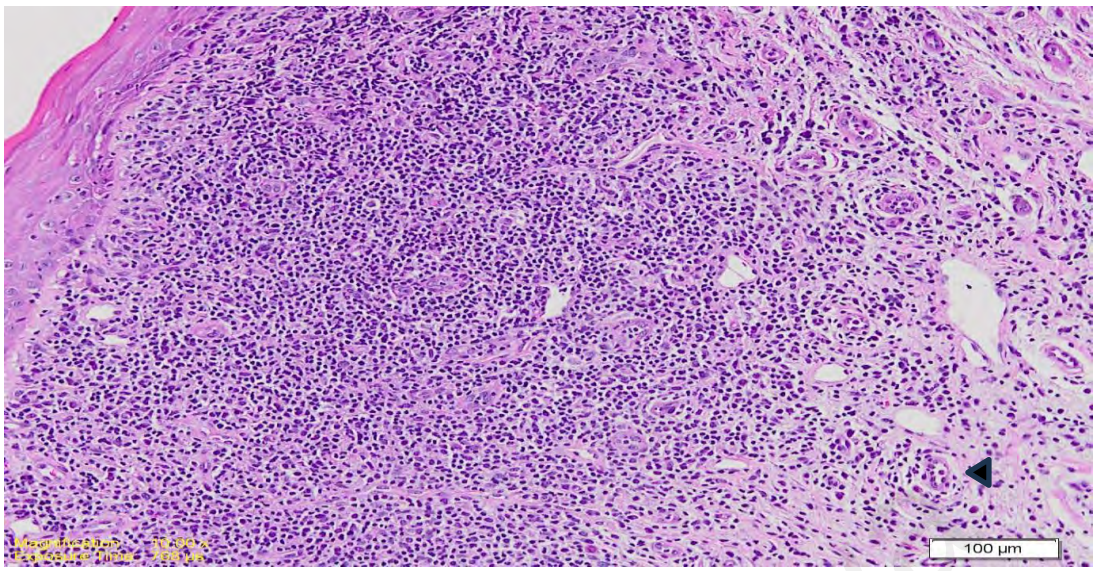

Figure 4.2: **Photomicrograph showing perivascular inflammation (arrowhead) with a mixed inflammatory infiltrate composed of lymphocytes and plasma cells**

4.5 OLP/OLL with dysplasia

Eight cases were classified as OLP/OLL with dysplasia, with six (75%) classified as mild dysplasia and two (25%) classified as moderate dysplasia using the WHO grading system. With the Binary system, all cases were considered low risk.

Premature keratinization in single cell and generalized premature keratinization were present in all the cases of OLP/OLL with dysplasia. All cases were positive for increased number and size of nucleoli. Only 1 case showed nuclear hyperchromasia. The frequency of architectural and cytological dysplastic features seen are shown in Figure 4.3 and 4.4 respectively. Figure 4.5 illustrated the histopathological features seen in OLP/OLL with dysplasia.

