CLINICOPATHOLOGICAL STUDY OF ORAL LICHEN PLANUS AND ORAL LICHENOID REACTION

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FACULTY OF DENTISTRY
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ABSTRACT

Introduction: Oral lichen planus is a chronic inflammatory disease that affects the mucosa of the oral cavity. Oral lichenoid reactions/ lesions share many clinical and histopathological features with oral lichen planus, and represent a response to extrinsic or causative factors (drugs, allergens). **Aim:** The purpose of this study was to evaluate the clinical and histopathological features of oral lichen planus and oral lichenoid reactions/ lesions. **Objectives:** The objectives of this study were to assess the clinical and histopathological features of patients diagnosed with oral lichen planus and oral lichenoid reaction/ lesions. This study also sought to investigate the association between clinicopathological characteristics and patients with/ without exposure to causative factors. Finally, this study compared the ratio of plasma cells to lymphocytes in patients with/ without exposure to causative factors. **Methods:** This study was conducted in a retrospective manner in patients who have been diagnosed with oral lichen planus and oral lichenoid reaction/ lesions in Faculty of Dentistry, University of Malaya. A total of 122 patients that met the inclusion criteria were studied. Socio-demographic and clinical data for each case were obtained from clinical folders in Oral medicine clinic and histopathology reports in Oral Pathology Research and Diagnostic Laboratory (OPDRL)**.** Histopathological data was extracted from the archived hematoxylin and eosin stained slides in OPDRL. Histopathological scoring of plasma cells and lymphocytes was done using 3D Histech and QuPath softwares. Data was analyzed using chi-square, logistic regression, and receiver operating curve analysis. **Results:** There were significant differences in plasma cells to lymphocytes ratio between patients who were exposed to causative factors and those who were not (p=0.043 and p=0.031). Plasma cells to lymphocytes ratio in patients exposed to causative factors was higher than those who were not (p=0.048 and p=0.032). Presence of eosinophils was significantly associated with exposure to causative factors (p=0.016 and p=0.011), deeper inflammatory infiltrate

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(p=0.016), and epithelial atrophy (p=0.043). **Conclusion:** This study demonstrated association between the presence of eosinophils and exposure to causative factors, which were consumption of medications that had been associated with oral lichenoid reaction, and also presence of restorative materials adjacent to lesions. Moreover, this study demonstrated higher plasma cells to lymphocytes ratio in patients exposed to causative factors than those who were not. These findings strongly support the role of causative factors, mainly the drugs and dental restorative materials in the etiology of oral lichenoid reactions/ lesions, although it is difficult to pinpoint. Thus, in clinical settings, together with proper history and clinical findings, these features may facilitate clinicians in planning appropriate management for patients.

Keywords: Oral lichen planus, Oral lichenoid reactions/ lesions, plasma cells, eosinophils

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ABSTRAK

Pendahuluan: "Oral lichen planus" adalah penyakit keradangan kronik yang menyerang mukosa rongga mulut. "Oral lichenoid reactions/ lesions" mempunyai banyak ciri klinikal dan histopatologi yang sama dengan "oral lichen planus", dan dianggap sebagai tindak balas terhadap agen ekstrinsik atau agen penyebab (seperti ubat, alergen). **Matlamat**: Tujuan kajian ini adalah untuk menilai ciri-ciri klinikal dan histopatologi "oral lichen planus" dan "oral lichenoid reaction". **Objektif**: Objektif kajian ini adalah untuk menilai ciri-ciri klinikal and patologikal pada pesakit menghidap penyakit "oral lichen planus" and "oral lichenoid reaction/lesions". Kajian ini juga bertujuan untuk mencari hubung-kait antara ciri-ciri klinikal and patologikal di kalangan pesakit yang terdedah kepada agen penyebab and pesakit yang tidak terdedah. Selain itu, kajian membandingkan nisbah sel plasma dengan limfosit antara di kalangan pesakit yang terdedah kepada agen penyebab, dan pesakit yang tidak terdedah. **Kaedah**: Kajian ini dilakukan secara retrospektif di kalangan pesakit yang telah didiagnosis dengan "oral lichen planus" and "oral lichenoid reactions/ lesions" di fakulti pergigian, Universiti Malaya. Sebanyak 122 pesakit yang memenuhi kriteria inklusi dikaji. Data sosio-demografi dan klinikal untuk setiap kes diperoleh dari folder klinikal di klinik perubatan mulut, dan laporan histopatologi di Makmal Penyelidikan dan Diagnostik Patologi Mulut (OPDRL). Data histopatologi diekstrak dari slaid hematoxylin dan eosin yang diarkibkan dalam OPDRL. Pemarkahan histopatologi sel plasma dan limfosit dilakukan menggunakan perisian 3D Histech dan QuPath. Analisis dengan Chi-square dan ujian regressi. **Keputusan**: Terdapat perbezaan yang signifikan dalam nisbah sel plasma dan limfosit antara pesakit yang terdedah kepada agen penyebab dan mereka yang tidak terdedah (p = 0.043 dan p = 0.031). Nisbah sel plasma dan limfosit pada pesakit yang terdedah kepada agen yang terlibat adalah lebih tinggi daripada pesakit yang tidak terdedah (p = 0.048 dan p = 0.032). Kehadiran eosinofil mempunyai kaitan yang signifikan dengan pesakit yang terdedah

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kepada agen penyebab (p = 0.016 dan p = 0.011), infiltrat inflamasi yang lebih dalam (p = 0.016), dan atrofi epitelium (p = 0.043). **Kesimpulan**: Kajian ini juga menunjukkan bahawa kehadiran eosinofil dikaitkan dengan pendedahan kepada faktor penyebab. Kajian ini juga menunjukkan bahawa terdapat perbezaan dalam nisbah sel plasma ke limfosit antara pesakit yang terdedah kepada agen penyebab dan mereka yang tidak. Nisbah sel plasma ke limfosit didapati lebih tinggi di kalangan pesakit yang terdedah kepada faktor penyebab. Penemuan kajian ini menunjukkan bahawa faktor penyebab iaitu ubat-ubatan dan bahan pergigian memainkan peranan dalam punca penyakit "oral lichen reactions/lesions". Penemuan ini bersama dengan ciri-ciri klinikal dan sejarah perubatan pesakit boleh membantu perawat untuk merancang rawatan bagi pesakit mereka.

Kata kunci: Oral lichen planus, oral lichenoid reaction/ lesions, sel plasma, eosinofil

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LIST OF ABBREVIATIONS

APC	Antigen presenting cell
C-D-R	Challenge-dechallenge-rechallenge
DC	Dendritic cells
DM	Diabetes mellitus
DIF	Direct immunofluorescence
ELP	Esophageal lichen planus
GM-CSF	Granulocyte-macrophage colony activating factor
HLA	Human leukocyte antigen
HMC	Human mast cell
HPT	Hypertension
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IL-6R	Interleukin-6 receptor
MHC	Major histocompatibility complex
NK	Natural killer
NOD	Nucleotide-binding oligomerization domain
NSAID	Non-steroidal anti-inflammatory drug
OPDRL	Oral Pathology Research and Diagnostic Laboratory
RANTES	Regulated upon Activation, Normal T cell Expressed, and Secreted
ROC	Receiver operating curve
SCC	Squamous cell carcinoma
TGF	Transforming growth factor
Th	T-helper
TIMP	Tissue inhibitors of metalloproteinases
TNF	Tumor necrosis factor
Treg	T-regulatory
UV	Ultraviolet

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CHAPTER 1 : INTRODUCTION

1.1 Research Background

Oral lichen planus is defined as a non-infectious, chronic inflammatory condition involving the oral mucosa and underlying lamina propria, and may be accompanied by skin lesions (Kurago, 2016). It is classified as one of the oral potentially malignant disorders (El-Naggar et al., 2017). Recent meta-analysis found that the malignant transformation rate of oral lichen planus was between 1.1% to 1.4% (Aghbari et al., 2017; Fitzpatrick et al., 2014; Giuliani et al., 2019; González-Moles et al., 2019; Shearston et al., 2019). Oral lichenoid lesions on the other hand are considered as clinical and histological contemporaries of oral lichen planus (Feldmeyer et al., 2020; Kamath et al., 2015). Unlike oral lichen planus, which is considered to be idiopathic in nature, oral lichenoid lesions are often associated with known identifiable cause or inciting factors (Feldmeyer et al., 2020; Kamath et al., 2015). There are several terms used interchangeably for oral lichenoid lesions, for example oral lichenoid reaction, and oral lichenoid drug reactions, oral lichenoid contact lesions (Al-Hashimi et al., 2007). Many systemic drugs have been reported to cause oral lichenoid lesions. For example, non-steroidal anti-inflammatory drugs [NSAID] (Cutler, 1980; Zain, 1989); antihypertensive agents (Giunta, 2001), angiotensin converting enzyme inhibitors (Firth & Reade, 1989); oral hypoglycemic agents (Lamey et al., 1990); and beta blockers (Hawk, 1980). There was also report of antiretroviral medications causing oral lichenoid reactions (Scully & Diz Dios, 2001). Oral lichenoid lesions induced by amalgam fillings have been reported in several studies (Camisa et al., 1999; Skoglund & Egelrud, 1991). Other studies have also found that 70% of amalgam contact hypersensitivity lesions which present as oral lichenoid lesions were patch test positive for amalgam or mercury compared with only 3.9% of oral lichen planus cases (Thornhill et al., 2003). Among other dental materials associated with oral lichenoid lesions are gold (Ahlgren et al., 2002), and composite

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restorations (Blomgren et al., 1996; Lind, 1988), and dental cast alloys (Hensten-Pettersen, 1992)

The diagnosis between oral lichenoid lesions and oral lichen planus has been a matter of debate until now. This is mainly because clinically and histologically they can appear similar, with subtle and non-specific differences. Clinically, oral lichen planus is considered as nearly always bilateral and symmetrical with various morphology (van der Waal, 2009). There had been several attempts to classify oral lichen planus and oral lichenoid lesions objectively based on histologic features. A study conducted attempting to elicit the most favorable features for diagnosis of both entity (Thornhill et al., 2006). They have found that pathologist will consider few aspects in making diagnosis of oral lichen planus and oral lichenoid reaction. For example, most pathologist would consider that the presence of deep inflammatory infiltrate, focal or perivascular infiltrate, plasma cells, and eosinophils will favor the diagnosis of oral lichenoid lesions (Thornhill et al., 2006). Conversely, the presence of band-shaped infiltrate, lymphocytes, histiocytes, juxta epithelial cell free zone will favor the diagnosis of oral lichen planus (Thornhill et al., 2006). It is important to distinguish between oral lichen planus and oral lichenoid lesions because the management and clinical outcome can be different (Thornhill et al., 2006), although in general both are treated mainly with topical corticosteroids. This study is designed to assess the clinical and histopathological characteristics of oral lichen planus and oral lichenoid reactions/ lesions, explore and compare the presence and levels of plasma cells in patients with exposure to causative factors and those who were not. The causative factors in this study refer drugs or medications that have been linked to oral lichen planus and oral lichenoid reaction/ lesions, and also the presence of dental restorative materials adjacent to oral lichen planus and oral lichenoid reactions/ lesions.

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1.2 Aims and objectives

The aim of this study is to evaluate the clinical and histopathological features of oral lichen planus and oral lichenoid reactions/ lesions in faculty of Dentistry, University of Malaya.

The specific objectives include:

1. To assess the clinical and histopathological features of patients diagnosed with oral lichen planus/ oral lichenoid reactions
2. To investigate the association between clinicopathological characteristics and patients with/ without exposure to causative factors
3. To investigate and compare the ratio of plasma cells to lymphocytes in patients with/ without exposure to causative factors

1.3 Research hypothesis

1. There are differences in clinical and histopathological features between oral lichen planus and oral lichenoid reaction/ lesions
2. There is association of clinical and histopathological characteristics with patients exposed to causative factors and those who were not.
3. There is difference in the ratio of plasma cells to lymphocytes between patients exposed to causative factors and those who were not.

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CHAPTER 2 : LITERATURE REVIEW

2.1 Oral lichen planus

2.1.1 Background

Lichen planus is a common subacute or chronic dermatosis that may involve the skin, mucous membranes, hair follicles, and nails (Elder, 2014). Oral lichen planus is a non-infectious, chronic inflammatory condition involving the oral mucosa and underlying lamina propria, and may be accompanied by skin lesions (Kurago, 2016). A study also shown that cutaneous lichen planus can be associated with mucosal lesion in 9% of cases (Parihar et al., 2015). Lichen planus is also recognized as the most common dermatological disorder that can present with oral lesion (Cassol-Spanemberg et al., 2019). On the other hand, oral lichen planus can be the sole manifestation of the disease, or it can present concurrently with cutaneous, and lesion on other mucosal sites such as genital, eye, or gastrointestinal (Gorouhi et al., 2014). Oral lichen planus is classified by WHO as one of the oral potentially malignant disease (El-Naggar et al., 2017). Historically, the first clinical description of lichen planus was attributed to Professor Ferdinand Ritter von Hebra of Vienna, where he designated the term lichen ruber to describe a peculiar form of papular eruption (Wilson, 1866). 'Lichen' is a Greek word, which has been frequently used in modern dermatology (Zaghi & Griffin, 2016). Hipocrates [460-371BC] described lichen as an "eruption of a papule" (Zaghi & Griffin, 2016). Subsequently, there were a number of descriptions given for lichen. Professor Hebra provided the modern description of lichen. To this day, Merriam Webster dictionary define lichen as "eruption of papulae" (Zaghi & Griffin, 2016). The term ruber, which was used by Professor Huber means red (Wilson, 1866). Planus means flat or smooth (Wilson, 1866). In 1869, English dermatologist Erasmus Wilson refined the term lichen ruber by Professor Huber to lichen planus (Zaghi & Griffin, 2016). According to

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Wilson, the term planus, which replace ruber is able to describe more accurately the majority clinical presentation of the eruption which is flat papules (Wilson, 1866). However, Professor Hebra's taxonomy is not totally forgotten, as "lichen ruber planus" is still used synonymously with lichen planus in the literature, although not common (Zaghi & Griffin, 2016).