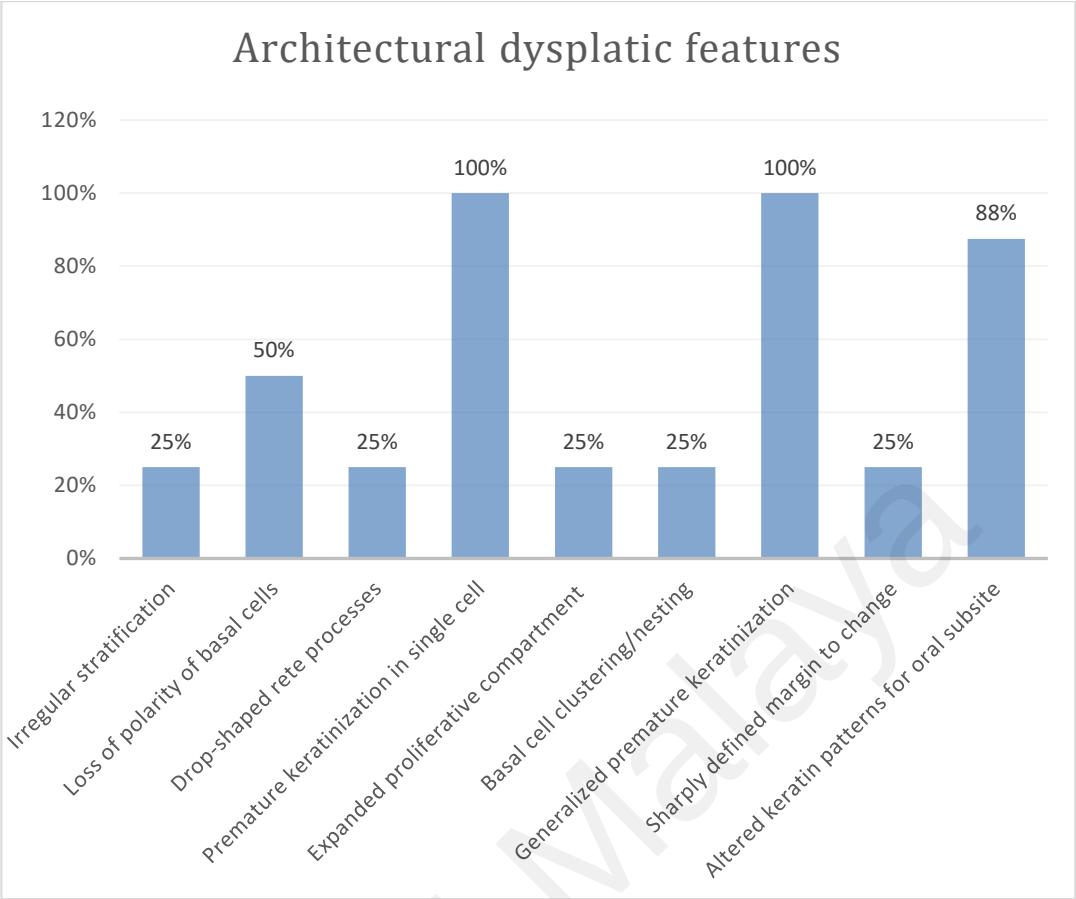

Figure 4.3: Architectural dysplastic features

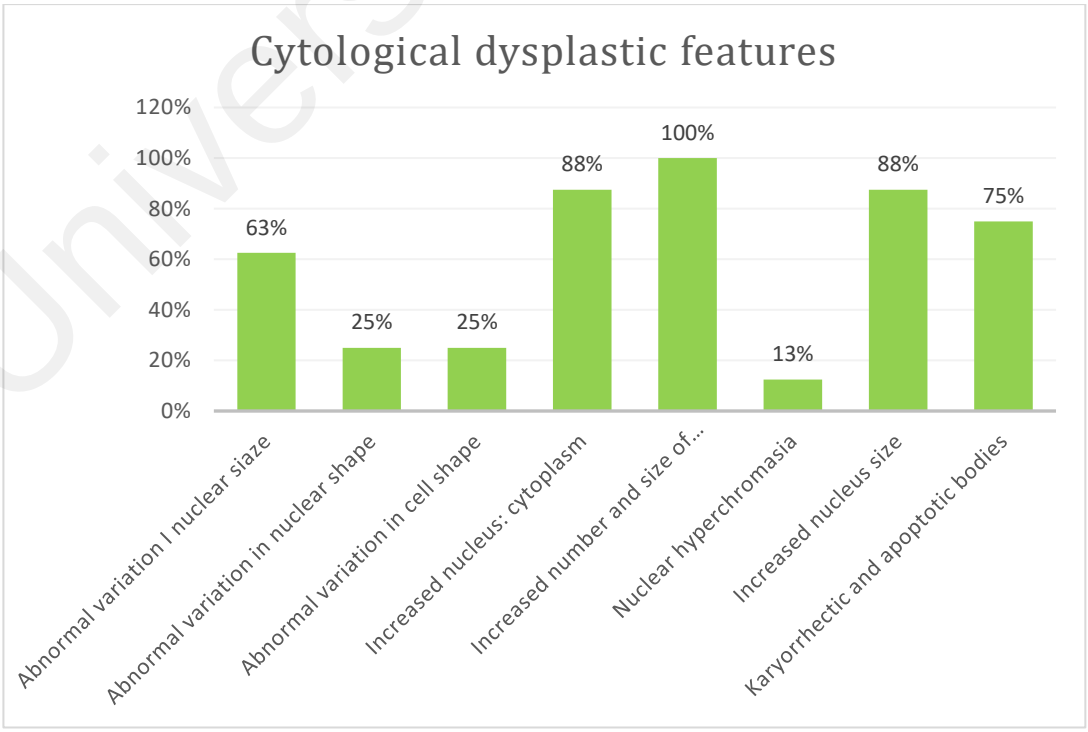

Figure 4.4: Cytological dysplastic features

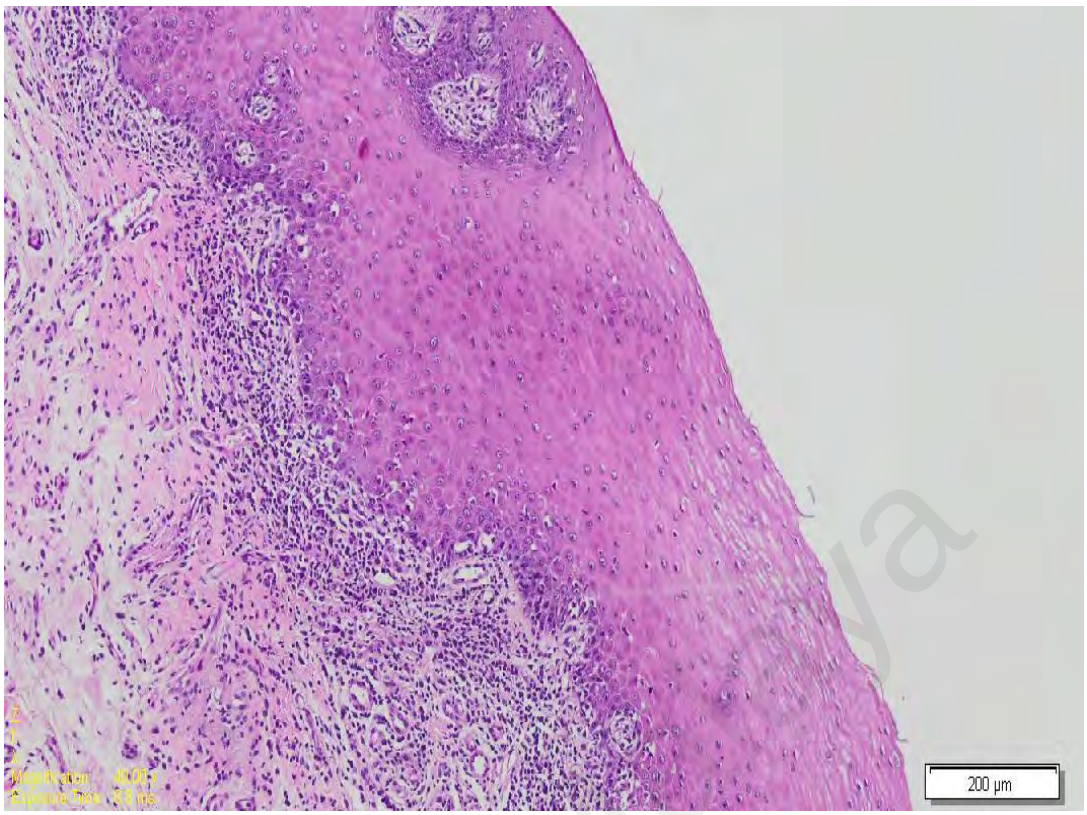

Figure 4.5: Photomicrography illustrating dysplastic epithelium with generalized premature keratinization

4.6 Association between socio-demographic characteristics and OLP, OLL and OLP/OLL with dysplasia

Chi-square test was used to analyse the association between socio-demographic characteristics and different groups. There were no significant differences in age, gender and ethnicity observed. The results were tabulated in Table 4.7.

Table 4.7: Socio-demographic data of different groups

Characteristics	**OLP n=13**	**OLL n=32**	**OLP/OLL with dysplasia n=8**	**p-value[a]**
Age (years) Mean ± standard deviation	49.5 ±15.8	54.1 ±11.1	56.0 ±7.5	0.401
Gender, n (%) Male Female	 4 (30.8) 9 (69.2)	 11 (34.4) 21 (65.6)	 3 (37.5) 5 (62.5)	0.948

Table 4.7, continued

Characteristics	OLP n=13	OLL n=32	OLP/OLL with dysplasia n=8	p-value[a]
Ethnicity, n (%)				0.060
Malay	4 (30.8)	4 (12.5)	0 (0)	
Chinese	5 (38.5)	17 (53.1)	1 (12.5)	
Indian	4 (30.8)	10 (31.2)	7 (87.5)	