Lichen ruber is miliary papules eruption that do not develop vesicles of pustules (Fox, 1871). At the initial stage, the papules are distinct from each other, but tend to coalesce and form patches. The papules are covered by red scales, thus the term ruber (Fox, 1871). When the skin is affected in a large surface area, the skin will appear reddish and covered by scale, and movement will be restricted (Fox, 1871). The nails can be affected as well, where nails will become thickened, opaque, and rough, while itching is a manifestation of lichen ruber at later stages (Fox, 1871). Terminal stages of the disease is when patient develop marasmus and eventually dies (Fox, 1871).

2.1.2 Epidemiology

There is a geographical variation in the worldwide prevalence of oral lichen planus. The estimated worldwide prevalence of oral lichen planus ranged from 0.5% to 2.6%, however, we still do not know the precise prevalence (Shirasuna, 2014). A systematic review and meta-analysis of global prevalence of oral lichen planus found that the overall estimated prevalence of oral lichen planus in the general population is 0.89%, while in the clinical settings, it is estimated to be 0.98% (Li et al., 2020). They also found that the prevalence of oral lichen planus in Asian countries is lower than the other part of the continents (Li et al., 2020). The country with the lowest prevalence of oral lichen planus is India, which is 0.02%, while Brazil has the highest prevalence with 6.04%. Moreover,

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this recent study also reported a higher prevalence of oral lichen planus among women, especially above 40 years of age (Li et al., 2020).

Occasionally, clinicians may encounter lesions that resemble oral lichen planus clinically and histologically. These lesions are given several terms, but they are commonly called as oral lichenoid lesion, or oral lichenoid reaction (Al-Hashimi et al., 2007). Among other terms usually used to name these lesions are oral lichenoid contact lesion and oral lichenoid drug reaction (Al-Hashimi et al., 2007). The prevalence of oral lichenoid reaction reported has been lower than oral lichen planus, an Italian study reported prevalence of oral lichenoid reaction to be 0.29%, compared to 1.46% for oral lichen planus (Pentenero et al., 2008). In Malaysia, the reported prevalence of oral lichen planus is 0.38% (Zain et al., 1997). These lesions are usually associated with some possible etiological factors, such as direct contact to dental restorative materials commonly amalgam, intake of certain medications or oral care products, and also in the setting of graft versus host disease (Al-Hashimi et al., 2007). It is often difficult to distinguish between a true oral lichen planus versus oral lichenoid reaction (Feldmeyer et al., 2020). However, considering that there can be difference in pathophysiology and management, it is important to distinguish these entities (Feldmeyer et al., 2020).

2.2 Etiology

Until today, the causes that initiate or perpetuate oral lichen planus remain unknown. However, there are few proposed factors that may play a role as a trigger factor. These are mainly genetic factors, local and systemic inducers of cell mediated hypersensitivity, stress, autoimmune response to epithelial antigens, and viral antigens.

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2.2.1 Genetics

Genetic predisposition has been hypothesized in the etiology of oral lichen planus. A number of studies have been conducted on the genetic aspect of oral lichen planus. There had been a reported case of 11-year-old monozygotic twin girls who are living together with concurrent skin lichen planus, which suggested that genetic factors may contribute to the etiology of lichen planus (Gibstine & Esterly, 1984). Another interesting twin study with regards to oral lichen planus was a case of oral lichen planus in monozygotic twins that were raised apart, thus excluding environmental role of oral lichen planus onset (Wei et al., 2018). Other than that, a familial study also observed that oral lichen planus can possibly be inherited (Ambrosio Bermejo-Fenoll & López-Jornet, 2006). It is also worthy to note that although familial occurrence of lichen planus is uncommon, it is well documented in several other studies (Katzenelson et al., 1990; Kofoed & Wantzin, 1985).

Another interesting observation is that compared to non-familial lichen planus, familial lichen planus tends to occur at an earlier onset and also present with more severe and extensive lesions (Ambrosio Bermejo-Fenoll & López-Jornet, 2006). Several gene studies in oral lichen planus have also been done. Previously, there were several studies conducted on the role of different genes on oral lichen planus (Hirota et al., 2002; Karatsaidis et al., 2003; Khan et al., 2003; X. J. Zhou et al., 2001). Most of these studies involve a single gene or a single gene family in oral lichen planus. A bioinformatic study also identified 132 genes involved or potentially involved in oral lichen planus (Orlando et al., 2013). These genes were then ranked based on their number of interactions. The study recognized 5 genes with the highest number of interactions, namely JUN, EGFR, FOS, IL2, and ITGB4 genes (Orlando et al., 2013).

Other than that, studies in the relationship between human leukocyte antigen [HLA] and oral lichen planus has shown that there is association of oral lichen planus with HLA-

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A, B and C antigens (Ognjenović et al., 1998; Porter et al., 1993; Watanabe et al., 1986). More interestingly, HLA-DR6 gene plays a role in hepatitis-C associated oral lichen planus (Carrozzo et al., 2005; Carrozzo et al., 2001). Other than that, a meta-analysis study found an association between polymorphism in the tumor necrosis alpha [TNF-α] gene and oral lichen planus (Y. Zhou & Vieira, 2018). Another genetic study that has caught particular interest is IL-18 gene polymorphism. There are studies that concluded there is an associated between interleukin [IL]-18 gene polymorphism and oral lichen planus (J Bai et al., 2007; Y. Zhang et al., 2012). However another study showed there was no association between IL-18 gene and oral lichen planus (Negi et al., 2019). Other gene polymorphism that was suspected to be contributing to oral lichen planus is IL-10 gene polymorphism (Jingping Bai et al., 2009)

2.2.2 Infectious agents

HCV is probably the microorganism that has the most relevant association with oral lichen planus. There are several reports regarding association of Hepatitis C virus [HCV] infection with oral lichen planus. Currently, there is strong evidence that oral lichen planus is associated with HCV, but this association varies geographically (Kurago, 2016). A systematic review confirmed the association between oral lichen planus and HCV (Lodi et al., 2010). They discovered that patients with oral lichen planus have five times increased risk of being HCV seropositive. The relationship between oral lichen planus and HCV is higher especially in Japan, Mediterranean countries, and the USA (Lodi et al., 2010). However, the association of oral lichen planus and HCV cannot be explained on the basis of high prevalence of HCV infection alone. This is because there are countries with high prevalence of HCV reported negative or insignificant associations (Lavanya et al., 2011).

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Other microorganisms that had been investigated for their relationship with oral lichen planus are mainly viruses, for example cytomegalovirus, herpes simplex virus-1, human herpes virus-6, Epstein-Barr virus, hepatitis-B virus, and human papilloma virus (Lodi et al., 2005). All these viral infections do not reveal any significant association with oral lichen planus (Lodi et al., 2005). Bacterial studies in oral lichen planus related to bacterial etiology are still at beginning stage (Kurago, 2016). *Helicobacterpylori* has shown no association with oral lichen planus (Lodi et al., 2005). Other bacteria of interest that have been observed are *Fusobacteria* and *Campylobacter*, which have been found to be increased in saliva of oral lichen planus patients (Wang et al., 2015).

2.2.3 Systemic associations

There are reports where oral lichen planus is associated with some systemic disorder. An entity that is worthwhile to be of note is thyroid disorder, mainly Hashimoto's thyroiditis and hypothyroidism (Muzio et al., 2013). A study found that 93.3% oral lichen planus cases were preceded by Hashimoto's thyroiditis (Muzio et al., 2013). This study also hypothesized that in Hashimoto's thyroiditis, the circulating thyroid antibodies potentially triggered organ specific immune response against the oral mucosa and skin, resulting in the development of oral lichen planus and cutaneous lichen planus. Another study also reported that patients with thyroid disorder have two-fold relative odds of having oral lichen planus/ oral lichenoid reaction compared to individuals without thyroid disorder (Siponen et al., 2010). This association is shown to be more prominent in hypothyroidism (Siponen et al., 2010). Other systemic disorders that are associated with oral lichen planus/ oral lichenoid reactions are systemic lupus erythematosus, Sjogren syndrome, and Good syndrome (Kurago, 2016). However, there is lack of documentation of criteria used to diagnose oral lichen planus in these cases (Kurago, 2016).

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2.2.4 Psychological factors

A study revealed that stress and anxiety levels among oral lichen planus patients are slightly higher than the population norms, however, the increase is not remarkable (McCartan, 1995). Moreover, the study also noted that presence of erosions in oral lichen planus is also not significantly related to anxiety (McCartan, 1995)

2.3 Pathogenesis

2.3.1 Immunology of the oral cavity

The oral cavity is composed of various sophisticated anatomical structures. There are multitudes of microorganisms mainly bacteria that reside in the oral cavity. Moreover, external substances also challenge the homeostasis of the oral mucosa (Wu et al., 2014). The oral epithelium and its underlying lamina propria are important for protection against microorganism's invasion into the body and also environmental threats (Feller et al., 2013). The oral mucosal immunity can neutralize harmful foreign antigens, limits colonization by pathogenic microbe, regulate the non-inflammatory protective responses, regulate tolerance to commensal microorganisms and various foreign or external exogenous proteins (Brandtzaeg, 2009; Wu et al., 2014). The mucosa can provide immune responses by means of immune cells within the mucosa (Wu et al., 2014). The mucosa contains cells of the innate immune system such as macrophages, dendritic cells, natural killer [NK] cells, polymorphonuclear leucocytes, and their associated inflammatory mediators such as cytokines, chemokines, antibacterial peptides, and complement system components (Feller et al., 2013). Other than that, salivary immunoglobulin [Ig] A, oral keratinocyte derived biologic mediators, and gingival

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crevicular fluid component also play their roles in oral immunity (Diamond et al., 2008; Fábián et al., 2012; Walker, 2004).

2.3.1.1 Pattern recognition receptors

In the events of microbial infections, the innate immune system is activated before the generation of the adaptive immune response. Oral keratinocytes and cells of the innate immune system can detect invading pathogens by means of germline encoded pattern recognition receptors that are specific for the common components of pathogenic microbes (Cook et al., 2004; Pivarcsi et al., 2003). The pattern recognition receptors can distinguish variable molecular components of microorganisms, for example, peptidoglycan of gram-positive bacteria, lipopolysaccharide of gram-negative bacteria, and mannan in the wall of yeast cells (De Koning et al., 2010; Palm & Medzhitov, 2009; Pivarcsi et al., 2003). More importantly, they can distinguish self and non-self-antigens, therefore avoiding detrimental immune responses against self-antigens (Palm & Medzhitov, 2009; Pivarcsi et al., 2003). In brief, the pattern recognition receptors consist of several families, namely Toll-like receptor family, C-type lectin receptor family, mannose receptor family and nucleotide-binding oligomerization domain –like receptor family. (Cassel et al., 2009; Gordon, 2002; Hoebe et al., 2004; Palm & Medzhitov, 2009). Among these, the Toll-like receptor family plays the most important role in resisting infections (Iwasaki & Medzhitov, 2004). These receptors can recognize various molecular patterns of bacterias, virus, fungi, and protozoas (Hoebe et al., 2004; Khader et al., 2009; Lee et al., 2012; Palm & Medzhitov, 2009). When activated, the pattern recognition receptors can mediate cytokines and chemokines productions, upregulate cell surface molecules, or induce peripheral immune tolerance (Cassel et al., 2009; Hoebe et al., 2004; Palm & Medzhitov, 2009). Moreover, the pattern recognition receptors also

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have important influence on the adaptive immune response, where it can initiate and determine the type of specific adaptive immune responses, regulate the magnitude and duration of the responses, and also influence the formation of memory T-cell (Palm & Medzhitov, 2009). Under normal physiologic condition, Toll-like receptor is considered to be involved in epithelial homeostasis and in repair after epithelial injury (Bäckhed & Hornef, 2003).

2.3.1.2 Oral Langerhans cells

These cells are myeloid dendritic cells which are also the permanent residents of the basal and suprabasal region of the oral epithelium (Bäckhed & Hornef, 2003). Oral Langerhans cells and other dendritic cells regulate T-cell responses [upregulate or downregulate], and also the immune tolerance and activation of the oral mucosa based on the signals obtained from the microenvironment (Allam et al., 2008; Novak et al., 2004). Under normal physiologic conditions, Langerhans cells maintain a state of immune tolerance, and will initiate adaptive immune responses when there is invasion by microorganisms (Novak et al., 2004; Novak et al., 2008). Langerhans cells express surface receptors CD1a, FcεRI, CD11b, and langerin/ CD207 (Cutler & Jotwani, 2004; Novak et al., 2004; Novak et al., 2008).

2.3.1.3 Oral keratinocytes

Keratinocytes express variety or pattern recognition receptors (Uehara et al., 2005). Among them are the Toll-like receptor 2, Toll-like receptor 4, and nucleotide-binding oligomerization domain [NOD]-like receptor 1 and 2, which can be activated upon encounter with molecular components of bacterial structures (Uehara et al., 2005). The

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Toll-like receptor 2 is a receptor for peptidoglycans, zymosan, lipoproteins, teichuronic acid, and fungal mannan; Toll-like receptor 4 is a receptor for lipopolysaccharides, and NOD1 and NOD2 proteins recognize bacterias (Uehara et al., 2005). When activated, Toll-like receptor family produce specific chemokines and cytokines which can activate adaptive immune response against the pathogen (Miller & Modlin, 2007). Moreover, without involvement of the Toll-like receptor, keratinocytes themselves are also capable of producing substances such as antibacterial peptides, eicosanoids, reactive oxygen metabolites and component of the complement system (Basset-Séguin et al., 1990; Brandtzaeg, 2013; Cerutti, 2008; Pasch et al., 2000; Pelle et al., 2005; Pivarcsi et al., 2003; Sivamani, 2014; Yancey et al., 1992).

2.3.1.4 Mucosal humoral immunity

Immunoglobulin A is the main Immunoglobulin isotype in involved in mucosal humoral immunity (Brandtzaeg, 2013; Cerutti, 2008). It is produced by B-cells that undergo class switching to Immunoglobulin A (Puga et al., 2010). This class switching can either be induced by T-helper cells, or can be independent of it (Puga et al., 2010), which can possibly be induced by antigen presenting cells via their mediators such as transforming growth factor-β and B-cell activating factor (Litinskiy et al., 2002). The class switching enable B cells to produce Immunoglobulin A (Stoel et al., 2005). Class switching mechanism that is dependent on T-helper cells will produce Immunoglobulin A with a high affinity for pathogens and their toxins (Cerutti, 2008; Macpherson et al., 2008). On the other hand, when class switching is independent of T-helper cells, the Immunoglobulin A produced have low affinity for commensal microbes (Cerutti, 2008; Macpherson et al., 2008). Site where class switching of B-cell can be in the lymphoid

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tissue of the Waldeyer ring, regional lymph nodes, and also isolated lymphoid foci of oral mucosal lamina propria (Kataoka et al., 2011; Kiyono & Fukuyama, 2004).

T-cell residing in the oral mucosa is the cornerstone of mucosal immunity and tolerance (Wu et al., 2014). Mucosal immune system is important in protecting the inner surface of the body. These include mucosal surface of the oropharynx, gastrointestinal tract, respiratory tract, urogenital tract, and exocrine glands (Janeway et al., 2008). Immune system of the mucosa has similar features despite their difference in locations (Wu et al., 2014). The oral mucosa forms a mechanical barrier that is thicker compared to the gastrointestinal mucosa (Squier & Kremer, 2001). The oral cavity is unique, because of the present of teeth, which is surrounded by the periodontal epithelium which form attachment and seal (Wu et al., 2014). The periodontal epithelium is also a weak spot where microorganisms can gain entry into the body (Wu et al., 2014). Thus, an impeccable oral immune system is crucial (Wu et al., 2014). The oral-pharyngeal mucosal immune system is considered to resemble the gastrointestinal mucosal immune system, which is composed of inductive and effector sites (Wu et al., 2014).

2.3.2 Immunopathogenesis of oral lichen planus

2.3.2.1 Unifying Hypothesis

The pathogenesis in oral lichen planus is indeed a complex process that involve variety of cells and soluble factors. Unifying hypothesis for oral lichen planus had been discussed by several outstanding authors (Lodi et al., 2005; Shiohara & Mizukawa, 2005; Sontheimer, 2009; Sugerman et al., 2002). Figure 2.1 illustrates unifying hypotheses for the immunopathogenesis of lichen planus (Sontheimer, 2009).

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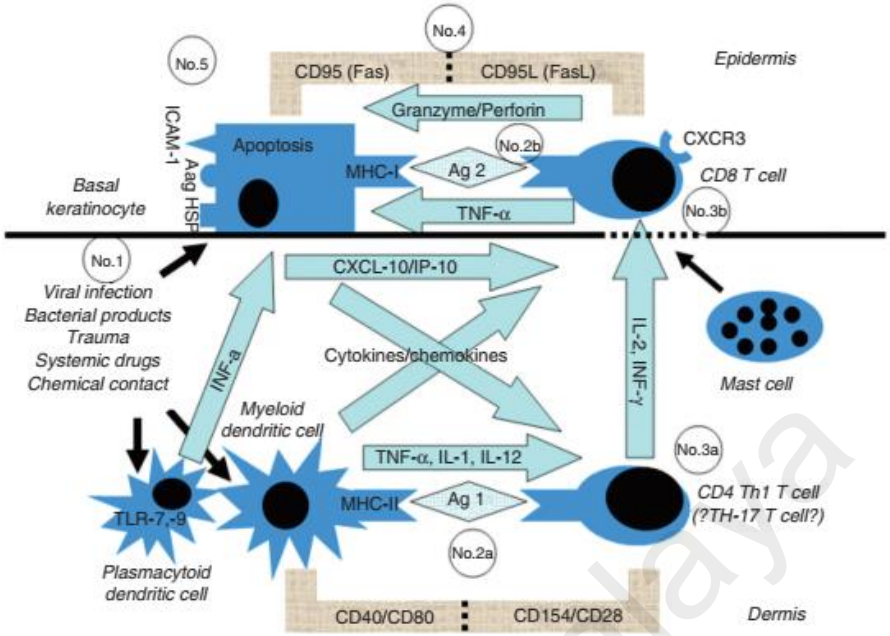

Figure 2.1 Composite representation of unifying hypotheses for the immunopathogenesis of lichen planus.

Descriptions of Figure 2.1 are as follow:

Stage 1. Basal keratinocytes and antigen presenting cells [APC] such as epidermal Langerhans cell and dermal dendritic cells are activated by viral infection, bacterial products, mechanical trauma, systemic drugs, contact sensitivity, ultraviolet [UV] light, or other unidentified agents. Plasmacytoid dendritic cells via their Toll-like receptor 7 and Toll-like receptor 9 signaling can produce interferon [IFN]-α which will amplify the activating effects of the earlier stimuli.

Stage 2a. Cytokines are secreted by the activated antigen presenting cells and keratinocytes, resulting in migration of lymphocytes into the developing lichen planus lesion. The activated dendritic APC present antigen associated with major histocompatibility complex [MHC] class II to CD4+ T-cell, which will then induce T helper-1 CD4+ T-cell response

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Stage 2b. Activated basal keratinocytes present antigen associated with MHC class I to CD8+ T-cell

Stage 3a. T-helper 1 CD4+ T-cells produce IL-2 and IFN-γ which will bind to CD8+ T-cell on their corresponding receptors. Mast cells also release products that help T-cells to breach the epidermal basement membrane and subsequently enter the epidermis.

Stage 3b. Chemokines such as CXCL-10 attracts CXCR3-expressing CD8+ T-cell into the developing lichen planus lesion.

Stage 4. Granzymes, perforin, and tumor necrosis factor [TNF]-α are secreted by activated antigen specific CD8+ cytotoxic T-cell.

Stage 5. Basal cell keratinocyte apoptosis is induced by granzymes, perforin and TNF-α. Injured keratinocytes also express heat shock proteins

2.3.2.2 Antigens

Antigens are structures that are recognized by the specific acquired immune response (Delves et al., 2017). Antigens can be composed of variety types of substances, examples are lipids, proteins, carbohydrates, nucleic acids, component of microorganisms, component of infectious agents such as parasitic worms, foods, pollens, transplanted organ or tissues, or own self. Antigens that are made of own self are also called 'self-antigens' (Delves et al., 2017). Antigens can be recognized by the lymphocytes of the adaptive immune system (Janeway et al., 2001). This recognition of antigen is achieved by B-cell receptor or T-cell receptor (Delves et al., 2017). Antigen specific B-cell receptors [BCRs] and T-cell receptors [TCRs] are found exclusively on the B and T lymphocyte of the adaptive immune system (Owen et al., 2013). The interaction of

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antigen and receptors can be of a very high affinity (Owen et al., 2013). In oral lichen planus, the cells that play the role of antigen presentation are known as antigen presenting cells (Kurago, 2016). Dendritic cells present antigens to T cells, and lead to the activation of T-cells (Kurago, 2016). The dendritic cells subsets in oral lichen planus include Langerhans cells, stromal dendritic cells, and plasmacytoid cells (Kurago, 2016). Moreover, macrophages also play a role in antigen presentation to T-cells. B-cell and plasma cells have no major role in oral lichen planus (Sugerman et al., 2002). The immune response in oral lichen planus mainly involve T-cell mediated immune response (Kurago, 2016). Antigens presented by MHC class I are processed through a cytosolic cellular pathway, and will be identified by CD8+ T-cell. On the other hand, antigens presented by MHC class II are processed through an endosomal cellular pathway, and will be presented to CD4+ T-cell (Roopenian, 1992). However, a single antigen also can be processed by both endosomal and cytosolic pathways, which will then activate both naïve CD4+ T-cell and CD8+ T-cell (Roopenian, 1992). It is speculated that antigen presentation to both CD4+ T-cell and CD8+ T-cell is necessary to produce CD8+ cytotoxic T-cell activity in oral lichen planus (Lodi et al., 2005)

The keratinocytes in oral lichen planus shows up-regulation of heat shock protein (Bramanti et al., 1995; Chaiyarit et al., 1999; Sugerman et al., 1995). This is interesting as in vitro study showed that oral lichen planus lesional T-cell can proliferate in response to heat shock protein (Sugerman et al., 1995). Heat shock proteins is a potent factor in maintaining homeostasis (Jee, 2016). Heat shock proteins are also known as stress proteins, they are highly conserved and are present in all cells of all organisms (Li & Srivastava, 2003). Heat shock proteins is critical in supporting protein-transport for degradation in order to produce antigenic peptides that can be presented by MHC molecules (Udono et al., 2009). The degraded protein that become antigen peptides are then presented mainly by MHC class I molecules, which are recognized by CD8+ T-cells

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(Udono et al., 2009). Other than that, heat shock protein also can induce dendritic cell maturation and pro-inflammatory cytokine release (Asea et al., 2000; Basu et al., 2000). Heat shock proteins expression in oral lichen planus may be an epiphenomenon of preexisting inflammation (Lodi et al., 2005), as heat shock proteins are induced by cell damage of stress (Beere, 2004). Heat shock proteins expression can also be a common pathway that link multiple exogenous agents that can be involved in disease pathogenesis, which can be composed of systemic drugs, contact allergens, mechanical trauma, bacterial or viral infection (Lodi et al., 2005). Dysregulated heat shock proteins gene expression by stressed keratinocytes can cause an individual to become susceptible to oral lichen planus (Lodi et al., 2005). By far, it is still not known what are the antigens that triggers the T-cell mediated response in oral lichen planus (Kurago, 2016). It was thought that the source of antigens could be exogenous, or autologous keratinocyte antigens (Kurago, 2016).

It was suspected that expression of lichen planus antigen by keratinocytes are limited to the lesion site, thus the clinical distribution of lichen planus is determined by the distribution of antigen (Lodi et al., 2005). It was also theorized that keratinocyte antigen expression can be induced by systemic drugs, contact allergens in dental restorative materials or toothpastes mechanical trauma, infections, or an unidentified agent (Lodi et al., 2005). After alteration of keratinocyte antigen expression, CD4+ T-cell and CD8+ T-cell may be attracted to the epithelium by keratinocyte-derived chemokines (Lodi et al., 2005). In addition, T-cell may also occasionally encounter the keratinocyte antigens during regular functional surveillance (Lodi et al., 2005). These events are then followed by keratinocyte apoptosis triggered by antigen specific CD8+ cytotoxic T-cells (Lodi et al., 2005).

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2.3.2.3 Cell mediated immunity

Much of the etiology and pathogenesis of oral lichen planus are unknown (DeAngelis et al., 2019). One of the well-established pathogenesis of oral lichen planus is the involvement of T cell, which is cell mediated immunity (Delves et al., 2017). This immunity mainly involves the response of T-cells, where the T-helper cells activate macrophages and cytotoxic T-cells directly kill infected cells (Delves et al., 2017). The interaction between a naïve T-cell and an antigen presenting cell [APC] marks the initiation of adaptive immune response (Punt et al., 2019). Before the interaction, innate immune system and antigen presenting cells need to be alerted for the presence of infection or tissue damage (Punt et al., 2019). The APC may either have engulfed the extracellular pathogens, or they may be infected with an intracellular pathogen (Punt et al., 2019). The protein antigens within cells are processed by intracellular proteases into simple peptides (Punt et al., 2019). These peptides will then be brought to the cell surface to be presented to the T-cell via T-cell receptor (Punt et al., 2019). An important molecule known as major histocompatibility complex [MHC] which is classified into class I and class II is involved in the process (Punt et al., 2019). MHC functions in transporting the newly generated peptides from intracellular to the cell surface (Punt et al., 2019). Subsequently, these APC will then migrate to secondary lymphoid tissues, which include local lymph nodes, Peyer's patches, or spleen (Punt et al., 2019). Upon being in these secondary lymphoid tissues, these APC will reside within T-cell zones, and are scanned by naïve CD8+ and CD4+ T cells, which will recognize MHC class I peptide and MHC class II-peptide complexes respectively (Punt et al., 2019). After engagement with a dendritic cell, a naïve T-cell enlarges to form a blast cells and undergoes repeated cell division to form memory T-cell and cytotoxic [or effector] T-cell (Punt et al., 2019). CD8+ cytotoxic T-cells will migrate out of the secondary lymphoid tissue and circulate to the sites of pathogen or infection, where they will bind and kill infected cells (Punt et

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al., 2019). CD4+ helper T-cells secrete cytokine that mediate the activity of other cells such as B-cells, macrophages, and other T-cells. Some CD4+ T-cells become memory T-cells and stay within the secondary lymphoid tissue (Punt et al., 2019).

There are some differences between the effector cells that derived from CD8+ T-cell and CD4+ T-cell. Effector T cell that derive from CD8+ T-cell acquire the ability to induce the death of target cells, thus becoming "killer" or "cytotoxic" T-cell (Punt et al., 2019). Cytotoxic CD8+ T-cell recognize antigen peptide that binds to MHC class I, which is expressed by almost all cells in the body (Punt et al., 2019). For this reason, their role is to clear the cells that have been internally infected with the pathogen that resulted in their activation (Punt et al., 2019). On the other hand, the effector cells that derive from the CD4+ T-cells, now called as activated CD4+ T-cells, or T helper cells obtain the ability to secrete molecules that can stimulate the activation and proliferation of other cells (Punt et al., 2019). This action will regulate the activation and antibody production of B-cells, augment the phagocytic, antimicrobial, and antigen presenting cell capacity of macrophages, and also facilitate in the development of B-cell, and CD8+ T-cell memory (Punt et al., 2019).