Others	0 (0)	1 (3.1)	0 (0)	

[a]Chi-square test for independence n= Frequency

4.7 Association between clinical characteristics and OLP, OLL and OLP/OLL with dysplasia

The association between clinical characteristics and subject groups were analysed. There was a significant association between habits and subject groups (p=0.036), where higher number of OLP/OLL with dysplasia patients had risky habits. Other clinical characteristics were not significantly associated with the subject groups. The results were shown in Table 4.8.

Table 4.8: Clinical characteristics of different groups

Characteristics	OLP n=13	OLL n=32	OLP/OLL with dysplasia n=8	p-value[a]
Comorbidities, n (%)				0.098
None	4 (30.8)	8 (25.0)	0 (0.0)	
Hypertension	4 (30.8)	12 (37.5)	4 (50)	
Diabetes mellitus	3 (23.1)	9 (28.1)	3 (37.5)	
Hypercholesterolemia	4 (30.8)	11 (34.4)	1 (12.5)	
Other diseases	6 (46.2)	13 (40.6)	5 (62.5)	
More than one comorbidity	8 (61.5)	13 (40.6)	4 (50)	
Medication, n (%)				0.136
Taking antihypertensive and/or oral hypoglycaemic agents	4 (30.8)	14 (43.8)	6 (75.0)	
Not taking antihypertensive and/or oral hypoglycaemic agents	9 (69.2)	18 (56.2)	2 (25.0)	