2.3.2.4 CD8+ T-cells

The lymphocytic infiltrate in oral lichen planus is composed of almost exclusively T cells (Sugerman et al., 2002). A significant proportion of the T cells within the epithelium and damaged basal cells of oral lichen planus are composed of activated CD8+ T cells [cytotoxic T cell] (Jungell et al., 1989; Khan et al., 2003; Kilpi, 1987; Lodi et al., 2005; Matthews et al., 1984). Moreover, it was also observed that CD8+ T cells tend to be in the same location as apoptotic keratinocytes in oral lichen planus (Sugerman et al., 2000). These data suggested that CD8+ T cells are involved in the pathogenesis of oral lichen

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planus, and they may have triggered the apoptosis of basal cells in oral lichen planus (Sugerman et al., 2002). Furthermore, it was also observed that T cell clones from lichen planus lesions were more cytotoxic towards autologous lesional keratinocytes compared to T cells clone of clinically normal skin of lichen planus patients (Sugerman et al., 2002). Majority of this cytotoxic clones are CD8+ T cells (Sugerman et al., 2000).

2.3.2.5 CD4+ T-cells

In oral lichen planus, most lymphocytes in the lamina propria were found to be CD4+ T-cell (Ishii, 1987; Lodi et al., 2005; Matthews et al., 1984). This is in contrast to the lymphocytes in the intraepithelial region, where most of them are CD8+ T-cell (Ishii, 1987; Lodi et al., 2005; Matthews et al., 1984). Furthermore, in previous studies it was demonstrated that T-cell clones with helper activity and cells that lack cytotoxic activity which are CD4+ T-cell can be extracted from oral and cutaneous lichen planus lesions (Sugerman et al., 2000; Sugerman et al., 1994). The CD4+ T-cells may be activated by Langerhans cells or keratinocytes (Lodi et al., 2005). This is based on the observation that there were increased Langerhans cells with upregulated MHC class II expression (Farthing et al., 1990; Lodi et al., 2005; Rich & Reade, 1989) and keratinocytes expressing MHC class II antigens (Farthing & Cruchley, 1989; L. Walsh et al., 1990) in oral lichen planus lesions. CD4+ T-cell then become activated following presentation of the antigens. High level of antigen expression, IL-12 secretion by MHC class II antigen presenting cells induce the CD4+ T-cell to secrete IL-2 and INF-γ (Constant & Bottomly, 1997). Moreover, the epidermal Langerhans cells and keratinocytes also can secrete IL-12 (Kang et al., 1996; Müller et al., 1994). Basal keratinocytes with MHC class I antigen presentation and CD4+ T-cell derived IL-2 IFN-γ may then activate CD8+ T-cell (Lodi et al., 2005). Furthermore, IFN-γ can aid in maintaining keratinocyte MHC class II

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expression, which in turn contribute to the chronicity of oral lichen planus (andrea Cavani & Girolomoni, 1998; Lodi et al., 2005; Morhenn & Wood, 1988).

2.3.2.6 Keratinolysis

There are few suggested theories on the mechanisms used by CD8+ cytotoxic T-cells to trigger keratinocytes apoptosis in oral lichen planus. These mechanisms are known to activate the caspase cascade that results in keratinocyte apoptosis. They include: 1. release of TNF-α that binds TNF-α receptor 1 on keratinocyte surface, 2. binding of T-cell surface CD95L to CD95 on the keratinocyte surface, or 3. granzyme B secreted by T-cell enters the keratinocyte by perforin induced membrane pores (Constant & Bottomly, 1997; Khan et al., 2003; Lodi et al., 2005; Sugermann et al., 1996). An observation that TNF-α is elevated in the serum of oral lichen planus patients suggests that TNF-α play a role in oral lichen planus pathogenesis (Khan et al., 2003; Simark-Mattsson et al., 1999; Sugermann et al., 1996). This theory is also strengthened by the findings that lesional T-cells contain TNF-α mRNA and secrete TNF-α in-vitro. Moreover, other studies also concluded that the basal keratinocytes and T-cell in the subepithelial infiltrate in oral lichen planus can express TNF-α, and furthermore its receptor, the TNF R1 is expressed by basal and suprabasal epithelium in oral lichen planus lesions (Khan et al., 2003; Lodi et al., 2005).

The early event of the disease involves keratinocyte antigen expression or unmasking of an antigen (Sugerman et al., 2000). CD8+ T cells recognize antigen associated with MHC class I on lesional keratinocytes (Sugerman et al., 2002). Following this, CD8+ T cell may induce keratinocyte apoptosis (Sugerman et al., 2000). The specific mechanism by which apoptosis is induced in keratinocyte is unclear, although it can occur through several mechanisms (Kurago, 2016). The activated CD8+ T cells then release chemokines that will attract additional lymphocytes and other immune cells into the developing oral

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lichen planus lesion (Yamamoto & Osaki, 1995; Yamamoto et al., 1994). Cytotoxic related molecules such as perforin, Tia-1, and granzyme can be detected in the epithelium and connective tissue of lichen planus. These molecules occur more frequently in oral lichen planus compared to cutaneous lichen planus (Lage et al., 2011). Th17 cells, which is a subset of CD4+ T cell also has been reported to be present in high number in oral lichen planus (Vered et al., 2013). Th17 T cells play a role in producing interleukin-17 [IL-17]. These cells play an important role in defense mechanism against bacteria, fungal, as well as involved in autoimmune conditions (Korn et al., 2009). T regulatory cells [T reg], which functions to suppress inflammation has been reported to be rare in oral lichen planus lesion (Vered et al., 2013).

2.3.2.7 Antigen presenting cells

The role of antigen presenting cells in oral lichen planus has also been explored. Professional antigen presentation to T cells that lead to activation or tolerance of T cells is an important role of dendritic cells (Santoro et al., 2005). Moreover, the study also concluded that in oral lichen planus, there is recruitment of different subset of dendritic cells, among them are Langerhans cell, stromal DC-SIGN+ dendritic cells, and plasmacytoid dendritic cells (Santoro et al., 2005). Also, CD1a+/ Langerin+ dendritic cells are significantly increased in the epithelium and within the lymphocytic infiltrate in oral lichen planus (Santoro et al., 2005). These cells induce continuous immune reaction in the inflammatory process of oral lichen planus, mainly by their secretory products and cellular interactions (Santoro et al., 2005). These dendritic cells are found to be predominantly located in the area where epithelial degeneration occur (Tanda et al., 2000). Moreover, mature dendritic cells are also reported to be found mainly in lamina propria, and they express molecules essential for T cell activation (Kurago, 2016).

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2.3.2.8 Mast cells

Mast cells have also been reported to be involved in the mechanism of oral lichen planus (Zhao et al., 2001). The density of mast cells is increased in oral lichen planus (Zhao et al., 1997). Moreover, about 60% of the mast cells in oral lichen planus are degranulated compared with only 20% in normal mucosa (Lodi et al., 2005; Zhao et al., 2001) These cells are often associated with mucosal vasculatures, nerve, and production of inflammatory mediators such as TNF-α, proteases, vasoactive mediators, matrix metalloproteinases [MMPs], and chemokine CCL5 (Kurago, 2016). Mast cell degranulation in oral lichen planus releases pro-inflammatory mediators such as TNF-α, chymase and tryptase (Klein et al., 1989; Lodi et al., 2005; Walsh et al., 1991). Mast cells also aid in the migration of inflammatory cells from the bloodstream (Kurago, 2016). This is achieved by TNF-α induced up-regulation of endothelial cell adhesion molecule [CD62E, CD54, and CD106] expression that is essential for lymphocyte adhesion to the blood vessel lumen (Klein et al., 1989; Lodi et al., 2005; Walsh et al., 1991; Walton et al., 1994). Other than that, it was observed that the number of mast cells and intra-epithelial CD8+ T-cell tend to be significantly greater in region where there are basement membrane disruption compared to region with intact basement membrane (Zhou et al., 2002), suggesting that mast cell may play a role in oral lichen planus (Lodi et al., 2005). The T-cell derived matrix metalloproteinase [MMP]-9 may be involved with basement membrane disruption, and also facilitate more T-cell migration in oral lichen planus (Zhou et al., 2001). The activation of the MMP-9 will require mast cell chymase (Fang et al., 1997). Thus, the basement membrane disruption in oral lichen planus is mediated by mast cell chymase and T-cell-secreted MMP-9 (Lodi et al., 2005; Zhao et al., 2001; Zhou et al., 2001). In another study, it was reported that lesional T cells in oral lichen planus produces RANTES [Regulated upon Activation, Normal T cell Expressed, and Secreted],

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which will trigger human mast cell degranulation (Zhao et al., 2001). These degranulating mast cells release TNF-α which will then upregulate RANTES production by T cells in oral lichen planus. It was hypothesized that this cyclical mechanism plays an important role in disease chronicity (Zhao et al., 2001).

2.3.2.9 Plasma cells

Plasma cells are the end stage cell type that arise from antigen-induced B-cell differentiation (Punt et al., 2019). These cells have the ability to secrete large quantities of soluble immunoglobulin protein (Punt et al., 2019). Plasma cells lose their expression of surface immunoglobulin and become highly specialized for secretion of antibody (Punt et al., 2019). These cells do not undergo cell division. Some of these cells will die in 1 or 2 weeks, while others travel to the bone marrow and reside there for years (Punt et al., 2019). A single plasma cell is capable of producing thousand molecules of antibody per second (Punt et al., 2019). Plasma cells can be divided on the basis of their life span into short lived and long-lived plasma cells (Ahuja et al., 2008; Ho et al., 1986; Manz et al., 1997). Activation of naïve B-cell results in clonal expansion and formation of short-lived plasma cells in the extra-follicular areas of secondary lymphoid tissues (Young et al., 2006). Simultaneously, memory B-cell and long-lived plasma cells are produced in the germinal centers (Odendahl et al., 2005; Young et al., 2006). The tissue homing of long-lived plasma cells is mediated by adhesion molecules, chemokines, and their receptors (Hargreaves et al., 2001; Moser et al., 2006). After production, these cells will be located at tissues such as bone marrow, mucosal tissues, or inflammation site (Hargreaves et al., 2001; Kabashima et al., 2006; Moser et al., 2006). In the inflamed tissue, the presence of high cytokine levels can support the survival of plasma cells (Moser et al., 2006).

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Several studies have shown the critical roles of B cells in human inflammatory and autoimmune disorders (Dörner et al., 2009; Streicher et al., 2014). B-cell can be activated and differentiate into autoreactive plasma cells, which produces autoantibodies and causes tissue damage (Burrows et al., 2000). Examples of autoimmune disease which are characterized by high titres of circulating autoantibodies are systemic lupus erythematosus, Sjogren's syndrome, and rheumatoid arthritis (Arce et al., 2002).

Plasma cells rarely dominate the inflammatory infiltrate of lichen planus, but occasionally they can be present in striking amount in oral lichen planus (Hall et al., 2008; Mravak-Stipetić et al., 2014). Also, it was noted that there was significant increase in the amount of plasma cells within the infiltrate of oral lichenoid reactions (Lage et al., 2012; Mravak-Stipetić et al., 2014). Another report documented a case of lichen planus of the nail matrix with predominant plasma cell infiltrate and lesser number of lymphocytes in a 66-year-old woman (Hall et al., 2008). The patient was a known case of diabetes mellitus, hypertension, hypercholesterolemia, eczema, and oral lichen planus. Moreover, she was taking medicine such as triamterene, Olmesartan, acetylsalicylic acid, ezetimibe, and esomeprazole, and allergic to sulfa-based drugs (Hall et al., 2008). Kappa and lambda immunohistochemical stains indicated polyclonal immunoglobulin light chain reaction (Hall et al., 2008). The author also considered lichenoid drug eruption as one of the differential diagnosis for the case. Another report documented a case of cutaneous lichen planus involving the nail and lower extremities in a 75-year-old woman with medical history of chronic liver disease, anemia, renal lithiasis, and hypertension (Roustan et al., 1994). The patient had been taking spironolactone for hypertension. Histologically the author noted band-like inflammatory infiltrate within the upper dermis composed of predominantly plasma cells. Furthermore, several authors have also suggested that the presence of plasma cells, eosinophils, and neutrophils favor the diagnosis of oral

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lichenoid lesions compared to oral lichen planus (Ismail et al., 2007; Juneja et al., 2006; Thornhill et al., 2006).

2.3.2.10 Eosinophils

Eosinophils are terminally differentiated leukocytes derived from the bone marrow (Weller & Spencer, 2017). These immune cells contain granules, as are neutrophils, basophils, and mast cells (Weller & Spencer, 2017). In physiological conditions, eosinophils are present in several organs, where these cells function in multiple homeostatic activities (Ramirez et al., 2018). The number of eosinophils in the circulation and blood can increase due to factors such as immune response, helminth parasite infections, and in allergic setting (Huang et al., 2014). Eosinophils are also involved in type IVb delayed hypersensitivity reaction (Uzzaman & Cho, 2012). Eosinophils can be stimulated by T-helper 2 cells (Th2), by their release of IL-5, or indirectly by facilitating the release of IgE (Bagnasco et al., 2017). IgE can be recognized by eosinophils, moreover, it can also activate mast cells in type I hypersensitivity response. Subsequently, mast cells derived compounds such as prostaglandins D2, leukotrienes, and Il-5 can stimulate eosinophils, which will result in tissue damage and facilitate the maintenance of immune response following mast cells activations (Galdiero et al., 2017). In addition, chymase is also released by activated mast cells, which can prevent eosinophils apoptosis (Wong et al., 2009). In the inflamed tissue, eosinophils generate eosinophil peroxidase, which causes oxidative stress, and then result in tissue damage (Ramirez et al., 2018). It is known that there were several skin diseases which shows increase in tissue and peripheral eosinophils. These include urticaria, atopic dermatitis, and delayed drug hypersensitivity reaction (Ramirez et al., 2018).

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2.3.3 Soluble factors

2.3.3.1 Cytokines

Cytokines technically refers to a molecule that is produced by one cell, and act on another cell (Ozaki & Leonard, 2002). They are mainly growth factors and hormones of the immune and hematopoietic systems (Ozaki & Leonard, 2002). Cytokines are involved in the communication between cells by acting as a key signaling molecule. Other name that had been applied to cytokines include lymphokine (cytokines produced by lymphocytes), monokine (cytokines produced by monocytes), chemokine (cytokines having chemotactic effects), and interleukin (cytokines produced by one leukocyte which will then act on another leukocytes) (Zhang & An, 2007). Cytokines bind to receptors on target cells, which then trigger intracellular signaling cascades, which cause a change in the phenotype and function of the target cells via gene alteration (Lu et al., 2015; O'Shea & Murray, 2008; Preshaw & Taylor, 2011). Cytokines can also induce each other's production by mean of autocrine, endocrine, or paracrine mode (Lu et al., 2015; Preshaw & Taylor, 2011; Sanchez-Muñoz et al., 2008). Majority of cytokines are pleiotropic, they can produce distinct effects depending on their target cells (Lu et al., 2015; Roescher et al., 2010). Cytokines play an important role in the host defense. They regulate innate immunity by inducing local inflammation and systemic acute phase responses (Holdsworth & Gan, 2015). Also, cytokine plays an important role in adaptive immune system in regards of its initiation, direction, and amplification (Holdsworth & Gan, 2015). Unfortunately, cytokines may also cause damage to the host, in the setting where there is aberrant production of the molecules, which can cause immune deficiency, autoimmunity and inflammation (Lu et al., 2015; Moudgil & Choubey, 2011; Roescher et al., 2009). There have been numerous studies on inflammation related cytokines in lesional, tissue of oral lichen planus, serum, saliva, and peripheral blood of oral lichen planus patients (Lu et al., 2015). Most studies described abnormal expression pattern of cytokines group

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of interleukins [ILs], transforming growth factor [TGF]-β, interferon [IFN]-γ and tumour necrosis factor [TNF]-α (Ge et al., 2012; Piccinni et al., 2014; Rhodus et al., 2007; Simark-Mattsson et al., 1999; Yamamoto & Osaki, 1995; Zhou et al., 2009). The cytokines involved in oral lichen planus are discussed below.

2.3.3.1.1 Interleukin

This cytokine was originally discovered in leucocytes (Brocker et al., 2010). This molecule is known to be produced by a many different cells (Brocker et al., 2010). Interleukin [ILs] have variety of roles in immunity and inflammation, these include immune cell proliferation, differentiation, maturation, and activation (Brocker et al., 2010). The ILs that were found to be involved in pathogenesis oral lichen planus are IL-1, 2, 4, 5, 6, 8, 10, 12, 17 (Lu et al., 2015). A brief description of ILs that have been implicated in oral lichen planus are as follows:

IL-1 is a general name for IL-1α and IL-1β. They act on the same receptor and have identical biological activities (Dinarello, 2010). IL-β is mainly produced by monocytes and macrophages, whereas IL-α is mainly produced by keratinocytes and endothelial cells (Dinarello, 2010). Both types of IL-1 have extensive functions. The main role of IL-1 is in the stimulation of T-helper cells (Dinarello, 2010; Sims & Smith, 2010). IL-1 also can activate neutrophils, monocytes, eosinophils, macrophages, and induce production of other cytokines such as TNF-α, IL-6, IL-8 and also itself (Dinarello et al., 2012; Lu et al., 2015; Sims & Smith, 2010). There is an abundant IL-1+ cells observed in the oral lichen planus lesion (Lu et al., 2015; Takeuchi et al., 1988). Moreover, it was also documented that the numbers of cell producing IL-β in the lesional tissue of oral lichen planus were increased compared to control (Lu et al., 2015; Yamamoto & Osaki, 1995; Yamamoto et al., 1994). Other than that, (Rhodus et al., 2007) also found that IL-1α level is significantly elevated in the whole unstimulated saliva of oral lichen planus patients. IL-β can stimulate

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keratinocytes and tissue infiltrating mononuclear cells to produce TNF-α, IL-6, and granulocyte-macrophage colony activating factor [GM-CSF] (Yamamoto & Osaki, 1995; Yamamoto et al., 1994).

IL-2 is produced by CD4+ T-cell, CD8+ T-cell, and NK-cell after cell activation. IL-2 exerts its effects by binding to IL-2 receptors [IL-2R], which are expressed by lymphocytes involved in cellular immunity (Malek & Castro, 2010). IL-2 can induce the differentiation of CD4+ and CD8+ T cells (Liao et al., 2011; Malek, 2008). Moreover, IL-2 also stimulate proliferation of B-cell, NK-cell, monocytes, and macrophages (Liao et al., 2011; Malek, 2008). Several studies have shown that IL-2 and its receptor are consistently expressed in oral lichen planus lesion (Hirota et al., 1990; Piccinni et al., 2014; Simark-Mattsson et al., 1999). An in-vitro study demonstrated that tissue infiltrating mononuclear cells from oral lichen planus lesion has the ability to produce more IL-2 than tissue infiltrating mononuclear cells from intact gingiva (Yamamoto & Osaki, 1995). Moreover, tissue infiltrating mononuclear cells from oral lichen planus patients have been demonstrated to produce IL-6 after being pretreated with IL-2 (Yamamoto & Osaki, 1995). These findings show that IL-2 plays an important role in oral lichen planus pathogenesis.

IL-4 is produced mainly by mast cells, Th2 cells, eosinophils, and basophils. (Gadani et al., 2012). IL-4 can induce the differentiation of naïve Th cell to Th2 cell (Paul & Zhu, 2010). Once activated by IL-4, Th2 cells produce more IL-4 by means of autocrine positive feedback system (Dorado et al., 2002; Kaiko et al., 2008; Paul, 2015). On the other hand, it can inhibit the production of TNF-α, IFN-γ, IL-17 (Cooney et al., 2011; Lee et al., 1995). This in turn will inhibit Th1 and Th17 mediated inflammation (Cooney et al., 2011; Lu et al., 2015). The expression patterns of IL-4 have shown inconsistent results across many studies. Study by Yamamoto and Osaki (1995) shown that oral lichen planus

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tissue have increased number of IL-4 producing cells compared to inflamed and normal gingival tissue. Moreover, studies by Piccinni et al. (2014) and Tao et al. (2008) shown that IL-4 protein and mRNA levels in oral lichen planus tissues were significantly higher than normal oral mucosa. On the contrary, studies by Khan et al. (2003); Simark-Mattsson et al. (1999) shown opposite result, where they were unable to detect significant presence of IL-4 from lesional oral lichen planus tissue, and mRNA study did not indicate presence of significant IL-4 mRNA.

IL-6 is mainly produced by antigen presenting cells [APC], which are composed of dendritic cells [DC], macrophages, and B cells. It can also be produced by non-immune cells like keratinocytes, fibroblasts, endothelial cells, and astrocytes (Kamimura et al., 2003). IL-6 acts on target cells through IL-6 receptor [IL-6R]. There are only a few cells known to express membrane-bound IL-6R, which makes IL-6 seems to have narrow spectrum of effect (Scheller et al., 2011). However, a complex composed of IL-6 and a soluble form of IL-6R can act on Glycoprotein 130 receptor, which is expressed on nearly all cell membrane, thus substantially expand the spectrum of IL-6 target cells (Scheller et al., 2011). IL-6 has a wide range of roles, which include immune regulation, inflammation, hematopoiesis, and oncogenesis (Lu et al., 2015). For example, IL-6 is involved in the differentiation of naïve CD4+ T-cell to Th17 cells and in overcoming the immune suppression regulated by T-regulatory [Treg] cells (Dienz & Rincon, 2009). These features show that IL-6 can mediate the state of immune response, mainly by changing it from tolerant state to active inflammatory conditions (Lu et al., 2015). There are studies that demonstrated an increase in IL-6 level in lesional tissues and oral fluid of oral lichen planus patients (Gu et al., 2004; Rhodus et al., 2006; Rhodus et al., 2005a). Moreover, previous studies have also shown that keratinocytes from oral lichen planus tissues can produce more IL-6 compared to normal and inflamed gingival tissue (Yamamoto & Osaki, 1995; Yamamoto et al., 1994). Other than that, there are several

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reported cases of increased serum IL-6 in oral lichen planus patients, especially in erosive form of the disease (Gu et al., 2004; Karagouni et al., 1994; Mukaida, 2003; Sun et al., 2002)

IL-8 is also known as CXCL8. It can be produced by various immune and non-immune cells like NK-cells, neutrophils, T-cells, monocytes, endothelial cells and fibroblasts (Mukaida, 2003). Its production is induced by cytokines such as IL-1, TNF-α, IL-17, bacterias [e.g *Helicobacter pylori, Pseudomonas aeruginosa*], viruses [e.g. adenovirus, rhinovirus], microbial products [e.g lipopolysaccharide by bacteria], and cellular stress (Mukaida, 2003). IL-8 induce the chemotaxis of immune cells including macrophages, basophils and T cells (Mukaida, 2003). This cytokine also augments the metabolism of reactive oxygen species and bolster mitosis of epithelial cells and angiogenesis (Waugh & Wilson, 2008). IL-8 have been consistently reported to be increased in serum and oral fluids of oral lichen planus patients (Dan et al., 2010; Rhodus et al., 2005a; Rhodus et al., 2005b; Rhodus et al., 2007; Y. Zhang et al., 2008). On the contrary, IL-8 was not detected in lesional tissue of oral lichen planus (Little et al., 2003). This indicates that IL-8 play a role in the systemic immune response of oral lichen planus patients (Lu et al., 2015).

IL-10 is mainly produced by monocytes, macrophages, and CD4+ Th cells, but other immune cells such as dendritic cells, B-cells, CD8+ T-cells, natural killer [NK] cells, mast cells, neutrophils, and eosinophils are also known to synthesize this cytokine (Sabat et al., 2010; Saraiva & O'garra, 2010). IL-10 has a variety of effects. It serves to suppress the release of pro-inflammatory cytokines and antigen presentation by macrophages (Sabat et al., 2010). This cytokine also can suppress proliferation and cytokine synthesis of T-helper [Th]-1 and Th2 cells (Sabat et al., 2010). Moreover, it also inhibits the pro-inflammatory mediators release by neutrophils (Sabat et al., 2010). On the contrary, it enhances the cytotoxic effects of NK cells (Sabat et al., 2010). Tissue infiltrating

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mononuclear cells from in oral lichen planus is capable to generate more IL-10 compared to normal tissue peripheral blood mononuclear cells (Yamamoto & Osaki, 1995). IL-10 was considered an important member in the local cytokine network of oral lichen planus, this was supported by, a previous study where the author detected positive mRNA signals for IL-10 in the T-cells of oral lichen planus lesions (Simark-Mattsson et al., 1999). However, this view was met with many challenges, as there were conflicting results of studies. For example, a 2003 study did not detect IL-10 in the lesional tissue of oral lichen planus T-cells (Khan et al., 2003). Moreover, serum IL-10 studies also produced controversial results. For example, there were studies which observed decrease serum IL-10 in oral lichen planus patients (Lu et al., 2015; Zhou et al., 2012), while other studies suggest opposite results (Dan et al., 2011; Pekiner et al., 2012).

IL-12 is mainly produced by monocytes, macrophages, dendritic cells, B-cell, and activated T-cell (Del Vecchio et al., 2007; Gee et al., 2009). IL-12 can stimulate the production of IFN-γ by NK and T-cells, and increase T-cell proliferation (Del Vecchio et al., 2007; Gee et al., 2009). Other than that, this cytokine also enhances the cytotoxicity of NK cells and T-cells (Del Vecchio et al., 2007). IL-12 has important role in resistance to bacterial and parasitic infections, as well as establishment of organ specific autoimmunity (Gee et al., 2009). IL-12 was found to be increased in the peripheral blood monocytes of oral lichen planus patients (Ohno et al., 2011). Other study demonstrated increased level of IL-12 in saliva of oral lichen planus patients (Janardhanam et al., 2012). Overall, the studies on IL-12 in oral lichen planus are scarce (Lu et al., 2015).

IL-17 is mainly produced by T-cell [especially Th17 cells], but it can also be produced by dendritic cells, macrophages, and NK-cells (Onishi & Gaffen, 2010). IL-17 can exert effects on different tissue cells and immune cells (Onishi & Gaffen, 2010). This cytokine is an important ‘bridging’ molecule between the adaptive and innate immunity (Yu &

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Gaffen, 2008). IL-17 can stimulate the production of chemokines that induce recruitement of neutrophils and macrophages to clear pathogens (Yu & Gaffen, 2008). Moreover, it can also stimulate monocytes, epithelial cells, endothelial cell, keratinocyte, and fibroblasts to produce inflammatory mediators like TNF-α, IL-β, IL-6, IL-8, and matrix metalloproteinases [MMP] (Onishi & Gaffen, 2010). IL-17 expression was found to be increased in the oral lichen planus lesions compared to the normal oral mucosa (Monteiro et al., 2015). Moreover, Th17 cells were observed to be increased predominantly in the erosive form of oral lichen planus (Xie et al., 2012). Other study also show that mRNA level of IL-17 is increased in lesional tissue of erosive oral lichen planus (Piccinni et al., 2014).

IL-18 can be produced by various immune and non-immune cells including T-cells, B-immature dendritic cells, macrophages, and epithelial cells (Boraschi & Dinarello, 2006). It can facilitate the differentiation and activation of Th cell subsets (Boraschi & Dinarello, 2006). IL-18 is also considered to play an important role in the modulation of immune response (Orozco et al., 2007). Some its effects depend of the presence of certain cytokines. For example, when IL-12 is present, IL-18 will induce NK-cells and T-cells to produce IFN-γ, and also stimulate Th1 cell development. On the contrary, when IL-12 is absent, IL-18 favors the development of Th2 cells, and also induce NK-cells and T-cells to produce IL-4, IL-5, IL-10, and IL-13 (Orozco et al., 2007). There are few studies regarding the role of IL-18 in oral lichen planus. There was no difference found in the mRNA expression of IL-18 in oral lichen planus lesion and normal mucosa (Piccinni et al., 2014). However, IL-18 is significantly elevated in serum and saliva of oral lichen planus patients, especially in severe disease (Zhang et al., 2012).