Table 4.8, continued

Characteristics	OLP n=13	OLL n=32	OLP/OLL with dysplasia n=8	p-value[a]
Habits, n (%)				
No habits	12 (92.3)	29 (90.6)	6 (75.0)	0.036
Smoking	0 (0.0)	3 (9.4)	0 (0.0)	
Alcohol drinking	0 (0.0)	0 (0.0)	1 (12.5)	
Betel quid chewing	1 (7.7)	0 (0.0)	0 (0.0)	
More than one risky habits	0 (0.0)	0 (0.0)	1 (12.5)	
Skin lesions, n (%)	0 (0.0)	6 (18.8)	1 (12.5)	0.242
Site of involvement, n (%)				
Buccal mucosa	13 (100)	27 (84.4)	8 (100)	0.163
Tongue	3 (23.1)	8 (25.0)	0 (0.0)	0.288
Palate	0 (0.0)	2 (6.2)	0 (0.0)	0.506
Gingiva	7 (53.8)	12 (37.5)	3 (37.5)	0.583
Alveolar ridge	1 (7.7)	1 (3.1)	1 (12.5)	0.553
Lips/labial mucosa	0 (0.0)	2 (6.2)	1 (12.5)	0.472
Floor of mouth	0 (0.0)	0 (0.0)	1 (12.5)	0.057
Retromolar trigone	1 (7.7)	4 (12.5)	0 (0.0)	0.540
Multiple sites	10(76.9)	19 (59.4)	5 (62.5)	0.536
Clinical presentation, n (%)				
Reticular	13 (100)	32 (100)	7 (87.5)	0.057
Papular	0 (0.0)	0 (0.0)	1 (12.5)	0.057
Plaque	1 (7.7)	2 (6.25)	0 (0.0)	0.740
Erosive	3 (23.1)	11 (34.4)	2 (25.0)	0.712
Atrophic	0 (0.0)	0 (0.0)	0 (0.0)	-
Bullous	0 (0.0)	0 (0.0)	0 (0.0)	-
Ulcerative	1 (7.7)	6 (18.8)	0 (0.0)	0.298
Desquamative gingivitis	3 (23.1)	6 (18.8)	1 (12.5)	0.834
Combined	5 (38.5)	20 (62.5)	3 (37.5)	0.220
Symptoms, n (%)				
No symptom	1 (7.7)	4 (12.5)	0 (0.0)	0.540
Pain/discomfort	3 (23.1)	15 (46.9)	1 (12.5)	0.105
Burning sensation	6 (46.2)	10 (31.2)	6 (75.0)	0.074
Mucosal roughness	1 (7.7)	0 (0.0)	0 (0.0)	0.208
Ulcers	2 (15.4)	6 (18.8)	1 (12.5)	0.901
Multiple symptoms	0 (0.0)	1 (3.1)	0 (0.0)	0.716
Treatment, n (%)				
Topical steroids	12(92.3)	27 (84.4)	8 (100)	0.410

[a]Chi-square test for independence n= Frequency

4.8 Association between histopathological characteristics with OLP, OLL and OLP/OLL with dysplasia

There were a significant number of cases in OLL and OLP/OLL with dysplasia groups associated with the presence of inflammation extending deep into the connective tissue ($p<0.001$). Presence of perivascular inflammation and mixed inflammatory infiltrate were also significantly associated with OLL groups (p-value=0.024; p-value<0.001). The results are shown in Table 4.8.

Table 4.9: Histopathological features of different groups

Histopathological features	**OLP n=13**	**OLL n=32**	**OLP/OLL with dysplasia n=8**	**p-value[a]**
Band-like inflammatory infiltrate confined to the epithelium-lamina propria interface, n (%)	13 (100)	32 (100)	7 (87.5)	0.057
Basal cell liquefactive degeneration, n (%)	13 (100)	30 (93.8)	8 (100)	0.506
Lymphocytic exocytosis, n (%)	12(92.3)	30(93.8)	8 (100)	0.740
Inflammatory cells, n (%): -Predominantly lymphocytes -Mixed inflammatory infiltrate including plasma cells and eosinophils	 13 (100) 0 (0.0)	 7 (21.9) 25 (78.1)	 4 (50.0) 4 (50.0)	 <0.001 <0.001
Inflammatory cells extending deep into the connective tissue, n (%)	0 (0.0)	18 (56.2)	4 (50.0)	0.002
Perivascular inflammation, n (%)	0 (0.0)	13 (40.6)	3 (37.5)	0.024

[a]Chi-square test for independence n= Frequency

4.9 MT rate of OLP, OLL and OLP/OLL with dysplasia

One case in the OLP/OLL with dysplasia group showed MT, with a grade of moderate epithelial dysplasia. This gives an overall MT rate of 1.89% (1 out of 53 cases). The MT rate for the three groups, OLP, OLL and OLP/OLL with dysplasia were 0%, 0% and 12.5% respectively. The mean time to MT was 6±0 years. The recorded case was a 72-year-old Indian female patient who had regular alcohol consumption and betel quid chewing habits. Her medical history included asthma and vertigo, for which she was taking medication. The clinical presentation consisted of reticular and erosive lesions that affected the bilateral buccal mucosa, maxillary and mandibular alveolar ridges. The lesion on the left buccal mucosa transformed into oral squamous cell carcinoma. She underwent surgical removal of the lesions and completed 33 cycles of radiotherapy. Currently, patient is disease free and under follow up in the Oral Medicine Clinic.

CHAPTER 5: DISCUSSION

5.1 Socio-demographic evaluation

This retrospective study investigated the prevalence, clinicopathological features and MT of OLP, OLL and OLP/OLL with dysplasia. By looking into these elements, we aimed to provide valuable information to the existing knowledge. The study showed that the prevalence of OLP/OLL diagnosed in the Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya, is 5.75%. This figure is higher than the global pooled prevalence of OLP, which is 1.01% (González-Moles, Warnakulasuriya, et al., 2020). It also exceeded the prevalence of 1.08% reported in Asian countries. Conversely, Li et al. (2020) reported a prevalence of 0.57% among Asian countries. However, our findings were close to the worldwide prevalence range of 0.22 – 5% documented in other studies (Cheng et al., 2016; Gorouhi et al., 2014; Hamour et al., 2020; Müller, 2017). The prevalence of OLL is 2.4% in the general population (Grossmann et al., 2015; Robledo-Sierra et al., 2013).

Our study included a sample size of 7580 biopsied cases with a statistical power of 1.0, indicating it is well-powered. This indicates that our study is highly reliable and almost certain to detect any significant effects or differences. In addition, OLP and OLL cases in this centre were not reported as two different entities, but rather as OLP/OLL. This reporting approach may contribute to the higher prevalence observed in our study. Besides that, the higher prevalence of OLP in our study may be attributed to the fact that the samples were obtained from cases with lesions that underwent biopsy, which could contribute to hospital-based bias.

The mean age of patients diagnosed with OLP/OLL was 53.2±12.0 years, which correspond to the findings of Li et al. (2020), where patients aged 40 years and above were predominantly affected by OLP. Our study showed a female-to-male ratio of 1.9:1,

which is also comparable to Li et al. (2020). Additionally, our study found that Chinese patients were most affected by OLP, followed by Indian and Malay patients. In contrast, a study by Yaacob et al. (2002) reported a higher prevalence in Indian patients compared to Chinese patients. However, the association between ethnicity and OLP was not significant.

5.2 Clinical evaluations

OLP and OLL shared many similarity in clinical and histopathological features and it is challenging to distinguish between them based on these characteristics alone. Indeed, Aguirre-Urizar et al. (2020) suggested grouping both under the term "oral lichenoid disease". Our study separated OLP and OLL based on a derived diagnostic criteria from 2003 modified WHO diagnostic criteria, AAOMP diagnostic criteria and 2020 WHO Collaborating Centre for Oral Cancers' diagnostic criteria (Cheng et al., 2016; Van der Meij et al., 2003; Warnakulasuriya et al., 2021). The diagnosis of OLP was based on both clinical and histopathological features. The diagnostic criteria for OLP used in our study is shown in Table 3.1.

OLL cases that lacked the typical clinical or histopathological features of OLP were further classified in our study into three categories: i) OLCL, when a topographic relationship between dental restoration was identified; ii) OLDR; iii) OLL of unknown cause, which included atypical OLP but a causative agent could not be identified.

This study recorded the distribution of the lesions. While all the OLP cases exhibited a bilateral and almost symmetrical distribution, 62.5% of OLL cases shared the same clinical presentation. These included 3 out 5 cases of OLCL. The clinical presentation of OLCL is typically unilateral and asymmetrical, demonstrating a topographic relationship with a dental restoration (McParland & Warnakulasuriya, 2012). However, in this study, the bilateral and symmetrical presentation of the 3 OLCL cases was due to presence of

multiple dental restorations on both side of the jaws. A recent study by Tsushima et al. (2022) found no significant difference in bilateral distribution of the lesions seen in OLP and OLCL, which was also attributed by the presence of dental metallic restorations on both sides of the jaw.

A high percentage of OLL with unknown cause cases showed typical clinical features of OLP, were only histopathologically, "compatible with" OLP. This meant that these lesions demonstrated OLL features under the microscope. However, a causative etiology could not be identified.

In our study on comorbidity among patients, we found that approximately half of them had multiple comorbidities, including hypertension (37.7%), DM (28.3%) and hypercholesterolemia (30.2%). According to the 2023 National Health and Morbidity Survey (NHMS) in Malaysia, 15.6% of Malaysians had DM, 29.2% had hypertension and 33.3% had high cholesterol. The higher percentage of diabetic patients in our study may be linked to the association between DM and OLP. A case control study by Dave et al. (2021) showed that type 2 diabetics were 2.5 times more likely to present with OLP compared to non-diabetics. In addition, a higher percentage of hypertensive patients could be associated with the higher percentage of diabetic patients, as these conditions often coexist (Rihab et al., 2023).