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2.3.3.1.2 Transforming growth factor-β

TGF-β is a part of a superfamily of structurally related growth and differentiation factors, it is present in nearly all multicellular organisms (Akhurst & Hata, 2012). In human, there are three isoforms of TGF-β, namely TGF-β1, TGF-β2, TGF-β3 (Akhurst & Hata, 2012). TGF-β suppresses immune system, and has broad effects on majority of immune cells (Akhurst & Hata, 2012). TGF-β play an important role in immune tolerance, as it can suppress differentiation of Th1 and Th2 cells, and also induce the development of Tregs (Akhurst & Hata, 2012). Other than that, TGF-β also inhibits IFN-γ production by NK-cells, and induces the change of pro-inflammatory type macrophage [M1] to anti-inflammatory type [M2] (Akhurst & Hata, 2012). In oral lichen planus, TGF-β1 mRNA expression has been demonstrated, but immunostaining results varied (Khan et al., 2003; Simark-Mattsson et al., 1999). A study had suggested that the suppressive TGF-β pathway is inhibited in oral lichen planus, thus contribute to the chronic inflammation in oral lichen planus (Prime et al., 2004).

2.3.3.1.3 Interferon- γ

IFN-γ is produced by CD4+Th cells, CD8+T cytotoxic cells, NK-cells, and other cells such as B-cells and antigen presenting cells (Schroder et al., 2004). IFN-γ is produced upon activation of the mentioned cells by cytokines such as IL-2, IL-12, and IL-18 (Schroder et al., 2004). One of the well-known functions of IFN-γ is activation of macrophages (Hu & Ivashkiv, 2009). IFN-γ also can enhance pro-inflammatory mediators' effects by suppressing several anti-inflammatory feedback loops (Hu & Ivashkiv, 2009). On the contrary, IFN-γ can limit tissue damage in inflammation site (Hu & Ivashkiv, 2009), and studies have also shown that IFN-γ can act by both enhancing or

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suppressing immune system (Hu & Ivashkiv, 2009; Kelchtermans et al., 2008). IFN-γ in oral lichen planus has been extensively studied. IFN-γ has been shown to be present in the mononuclear cells of the subepithelial infiltrate in oral lichen planus lesions (Khan et al., 2003; Mattsson et al., 1998). Moreover, CD4+ Th cells of oral lichen planus lesional tissue also show IFN-γ expression (Xie et al., 2012). Furthermore, there is increased expression of IFN-γ in erosive oral lichen planus lesion compared to reticular oral lichen planus (Piccinni et al., 2014; Tao et al., 2008).

Interestingly, the salivary level of IFN-γ in oral lichen planus patient showed variation in pattern, where a study reported lower level of salivary IFN-γ in oral lichen planus patients (Liu et al., 2009). On the other hand, some studies yield opposite results, where they observed increased salivary level of IFN-γ in the erosive and ulcerative form of oral lichen planus (Ghallab et al., 2010; Tao et al., 2008). Moreover, study on serum level of IFN-γ also showed variation of data. For example, it was reported that IFN-γ is increased in the serum of oral lichen planus patient (Hu et al., 2013), while another study showed there was no significant difference with controls (Kalogerakou et al., 2008).

2.3.3.1.4 Tumor Necrosis Factor- α

This is by far the most commonly studied cytokine in oral lichen planus. TNF-α can be produced by a variety of cells including activated macrophages and T-cells, B cells, dendritic cells, NK cells, neutrophils, keratinocytes, fibroblasts, astrocytes, glial cells (Silva et al., 2010). TNF-α is a predominant early mediator in inflamed tissue, and it is immediately released after trauma, infection, or exposure to pathogen (Parameswaran & Patial, 2010). Its effect on T-cell is dependent on the exposure periods (Postal & Appenzeller, 2011). Short term exposure causes activation and proliferation of T-cells. On the contrary, long term exposure to TNF-α causes hyporesponsiveness of T cells, due to reversible loss of T-cell surface receptor (Postal & Appenzeller, 2011). Moreover,

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TNF-α also induce production of IL-12 and IL-18, thus enhancing Th1 response (Lu et al., 2015; Schottelius et al., 2004). Furthermore, several studies have shown that TNF-α induce the production of inflammatory mediators such as RANTES, MMP-9, and TNF-α itself (Hirano et al., 2003; Khan et al., 2003; Yamamoto et al., 1994). TNF-α has been shown to be consistently elevated in the lesional tissue of oral lichen planus compared to normal mucosa (Karatsaidis et al., 2007; Sklavounou et al., 2000; Thongprasom et al., 2006; Younes et al., 1996). More interestingly, the elevated expression of TNF-α can be inhibited by topical steroid such as 0.1% fluocinolone, this further strengthen the view that over-expression of TNF-α may be associated with pathogenesis of oral lichen planus (Thongprasom et al., 2006). Other studies also shown that keratinocytes from oral lichen planus lesions produce more TNF-α than keratinocytes of chronically inflamed and non-inflamed gingiva (Yamamoto & Osaki, 1995; Yamamoto et al., 1994). CD4+ T-cell in oral lichen planus lesions also shown to produce more TNF-α than the normal mucosal tissue (Piccinni et al., 2014). The elevated TNF-α in lesional tissue of oral lichen planus emphasized its role in the pathogenesis of this disease. The level of salivary TNF-α in oral lichen planus patient also shown to be consistently increased (Ghallab et al., 2010; Pezelj-Ribaric et al., 2004; Rhodus et al., 2006; Rhodus et al., 2005a; Zhang et al., 2008). Many studies also demonstrated increased TNF-α levels in the serum of oral lichen planus patient (Pezelj-Ribaric et al., 2004; Sklavounou-Andrikopoulou et al., 2004; Sun et al., 2007).

2.3.3.1.5 Chemokines

Chemokines are also known as chemotactic cytokines, they are a large family of secreted protein that signal via surface G protein-coupled heptahelical chemokine receptors (Hughes & Nibbs, 2018). They mediate directional migration and regulate organ-specific homing of leukocyte subsets (Meller et al., 2009; Sallusto et al., 1999; Zlotnik et al.,

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2006). They are important for the development and homeostasis of the immune system, and involve in immune responses (Hughes & Nibbs, 2018). Chemokines are defined by their primary amino acid sequence and their cysteine residues arrangement (Hughes & Nibbs, 2018). Chemokines are divided into 4 subfamilies, namely CC, CXC, CX3C and XC. RANTES [regulated on activation, normal T-cell expressed and secreted] is a member of the CC chemokine family (Sugerman et al., 2002). It can be produced by activated T-cell, bronchial epithelial cells, rheumatoid synovial fibroblasts, oral keratinocytes, and mast cells (Lodi et al., 2005). There are several RANTES receptors known, namely CCR1, CCR3, CCR4, CCR5, CCR9, and CCR10 (Sugerman et al., 2002). RANTES and other CC chemokine can induce mast cell migration and degranulation via G protein coupled receptors. (Bischoff et al., 1993; Sugerman et al., 2002). Zhao et al. (2002) demonstrated that oral lichen planus lesional T-cell express mRNA for RANTES, and that TNF-α stimulation can upregulate lesional T-cell RANTES secretion in vitro. Moreover, Zhao et al. (2002) also reported that mast cells in oral lichen planus lesion express the CCR1 RANTES receptor. Another study reported that an unidentified factor in oral lichen planus lesional T cell supernatant can up-regulate human mast cell line [HMC-1] CCR1 mRNA expression (Zhao et al., 2002). Also, their study demonstrated that oral lichen planus T-cell supernatants induced the migration of HMC1, and this can be inhibited by the anti-RANTES antibody (Zhao et al., 2002). The study also noted that RANTES and its CCR1 receptor may be involved in the accumulation inflammatory cells in oral lichen planus, and T-cell in oral lichen planus can up-regulate mast cell CCR1 expression (Zhao et al., 2002). Thus, in oral lichen planus, T-cell release RANTES, which may then attract mast cells into the developing oral lichen planus lesion, and subsequently stimulate mast cell degranulation (Sugerman et al., 2002). These mechanisms are thought to prolong the inflammation in oral lichen planus (Sugerman et al., 2002).

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2.3.3.2 Matrix metalloproteinase

Matrix metalloproteinase [MMP], also called matrixins, are a family of enzymes that are structurally related but genetically distinct (Sorsa et al., 2004). MMP degrade extracellular matrix and basement membrane components (Uitto et al., 2003). MMPs are involved in tissue development, remodeling, and wound healing (Uitto et al., 2003). They are also essential for cellular communication, molecular shedding and immunity (Sorsa et al., 2004; Uitto et al., 2003). Their proteolysis activities are regulated by tissue inhibitors of metalloproteinases [TIMPs] (Nagase et al., 2006). MMP share common biochemical properties but have specific substrates (Sugerman et al., 2002). Examples of MMP subfamilies are collagenases, gelatinases, stromelysins, matrilysins, macrophage elastase, membrane-type MMP and others (Nagase et al., 2006). The gelatinases [e.g. MMP-2, MMP-9] cleave collagen type IV, and the stormelysins [e.g. MMP-3 and MMP-10] cleave collagen type IV and laminin (Sugerman et al., 2002). A study demonstrated epithelial basement membrane disruption in oral lichen planus tissue that were stained with collagen IV (Zhou et al., 2001). MMP-2 and MMP-3 were found to be expressed primarily in the oral lichen planus epithelium, while MMP-9 were mainly found associated with the inflammatory infiltrate in the lamina propria (Zhou et al., 2001). Furthermore, ELISA study also demonstrated that the concentration of MMP-9 in oral lichen planus lesional T-cell culture supernatants was higher than those in peripheral blood T-cell of oral lichen planus patients and healthy controls (Zhou et al., 2001). In addition, it was also found that after stimulation by TNF-α, the concentration of MMP-9 in peripheral blood T-cell of oral lichen planus patients were greater than in the healthy subjects (Zhou et al., 2001). An important finding by their study was MMP-9 secretion by T-cells were increased after TNF-α stimulation, and TIMP-1 secretion show no increase (Zhou et al., 2001). Hence, T-cells in oral lichen planus may be induced by TNF-α to secrete MMP-9 (Sugerman et al., 2002). The T-cell secreted MMP-9 has the ability

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to damage the epithelial basement membrane in oral lichen planus, this may trigger keratinocyte apoptosis (Sugerman et al., 2002). Moreover, the damaged basement membrane may then allow the passage of antigen specific CD8+ T-cell into the oral epithelium, and this may cause more keratinocyte apoptosis (Zhou et al., 2001). In addition, TNF-α is synthesized as membrane bound precursor protein which need to be cleaved to yield mature amino acid soluble cytokine (Black et al., 1997; Gearing et al., 1995; Itai et al., 2001; McGeehan et al., 1994; Moss et al., 1997). The precursor TNF-α is cleaved by TNF-α converting enzyme, which is a membrane bound disintegrin metalloproteinase (Black et al., 1997; Gearing et al., 1995; Itai et al., 2001; McGeehan et al., 1994; Moss et al., 1997; Sugerman et al., 2002). Thus, MMPs in oral lichen planus can be considered to be involved in the release of active TNF-α from oral lichen planus lesional T-cell (Sugerman et al., 2002).

2.4 Clinical features

In general, lichen planus can be divided into cutaneous and mucosal lichen planus (Weston & Payette, 2015). Oral lichen planus will be discussed as it is the most relevant for this study.

2.4.1 Clinical presentation of oral lichen planus

Oral lichen planus is a common presentation of lichen planus. It can either occur alone or simultaneously with skin lesions (Weston & Payette, 2015). Oral lichen planus is considered to be a common disease, as it is estimated to affect about 1-2% of the population (Carrozzo et al., 2019). Oral lichenoid lesion is a term that is used to refer to oral lesions that have clinical and histological similarities to oral lichen planus, or to

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indicate uncertain diagnosis of oral lichen planus (Carrozzo et al., 2019). Historically there were many disputes around the term oral lichen planus and oral lichenoid reaction (Carrozzo et al., 2019). Oral lichen planus usually occurs among middle aged adults, with slight female predilection with no obvious racial propensity (Eisen et al., 2005). Oral lichen planus usually manifest on the bilateral buccal mucosa, borders and dorsum of tongue and gingiva (Carrozzo et al., 2019). It less commonly appears on the hard and soft palate, lips, and floor of mouth (Carrozzo et al., 2019). The most commonly affected sites are the buccal mucosa, which is involved in 80-90% of cases (Gorouhi et al., 2014a). Typically, oral lichen planus is characterized by the presence of white papules that can enlarge and coalesce to form, reticular, annular, or plaque-like pattern (Carrozzo & Thorpe, 2009). Oral lichen planus has several subtypes, namely reticular, erosive, atrophic, papular, plaque-like, and bullous subtypes (Gorouhi et al., 2014). The subtypes of oral lichen planus can present alone, or in combinations (Weston & Payette, 2015). The most common subtype is the reticular subtype, it is usually detected incidentally as it is typically asymptomatic (Gorouhi et al., 2014). This reticular subtype shows white lacy lines in a background of erythematous areas (Thorn et al., 1988). The reticular subtype may eventually progress to more severe subtypes, for example the erosive subtype (Gorouhi et al., 2014). Papular oral lichen planus usually shows small pinpoint papules (Gorouhi et al., 2014). It is considered as the initial and transient phase of oral lichen planus (Thorn et al., 1988), which causes it to be missed occasionally (Gorouhi et al., 2014). Plaque-like oral lichen planus shows homogenous white patches, which clinically appear like oral leukoplakia (Gorouhi et al., 2014). This variant is also commonly seen among smokers (Thorn et al., 1988), and also in long standing lesion (Carrozzo et al., 2019). Erosive oral lichen planus is considered as the most severe among the subtypes (Gorouhi et al., 2014). It clinically appears as erosions or ulcerations of the mucosa with faint radiating white striae (Gorouhi et al., 2014). Pseudomemembrane can

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occasionally be seen covering the ulcers (Gorouhi et al., 2014). Erythematous, erosive or ulcerative lesions often causes pain and discomfort (Carrozzo et al., 2019). Extensive erosive and ulcerative presentation may raise the suspicion of diseases such as pemphigus vulgaris, mucous membrane pemphigoid and erythema multiforme (Carrozzo & Thorpe, 2009; Eisen et al., 2005; Scully & Carrozzo, 2008). The atrophic subtype commonly involves the gingiva (Mollaoglu, 2000). Tongue involvement may cause dysgeusia (Schlosser, 2010). Other form of oral lichen planus is less commonly seen (Weston & Payette, 2015). Koebner phenomenon is also associated with oral lichen planus (Gorouhi et al., 2014). Mechanical trauma on the mucosa such as friction from sharp cusps, trauma from dental procedures, and habits such as lip chewing can cause exacerbations of signs and symptoms of oral lichen planus (Eisen, 2002).