Our study also found that 45.3% of the patients were taking anti-hypertensive medications and/or oral hypoglycaemic agents. However, we did not find a significant association between OLP, OLL or OLP/OLL with dysplasia and medication use. Only one OLL patient reported developing bilateral oral lesions a few months after starting medication for a heart condition. This is contradictory to the typical unilateral clinical presentation of OLDR (González-Moles & Ramos-García, 2022). However, the patient was also taking several medications for hypertension, DM and dyslipidemia, all of which

were possible to contribute to the occurrence of OLL. Despite the atypical clinical presentation for an OLL, histopathologically, the lesion exhibited mixed inflammatory infiltrate extending deep into the connective tissues, along with perivascular inflammation supporting its classification as an OLDR.

Furthermore, our study noted that approximately 90% of the OLP and OLL patients did not practise any form of risky habits. This may account for the low MT rate in OLP and OLL groups, as smoking and alcohol consumption are known risk factors for MT of OLP (Idrees et al., 2020). Interestingly, Michelon et al. (2022) found that smokers with Thr102Cys polymorphism had a reduced risk of developing OLP compared to non-smokers. The presence of the Thr allele in the Thr102Cys polymorphism might provide some protection against OLP for smokers, despite the overall harmful effects of smoking. Consequently, only 5.7% of the patients in our study were smokers.

A higher proportion of patients in the OLP/OLL with dysplasia group reported practising risky habits, including alcohol drinking and betel quid chewing. A study by Worakhajit et al. (2021) reported that betel quid chewing was the most potent risk factor for OPMD, followed by alcohol consumption. The risk increased by 20.96-fold when smokeless tobacco was used in combination with betel quid chewing and alcohol drinking. It is important to note that malignancies arising in OLP in patients with major risk factors, such as alcohol or smoking should not sorely attributed to OLP itself (Idrees et al., 2020).

In this study, we observed that the most common site of involvement for OLP was the buccal mucosa. This finding is consistent with González-Moles, Warnakulasuriya, et al. (2020), who reported that 67.15% of OLP cases occurred in the buccal mucosa. Additionally, half of the patients presented with involvement of multiple oral sites, which aligns with OLP's typical multifocal presentation (Cheng et al., 2016; Müller, 2017).

Clinically, OLP can manifest as reticular, erosive, atrophic, plaque-like, papular and/or bullous forms. The most characteristic clinical presentation is well-defined interlacing white striations against a background ranging from minimal to substantial erythema (Cheng et al., 2016). In our study, the most frequently observed clinical subtype was the reticular form, followed by erosive form, consistent with findings by Yaacob et al. (2002), who also reported the reticular type as the most common among Malaysians, with erosive type following as the second most common type.

Cutaneous lichen planus typically affects the flexor surface of the wrists, lower legs, trunk and lower back, presenting as a pruritic rash of shiny, flat-topped papules with a purple hue and superimposed white lacy "Wickham striae". In our study, 13.2% of the patients exhibited cutaneous lesions, a proportion similar to the 15% reported by Carrozzo et al. (2019).

Our study also documented patient complaints. The most commonly reported symptom was burning sensation, mentioned by 41.5% of the patients. A study by Thongprasom et al. (2010) similarly found that the most common symptoms reported by their patients was burning sensation, followed by pain and mucosal roughness, with 7.9% reporting no symptoms. In our study, the second most commonly reported symptoms were pain/discomfort and ulcers. Approximately 9.4% of our patients were asymptomatic, a proportion similar to that reported by Thongprasom et al. (2010). In addition, our study found that 88.7% of patients were treated with topical steroid, consistent with findings from a systematic review by Serafini et al. (2023) that identified topical corticosteroid as the first-line treatment in management of symptomatic OLP.

5.3 Histopathological evaluation

5.3.1 OLP

In this study, all cases of OLP exhibited a band-like, predominantly lymphocytic infiltrate at the epithelium-lamina propria interface, accompanied by basal cell liquefactive degeneration. These features are recognized as hallmark features of OLP in various studies (Aguirre-Urizar et al., 2020; González-Moles, Warnakulasuriya, et al., 2020; Van der Meij et al., 2003). Lymphocytic exocytosis, defined as the migration of lymphocytes into the overlying epithelium, was considered an optional criterion for OLP in our study. This histopathological feature is commonly observed in various inflammatory and immune-mediated conditions (Cheng et al., 2016), such as mucous membrane pemphigoid, mycosis fungoides, graft-vs-host disease and lupus erythematosus. Nevertheless, only 1 out of 13 cases of OLP in this study did not exhibit lymphocytic exocytosis.

5.3.2 OLL

On the other hand, all cases of OLL also demonstrated a band-like inflammatory infiltrate confined to the superficial lamina propria. However, a majority of OLL cases exhibited mixed inflammatory infiltrate including plasma cells and eosinophils. Additionally, perivascular inflammation was observed in 40.6% of cases, while 56.2% showed extension of inflammatory cells deep into the connective tissue. These features have been reported to be more prevalent in OLL compared to OLP (Cheng et al., 2016; González-Moles & Ramos-García, 2022; Lodolo et al., 2023). While the histopathological features of OLL overlap with those of OLP, the presence of mixed inflammatory infiltrate, perivascular inflammation and extension of inflammatory cells deep into the connective tissue aid in distinguishing between the two conditions.

5.3.3 OLP/OLL with dysplasia

Basal cell liquefactive degeneration and lymphocytic exocytosis were consistently observed in all cases of OLP/OLL with dysplasia. Basal cell liquefactive degeneration in OLP can obscure the detection of dysplastic features, particularly in mild to moderate epithelial dysplasia. This is especially challenging when evaluating for the presence of dysplastic features such as loss of basal cell polarity, expanded proliferative compartment and basal cell clustering/nesting, wherein most of the basal cells were degenerated in OLP. Notably, the most common dysplastic features observed in our study included premature keratinization in single cells (dyskeratosis) and generalized premature keratinization. Premature keratinization in single cell is defined as individual cells with keratinisation giving the cytoplasm a strongly eosinophilic appearance with retraction from neighbouring keratinocytes (Hankinson et al., 2024). Meanwhile, generalized premature keratinization is defined as increased prickle cell cytoplasmic eosinophilia due to keratinisation in excess of what is normally expected at that oral cavity site (Hankinson et al., 2024). Civatte bodies, also known as hyaline bodies, are eosinophilic round to oval structures, commonly found in the epithelium of OLP. They are apoptotic keratinocytes, first described by Raymond Sabouraud in 1912. Dyskeratotic bodies, on the other hand, are cells with abnormal keratinization usually found in dysplasia and squamous cell carcinoma. Civatte bodies can be easily confused with dyskeratotic cells (González-Moles et al., 2021). Due to the similarity between Civatte bodies and dyskeratotic cells, the possibility of overlooking dysplasia in a lesion with prominent lichenoid features is raised (Fitzpatrick, Honda, et al., 2014).

Common dysplastic features reported in OLD by González-Moles et al. (2021),such as basal cell hyperplasia with basaloid appearance, loss of basal cell polarity, cellular and nuclear pleomorphism and irregular stratification, were also observed in our study.

Furthermore, presence of candida infection can mimic oral epithelial dysplasia. Hence, PAS staining was done for all the OED cases with a provisional diagnosis of OLP/OLL. Cases showing presence of candida infection were excluded from further analysis. As proposed by González-Moles et al. (2021), OED cases were histologically evaluated by two experienced oral pathologists. A final diagnosis was reached through consensus based on comprehensive histological evaluation.

5.4 MT rate

In this study, the MT rate of OLP was 1.89%. The MTR of OLP reported by Warnakulasuriya et al. (2023) in an umbrella review of systemic studies was 1.1-1.4%, making our results comparable. However, when we further studied the MT rate according to each subgroups of OLP, OLL and OLP/OLL with dysplasia, the rates were 0%, 0% and 12.5% respectively. The reported MT rate for OLP in the literature ranges from 0%-12.5% (Fitzpatrick, Hirsch, et al., 2014; Giuliani et al., 2019), and our results were within this range. However, González-Moles and Ramos-García (2024) recently reported MT rates of 1.43% for OLP, 1.38% for OLL, 5.13% for OLP with dysplasia, which differ from our findings. Our study had a sample size of 53 patients, resulting in a power of 0.1977. To detect difference in MT rate with 80% power, a sample size of 340 would be required, indicating that a larger sample size is needed to confirm our findings.

Nevertheless, we recorded a case of OLL with dysplasia that transformed into OSCC. Various studies have demonstrated a higher MT rate in OLP with dysplasia (González-Moles et al., 2021; Shearston et al., 2019). It is highly debated whether the presence of epithelial dysplasia should exclude the diagnosis of OLP. The exclusion of epithelial dysplasia in the diagnosis of OLP originates from the 2003 WHO diagnostic criteria proposed by Van der Meij et al. (2003), favouring the term “OLL” for OLP lesions with epithelial dysplasia. The exclusion of epithelial dysplasia had led to an underestimation

of OLP (González-Moles et al., 2021). The presence of epithelial dysplasia is a gold standard for evaluating MT in OPMD (Warnakulasuriya et al., 2021). Given that OLP is classified as an OPMD, it may naturally develop epithelial dysplasia as a step towards OSCC. Besides that, Sivapathasundharam and Protyusha (2023) pointed out that an initial benign OLP should not be re-diagnosed as OLL if dysplastic features developed during follow-up examination. Molecular studies on OLP have shown that loss of heterozygosity (LOH) in OLP with dysplasia is comparable to other dysplastic OPMDs without lichenoid features, suggesting OLP provides a fertile field for the development of dysplasia (Zhang et al., 2000). Besides that, immunohistochemical studies have demonstrated overexpression of the anti-apoptotic protein Bcl-2 and survivin, as well as increased in cell proliferation markers like PCNA, Ki-67, and cyclin D1 in OLP (González-Moles et al., 2021). These factors may contribute to the development of OED in OLP which later progresses into OSCC. In addition, chronic inflammation in OLP may also aid in proliferation and survival of keratinocytes with genomic alterations. The persistent chronic inflammation is thought to initiate and promote cancer development (Warnakulasuriya et al., 2023).