2.5 Histopathological features

The classic histological features of oral lichen planus include hyperparakeratosis or hyperorthokeratosis, presence of civatte bodies [also known as colloid, hyaline or cytoid bodies] (Burgdorf & Plewig, 2014), basal cell hydropic change, and a band-like predominantly lymphocytic infiltrate in the lamina propria (Cheng et al., 2016; Kramer, 1978). Other findings include saw tooth rete ridges, atrophy, acanthosis, homogenous eosinophilic deposit at the epithelium-connective tissue interface, and also ulceration (Cheng et al., 2016). The histological features of oral lichen planus and oral lichenoid reaction are very similar (Ismail et al., 2007). There are however, several studies that suggests some distinguishing features of lichenoid drug reaction, such as presence of areas with inflammatory infiltrate that is deep to the superficial infiltrate, focal perivascular infiltrate, and presence of plasma cells and neutrophils in the connective tissue (Rice & Hamburger, 2002; Thornhill et al., 2006). There are several features that

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are considered as exclusion criteria for oral lichen planus, namely absence of basal cell liquefaction degeneration, heterogenous population of infiltrate, cytological atypia, enlarged nuclei, increased mitosis, abnormal keratinization, and absence of civatte bodies (Eisenberg, 2000). Cytological atypia, enlarged nuclei, increased mitoses, and abnormal keratinization are among the features of dysplasia (Ismail et al., 2007).

Direct immunofluorescence [DIF] is a test used to support the diagnosis of oral lichen planus. It is especially useful in distinguishing oral lichen planus from autoimmune blistering diseases that manifest as desquamative gingivitis (Morrison, 2001; Suresh & Neiders, 2012). The characteristic pattern of DIF seen in oral lichen planus is deposition of fibrinogen in a shaggy pattern along the basement membrane zone, with lack of immunoglobulin deposition [except for cytoid bodies] and complement deposition (Abell et al., 1975; Cheng et al., 2016; Crincoli et al., 2011). However, this DIF finding may not be specific for oral lichen planus (Cheng et al., 2016), as there are reports of malignant and potentially malignant oral lesion with deposition of fibrinogen at the basement membrane (Montague et al., 2015).

2.6 Oral lichenoid lesions

2.6.1 Background

Oral lichenoid lesions or reactions are considered as clinical and histological contemporaries of oral lichen planus. There have been numerous debates on oral lichen planus and oral lichenoid lesions in the past. Unlike oral lichen planus, which is considered to be idiopathic in nature, oral lichenoid lesions are often associated with known identifiable cause or inciting factors (Feldmeyer et al., 2020; Kamath et al., 2015). In the perspective of nomenclature, there are several terms used to describe lesions that

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clinically and histologically resemble oral lichen planus, but with known cause, namely oral lichenoid lesions, oral lichenoid reaction, oral drug induced lichenoid reactions, oral lichenoid drug reactions, and oral lichenoid contact lesion (Al-Hashimi et al., 2007). Historically, the first occurrence of oral lesions due to drug interactions were documented in 1971 (Almeyda & Levantine, 1971). The usage of antimalarials by soldiers in World War II, were also documented to result in lichenoid reactions (Almeyda & Levantine, 1971). The risk factors that are considered to be involved in the pathogenesis of oral lichenoid lesions include drugs, dental restorative materials, and graft versus host disease [GVHD] (Kamath et al., 2015).

2.6.2 Oral lichenoid drug reactions

Oral lichenoid drug reactions are caused by exposure to certain medications (Carrozzo et al., 2019). There is no specific time window for occurrence of oral lichenoid drug reaction, as it can manifest years after initiation of the offending drugs (Thompson & Skaehill, 1994). Although occasionally there are reported cases of temporal association between appearance of oral lesions and usage of certain drugs (Al-Hashimi et al., 2007). Oral lichenoid drug reactions are considered to be much less frequent compared to cutaeous lichenoid drug reactions, but it is also likely that they are being under-reported (Carrozzo et al., 2019). Moreover, there are currently no tests available to confirm oral lichenoid drug reactions. Clinically, lesions are indistinguishable from oral lichen planus (DeRossi & Ciarrocca, 2005). It is usually observed to occur unilaterally (Fortuna et al., 2017), but there are cases where occurrence are bilateral (Giudice et al., 2019; Kadam et al., 2015). The most commonly affected sites are the buccal mucosa, followed by tongue, and lips (Bariş et al., 2014). The lesion can involve solely oral cavity, or together with skin lesion (Bariş et al., 2014).

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Drugs that are most commonly reported to be associated with oral lichenoid drug reactions are non-steroidal anti-inflammatory drugs [NSAID] and angiotensin converting enzymes inhibitors (Eisen et al., 2005; Potts et al., 1987; Robertson & Wray, 1992). An earlier study also noted that beta blockers, methyldopa, penicillamine, and non-steroidal anti-inflammatory drugs to be associated with lichenoid eruption (Eisen et al., 2005; Thompson & Skaehill, 1994). Other drugs that also observed to be involved are imatinib and infliximab (Fortuna et al., 2017). The examples of medications associated with oral lichenoid drug reaction are shown in Table 2.1 (Muller, 2011; Schlosser, 2010).

However, it was also noted that in most of the reported cases of oral lichenoid drug reactions, there were no standard protocol used to prove definitive causal relationship (Fortuna et al., 2017). In order to establish causal relationship in a suspected case of drug induced reaction, C-D-R [challenge-dechallenge-rechallenge] protocol or any internationally accepted protocols of drug reactions should be used (McCartan et al., 2003). Furthermore, in some cases, subjecting patients to C-D-R protocols can be dangerous, as there may not be other pharmacologically compatible drugs, and also risks of developing anaphylactic reactions which can be life threatening (Fortuna et al., 2017). Moreover, in oral lichenoid drug reaction, resolution of oral lesions may take months, which make the assessment of C-D-R difficult or controversial (Fortuna et al., 2017).

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Table 2.1 Examples of medications related to oral lichenoid lesions and oral lichen planus

Types	Specific example
Antianxiety/ psychotropic	Benzodiazepines, lithium, tricyclic antidepressants
Antibiotics	Isoniazid, rifampin, tetracycline, streptomycin
Anticonvulsants	Carbamazepine, phenytoin, valproate
Antidiabetics	Glipizide, insulin, tolbutamide
Antifungal	Amphotericin B, ketoconazole
Antihypertensives	Atenolol, captopril, chlorothiazide, enalapril, furosemide, hydrochlorothiazide, metoprolol, propanolol
Antimalarial	Chloroquine, hydroxychloroquine, quininacrine, quinidine
Antiretroviral	Zidovudine
NSAID	Naproxen, ibuprofen, diclofenac, indomethacin, aspirin
Miscellaneous	Bismuth, dapsone, gold, penicillamine, allopurinol

2.6.3 Oral lichenoid contact lesions

The clinical features of oral lichenoid contact lesions are usually described as unilateral, which is less symmetrical compared to oral lichen planus (Carrozzo et al., 2019). It usually lacks the commonly seen reticular appearance of oral lichen planus lesion, and are commonly patch-like or atrophic (Carrozzo et al., 2019). The most common sites are posterior buccal mucosa and lateral borders of tongue (Carrozzo et al., 2019). Oral lichenoid contact lesions are also commonly reported to be in close relationship with amalgam restorations (Carrozzo et al., 2019). Oral lichenoid contact lesion to amalgam are considered as delayed hypersensitivity reaction to low level mercury exposure (McParland & Warnakulasuriya, 2012). Patch tests are commonly conducted in suspected cases of oral lichenoid contact reactions, but their usefulness is sometimes controversial (Thornhill et al., 2003). A study found that a positive patch test may not be able to predict complete healing of oral lichenoid contact lesion, and patients should be informed that positive patch test result does not guarantee healing if they decide to have their amalgam restorations replaced (Suter & Warnakulasuriya, 2016; Thornhill et al., 2003). Furthermore, evidence to support the removal of amalgam restorations in patients with

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oral lichen planus or oral lichenoid contact lesions are considered inadequate (Baccaglini et al., 2013).

2.7 Challenges in the diagnosis of oral lichen planus and oral lichenoid lesions

The diagnosis of oral lichen planus and oral lichenoid reaction are controversial. Many of the histopathologic features of oral lichen planus appears to fall in a spectrum (Cheng et al., 2016). It can be influenced by phase of disease activity at biopsy, recent treatment of the condition, clinical types [reticular/ erosive], and location of lesion (Cheng et al., 2016). Some histological features of oral lichen planus are not unique, and often observed in other diseases, which occasionally causes uncertainty in diagnosis (Cheng et al., 2016). Majority of time, oral lichen planus cannot be differentiated from oral lichenoid reaction, either clinically or histologically (Ismail et al., 2007). There is lack of distinguishing features between oral lichen planus and oral lichenoid lesions (Ismail et al., 2007). Currently there is no definitive features that can reliably differentiate oral lichenoid lesions and oral lichen planus (Thornhill et al., 2006; Van den Haute et al., 1989). However, there are several studies that pointed out certain features that may be useful in differentiating oral lichen planus and oral lichenoid reaction. For example, the histological features that may prompt pathologist to consider more about oral lichenoid lesions are deep diffuse inflammatory infiltrate, presence of mixed plasma cells, eosinophils and neutrophils within the infiltrate, perivascular infiltration, and intraepithelial colloid bodies (Thornhill et al., 2006; Van den Haute et al., 1989). Nonetheless, these features are also observed in oral discoid lupus erythematosus (Ranginwala et al., 2012; Schiødt, 1984; Schlosser, 2010; Van den Haute et al., 1989). In addition, the DIF of both oral lichen planus and oral lichenoid reaction can show similar features, where both entities can present with shaggy deposition of fibrinogen along the basement membrane zone, and colloid bodies that are positive for immunoglobulin M

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(Helander & Rogers III, 1994; Raghu et al., 2002; Schlosser, 2010). Despite that, a study which used modified WHO criteria (E. Van der Meij & Van der Waal, 2003) to classify the cases concluded that cases which are clinically and histologically typical of oral lichen planus show higher sensitivity for positive-fibrinogen compared to cases with only compatible features (Yamanaka et al., 2018). Other previous studies also concluded that although DIF results being not specific, the presence of fibrinogen in the basement membrane zone and absence of other proteins favors the diagnosis of oral lichen planus (Buajeeb et al., 2015; Daniels & Quadra-White, 1981; Firth et al., 1990; Kilpi et al., 1988; Kolde et al., 2003).

At present, there is no widely accepted diagnostic criteria for diagnosis of oral lichen planus (Cheng et al., 2016). The most commonly used criteria are the WHO criteria (Kramer, 1978) and modified diagnostic criteria proposed by (Van der Meij & Van der Waal, 2003). Study on the usage of the WHO criteria (Kramer, 1978) has shown to produce high interobserver variability (Van der Meij et al., 2002). Moreover, with the modified WHO criteria, the presence of epithelial dysplasia will exclude the diagnosis of oral lichen planus (Cheng et al., 2016; Van der Meij & Van der Waal, 2003).

2.8 Malignant potential

One of the most concerning issues regarding oral lichen planus and oral lichenoid reaction is the risk of transformation to oral squamous cell carcinoma. Oral lichen planus is well known under the category of oral potentially malignant disorder (El-Naggar et al., 2017). Despite this, there are many debates in the literature regarding not only malignant potential of oral lichen planus, but also oral lichenoid reaction. A major factor in this controversy is the lack of universally accepted diagnostic criteria for oral lichen planus

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and oral lichenoid reaction (van der Meij et al., 2003). The mean time for transformation is 61.9 months (Giuliani et al., 2019), while other study observed that mean time of transformation from diagnosis is 51.4 months (Fitzpatrick et al., 2014).

2.8.1 Oral lichen planus malignant transformation

A recent meta-analysis by which involved 6559 oral lichen planus patients documented a malignant transformation rate of 1.40% (Giuliani et al., 2019). Another study by that involved 25848 patients showed a transformation rate of 1.14% (González-Moles et al., 2019). A meta-analysis of 57 studies [20095 cases of oral lichen planus] conducted found that the malignant transformation rate of oral lichen planus was 1.1% (Aghbari et al., 2017). Another study found a malignant transformation rate of 1.09% for oral lichen planus (Fitzpatrick et al., 2014). Moreover, there is another smaller scale study observed that the risk of transformation of oral lichen planus was 0.49% (Shearston et al., 2019).

2.8.2 Oral lichenoid lesions malignant transformation

Another study documented malignant transformation rate of 1.88% for oral lichenoid lesions, and 1.71% for oral lichenoid reactions (González-Moles et al., 2019). In the study, oral lichenoid lesions refer to lesions that are only compatible with oral lichen planus when evaluated using the criteria in modified WHO criteria (van der Meij et al., 2003). Moreover, the same study described oral lichenoid reaction as cases that resembles oral lichen planus and are induced by drugs or contact with dental restorative materials (González-Moles et al., 2019). Another recent study that involved 206 patients with oral lichenoid lesions documented malignant transformation rate of 2.43% (Giuliani et al., 2019), a figure which is not far from the previously mentioned study. In addition, another

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study by Fitzpatrick et al. (2014) documented a slightly higher malignant transformation rate of 3.2% for oral lichenoid lesions. Moreover, another study by (Aghbari et al., 2017) which involved 419 oral lichenoid lesions patients observed a transformation rate of 2.5%. interestingly, there was one study which found that oral lichenoid lesions did not undergo malignant transformation (Shearston et al., 2019).