In this study, the patient who developed OSCC had been under follow-up for over six years and had a history of betel quid chewing and alcohol consumption. The clinical presentation included reticular and erosive lesions affecting the bilateral buccal mucosa, maxillary and mandibular alveolar ridges. This case demonstrated several risk factors for malignant transformation of OLP as outlined by González-Moles et al. (2019): presence of dysplasia in OLP, presence of atrophic-erosive lesions and alcohol consumption. Betel quid chewing, smoking and alcohol consumption are known to significantly increase OPMD risk (Lin et al., 2022). Studies have shown a synergistic effect of betel quid chewing and alcohol consumption in the development of oral malignancy (Petti et al.,

2013). Hence, it is important to advise patient to stop any risky habits and closely monitor them long-term. A re-biopsy should be performed if any suspicious changes arise.

Histologically, this case showed a dysplastic epithelium with band-like inflammatory infiltrate confined to the juxta-epithelial region, liquefactive degeneration of basal cells, mixed inflammatory cells including lymphocytes and plasma cells extending deep into the connective tissue, and perivascular inflammation. Apart from the dysplasia, these histopathological features were suggestive of OLL. Interestingly, given the patient's habit of betel quid chewing, these lesions might be an oral lichenoid contact reaction to betel quid. Reichart and Warnakulasuriya (2012) described a lesion named betel-quid induced OLL (BQOLL), which had a direct topographical relationship to where the betel quid was kept in the buccal sulcus for a prolonged period. These lesions resemble OLP both clinically and histopathologically. Clinically, BQOLL appears as fine, white, linear, wavy, parallel striations resembling fingerprints, occasionally radiating from a central erythematous area. The common sites affected are buccal mucosa and mandibular vestibule where betel quid is usually placed. Histologically, they are similar to OLP, demonstrating liquefactive degeneration of basal cells and band-like inflammatory cell infiltrate with lymphocytes and plasma cells. However, the malignant potential of BQOLL is unknown due to a lack of studies.

The study of MT in OLP highly depends on the study methodology. Idrees et al. (2020) highlighted several factors that can affect the reliability of a study. Firstly, the cases should have a confirmed OLP diagnosis based on a well-defined diagnostic criteria. The absence of a widely accepted diagnostic criteria for OLP is a major confounding factor in studying MT in OLP (González-Moles, Ramos-García, et al., 2020). Various diagnostic criteria have been proposed for OLP (Cheng et al., 2016; Van der Meij et al., 2003; Warnakulasuriya et al., 2021), but all lack validation. Nevertheless, OLP should be

diagnosed following criteria that include both clinical and histopathological features. Secondly, the presence of epithelial dysplasia in OLP highly influences the MT rate. The exclusion of epithelial dysplasia in diagnosing OLP remains a highly debated topic. Studies including OLP with epithelial dysplasia report higher MT rates (González-Moles et al., 2019; Shearston et al., 2019).

González-Moles, Ramos-García, et al. (2020) suggested future studies should focus on OLP without initial dysplasia to examine whether epithelial dysplasia can develop in OLP. With this, a properly designed prospective study is preferred.

5.5 Limitations of the study

Owing to the relatively small sample size (n=53) and the low power of this study, the findings may not fully reflect the study population. Many cases with missing or incomplete clinical data reduced the sample size. Additionally, some cases were not biopsied, contributing to the low sample size. Moreover, there was a loss of follow-up during the Covid-19 pandemic. There were some cases with insufficient clinical data to document lesions as OLDR/OLCL.

CHAPTER 6: CONCLUSION

Our study found that prevalence of OLP/OLL diagnosed at Diagnostic Oral Pathology Unit, Faculty of Dentistry, Universiti Malaya is 5.75%. The clinical and histopathological characteristics of OLP/OLL patients seen in Oral Medicine Clinic, Faculty of Dentistry, Universiti Malaya is comparable to the literature.

In our study, we found that all cases of OLP/OLL with dysplasia exhibited basal cell liquefactive degeneration. The presence of basal cell liquefactive degeneration may obscure the detection of mild to moderate epithelial dysplasia. The most common dysplastic features seen were dyskeratosis and premature keratinization. Given the similarity between Civatte bodies and dyskeratotic bodies, there is a potential for overlooking dysplasia in lesions with prominent lichenoid features.

Our study recorded a case of OLL with dysplasia which transformed into malignancy. This finding emphasizes the importance of close monitoring of OLP and OLL patients, especially those with dysplasia. Our study also highlights the need for a standardized diagnostic criteria for diagnosing OLP. To better understand the pathogenesis and MT of OLP, a properly designed prospective study with a large cohort involving multiple centers is recommended.

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