2.8.3 Risk factors

2.8.3.1 Gender

It is generally agreed that malignant transformation is higher among women (Bombeccari et al., 2011; Gandolfo et al., 2004; Giuliani et al., 2019; Holmstrup et al., 1988; Mignogna et al., 2001; Rajentheran et al., 1999; Shen et al., 2011). However, there are studies that reported higher transformation rate among male (Aghbari et al., 2017; González-Moles et al., 2019; van der Meij et al., 2003).

2.8.3.2 Location

The tongue has a higher risk of transformation, especially at the lateral border (Fitzpatrick et al., 2014; Giuliani et al., 2019). Other studies also supported that tongue has the highest transformation (Bombeccari et al., 2011; van der Meij et al., 2003). However, a study by (Mignogna et al., 2001) concluded that lips, gingiva, and midpalate has higher frequency of malignant transformation.

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2.8.3.3 Infections

One of the factors that is considered important in the malignant transformation of oral lichen planus is candida albicans infections (Eisen, 2002; van der Meij et al., 2003). This fungal organism produces N nitrosobenzylmethylamine, which is a carcinogen (Domingues-Ferreira et al., 2009). Other than that, there are studies suggesting there is a higher risk of malignant transformation among patients infected with Hepatitis C virus (Gandolfo et al., 2004; Muzio et al., 1998). It was suggested that the presence of Hepatitis C virus in the saliva may increase the risk of malignant transformation of oral lichen planus (Nagao & Sata, 2004). A connection between human papilloma virus infection [HPV] and malignant transformation of oral lichen planus has also been considered, and it is a subject of debate (Ishibashi et al., 2011; Szarka et al., 2009). There is significant increase of HPV16 in oral lichen planus (Siribang-on et al., 2008). But whether HPV16 can have a significant role in malignant transformation of oral lichen planus or oral lichenoid lesions still need to be elucidated.

2.8.3.4 Tobacco and alcohol consumption

There are several factors that are considered to be associated with increased risk of transformations, most commonly noted are smoking and alcohol intake (Aghbari et al., 2017; González-Moles et al., 2019; Idrees et al., 2020). Moreover, there are studies that suggests tobacco increases the risk of transformation (Fang et al., 2009; Murti et al., 1986). Nevertheless, some studies reported that there is no association between alcohol and tobacco consumption with malignant transformation of oral lichen planus (Bermejo-Fenoll et al., 2009; Eisen, 2002; Shen et al., 2011).

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2.8.3.5 Clinical form of oral lichen planus

The clinical form of oral lichen planus that most often develop malignant transformation are the erythematous, atrophic or erosive forms (Eisen, 2002; Giuliani et al., 2019; González-Moles et al., 2019). Exclusively reticular lesions show no risk of malignant transformation (González-Moles et al., 2019). On the contrary, other study suggested higher transformation rate in reticular and plaque type (Muzio et al., 1998). Moreover, another study also did not support the view that malignant transformation risk is greater in atrophic and erosive oral lichen planus (Gandolfo et al., 2004). Interestingly, it was also suggested that the transformation of oral lichen planus is not related to any specific clinical features because different types of oral lichen planus also show close rate of transformation (Mattsson et al., 2002).

2.8.3.6 Allelic imbalance in oral lichen planus

Dysplasia and squamous cell carcinoma [SCC] have significant positive correlation to loss of heterozygosity at more than one locus, mainly at 3p and 9p (Mao et al., 1996; Rosin et al., 2000). It was also observed that loss of heterozygosity also occurs in oral lichen planus, however the frequency is significantly lower than in squamous cell carcinoma (Accurso et al., 2011). Allelic imbalance, for example when there is loss of heterozygosity, can increase the risk of malignancy by inactivating 1 or 2 alleles of the tumor suppressor genes (Shumway et al., 2008).

2.8.3.7 Cell proliferation and apoptosis

Mutation of the p53 tumor suppressor gene is one of the most frequent genetic alterations in tumorigenesis (Rivlin et al., 2011). P53 activation after DNA damage can stimulate

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DNA repair and induce apoptosis in the affected cells (Williams & Schumacher, 2016). Mutant p53 proteins lose their tumor suppressive ability and gain oncogenic properties which can stimulate cell growth and survival (Rivlin et al., 2011). Other than that, bcl-2 and bax play important role in carcinogenesis. Bcl-2 proteins are important in the regulation of apoptosis (Tzifi et al., 2012). Bax proteins are also an important component in apoptosis, these proteins are known for their ability to pierce the outer membrane of mitochondria to mediate cell death by apoptosis (Westphal et al., 2011) The risk of malignant transformation of oral lichen planus can be indicated by the presence of altered expression of protein related to cellular proliferation and apoptosis (de Sousa et al., 2009). The study also observed that there is no difference in the expressions of p53, bcl-2 and bax in oral SCC and oral lichen planus. Interestingly, it was also suggested that plaque form oral lichen planus is not considered as having low risk of malignant transformation, as it was observed that the concentration of salivary p53 was significantly higher in patients with plaque-like form compared to erosive oral lichen planus (Agha-Hosseini & Mirzaii-Dizgah, 2013).

2.8.3.8 Inflammation and malignancy

Inflammation is considered to have opposing effects on the development of cancer (Philip et al., 2004). Cancer development is limited by acute inflammation, while chronic inflammation promotes cancer development (Philip et al., 2004). However, chronic inflammatory mediators also can exert pleiotropic effects on tumorigenesis (Multhoff et al., 2012). Several studies have shown that chronic inflammation can escalate the risk of malignancy, tumor progression, and supports metastasis (Aggarwal & Gehlot, 2009; Mantovani et al., 2008). In the early stage of tumorigenesis, inflammatory mediators such as cytokines, reactive oxygen species, and reactive nitrogen species can induce genetic

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alteration and inhibit the action of tumor suppressor genes (Grivennikov & Karin, 2010). Immune cells can produce cytokines and chemokines which aid in the survival and proliferation of tumor cells (Zumsteg & Christofori, 2009).

2.9 Management

The main aim in management of oral lichen planus/oral lichenoid reaction is to control the symptoms of the disease (Carrozzo & Thorpe, 2009; Thongprasom et al., 2011). Patients presented with only reticular lesions do not need any active therapy (Carrozzo et al., 2019). Most oral lichen planus and oral lichenoid reaction lesions are responsive to topical therapy (Carrozzo et al., 2019). For patients with oral lichenoid reaction induced by drugs, the offending medications should ideally be stopped, but such measure is often difficult due to unavailability of suitable alternative medications (Carrozzo et al., 2019). Moreover, oral lichenoid reaction lesion can persist for substantial amount of time after medications withdrawal (McCartan & McCreary, 1997). In patient with oral lichenoid reaction suspected to be associated with amalgam restorations, counseling is advised. Patient should be informed about the risk and benefits of amalgam replacement before carrying out any replacement procedures (Carrozzo et al., 2019). Unpredictability of the result of amalgam replacement should also be informed to the patient (Carrozzo et al., 2019). Good oral hygiene instruction should be given, and any structures causing irritation to the mucosa such as calculus, sharp edges of tooth and restorations should be removed or adjusted as necessary (Carrozzo et al., 2019). Good oral hygiene and usage of antibacterial mouthwash which can reduce plaque formation are also beneficial to the patient (Holmstrup et al., 1990). Moreover, patient should be advised to avoid consumption of alcohol and tobacco products, as these have been linked to higher incidence of malignant transformation (Aghbari et al., 2017).

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There is no permanent cure for oral lichen planus and oral lichenoid reaction, as the disease is characterized by spontaneous remission and exacerbation (Carrozzo et al., 2019). The first line treatment for oral lichen planus and oral lichenoid reaction are topical agents, mainly corticosteroids, although there is no standard of care which describe the potency, formulation, concentration or dosage regimen to be used (Thongprasom et al., 2011). Steroid ointments and suspension are commonly used for oral lesion (Carrozzo et al., 2019). Steroid in cream form is bitter and does not adhere well to the oral mucosa (Carrozzo et al., 2019). Examples of topical corticosteroids that are commonly used are triamcinolone acetonide 0.1% and betamethasone [mid-potency], fluocinonole acetonide 0.1% and fluocinonide 0.05% [potent], and clobetasol propionate 0.05% [super-potent] (Buajeeb et al., 2000; Carbone et al., 2009; Carbone et al., 1999; Lozada-Nur et al., 1994; Rödström et al., 1994; Thongprasom et al., 2003; Voûte et al., 1993). To improve the adherence of topical corticosteroids to the oral mucosa, sodium carboxymethyl cellulose and hydroxymethyl cellulose are integrated into the topical corticosteroid formulation, in addition, mixture with adhesive denture paste and special delivery system such as lipid loaded microspheres was also recommended (Campisi et al., 2004; Carbone et al., 1999; Lozada-Nur et al., 1994; Muzio et al., 2001). Steroid in spray form that are used for asthma and nasal allergies can also be used intra-orally (Carrozzo et al., 2019). Systemic corticosteroid therapy is reserved for recalcitrant lesion and also widespread cases that involve the skin and other mucosa (Carrozzo et al., 2019).

Besides topical corticosteroids, other topical and immunomodulatory agents have also been reported to be beneficial, for example, calcineurin inhibitors [cyclosporine, tacrolimus, pimecrolimus], and retinoids (Carrozzo et al., 2019). There are studies assessing the usage of cyclosporine in the form of adhesive paste and mouthrinse to treat oral lichen planus, and it was observed that topical cyclosporine therapy offers no advantage compared to topical corticosteroid therapy (Conrotto et al., 2006; Eisen et al.,

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1990; Gupta et al., 2017; Itin et al., 1992; Levell et al., 1991; Sieg et al., 1995; Voûte et al., 1994). Moreover, the daily costs of cyclosporine are much higher than the cost of super-potent topical corticosteroid such as clobetasol (Conrotto et al., 2006).

Topical tacrolimus is reported to be more efficient than cyclosporine, there are several studies that noted the efficacy of tacrolimus in managing recalcitrant oral lesions, and tacrolimus 0.1% is the concentration that is most commonly reported to be beneficial in the treatment of oral lichen planus (Hodgson et al., 2003; Kaliakatsou et al., 2002; Lener et al., 2001; Morrison et al., 2002; Olivier et al., 2002; Rozycki et al., 2002). However, topical tacrolimus can cause burning sensation in some patients (Resende et al., 2013). Moreover, tacrolimus can demonstrate significant per-cutaneous absorption, and circulating therapeutic level can be present after topical tacrolimus application, which can lead to systemic adverse effects (Conrotto et al., 2006). Another new calcineurin inhibitor is pimecrolimus. A formulation of 1% pimecrolimus has been shown to have similar efficacy to 0.1% tacrolimus (Arduino et al., 2014). It also has been shown to have less percutaneous absorption compared to tacrolimus (Yan et al., 2010). On the other hand, although seems promising, there are reported cases of development of oral squamous cell carcinoma in patient with history of tacrolimus applications (Becker et al., 2006; Mattsson et al., 2010). Moreover, the US Food and Drugs administration has issued a 'Black Box' warning regarding the use of topical tacrolimus and pimecrolimus for skin diseases because of possible risk of squamous cell carcinoma and lymphoma associated with these medications (Ring et al., 2008). However, this black box issuance decision remains controversial (Hanna et al., 2019; Siegfried et al., 2013).

Another topical medication that has been shown to be beneficial in treatment of refractory oral lichen planus is topical rapamycin (Soria et al., 2009). Rapamycin disrupts the cytokine signaling that promotes the growth and differentiation of lymphocytes that

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mainly involve interleukin 2 and interleukin 4 (Dumont & Su, 1995). Other than immunosuppressive properties, rapamycin also can lessen tumor risk as it possesses tumor inhibiting properties (Law, 2005). Rapamycin can inhibit tumor growth by halting tumor cell proliferation, inducing tumor cell apoptosis, and suppressing tumor angiogenesis (Law, 2005). The mechanisms whereby rapamycin inhibit the growth of tumor and lymphocytes proliferation are the same (Law, 2005).

Other group of drugs are comprised of topical retinoids such as tretinoin, isotretinoin, fenretinide, and tezarotene, these topical medications have also been reported to be useful in the management of oral lichen planus, although less commonly used (Petruzzi et al., 2002; Petruzzi et al., 2013; Scardina et al., 2006; Tradati et al., 1994).

Systemic therapy is reserved for severe cases where there is painful lesion that does not respond to topical therapy or when there are extensive involvements of other sites such as skin, genital, esophagus or scalp (Carbone et al., 2003). The most commonly used drug for systemic therapy is corticosteroid (Carrozzo et al., 2019). For example, prednisolone with initial dosage of 40mg-80mg daily for 1-4 weeks is enough to achieve acceptable response, and then followed by tapering down of the dosage (Eisen et al., 2005). However, patient will need close monitoring for possible adverse effects especially in long term therapy (McDougall et al., 1994; Moghadam-Kia & Werth, 2010; Saag et al., 1994; Schäcke et al., 2002; Waljee et al., 2017). Due to the adverse effects of long-term systemic corticosteroid therapy, corticosteroid-sparing agents such as azathioprine and mycophenolate mofetil are required as part of the therapy (Frieling et al., 2003; Verma et al., 2001; Wee et al., 2012). In the latest development, biologic agents such as, Efalizumab, and Alefacept have been proposed for treatment of severe and recalcitrant oral lichen planus (Chang et al., 2008; Cheng & Mann, 2006; Yarom, 2007).

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CHAPTER 3 : METHODOLOGY

3.1 Study design

This was a retrospective study conducted to investigate the association between clinical and histopathological characteristics of oral lichen planus and oral lichenoid reactions/ lesions. Cases diagnosed between the year 2010 and January 2020 which fulfilled the inclusion and exclusion criteria were selected. The clinical information for each case was collected, and their histopathological features were assessed from the respective biopsy tissue slides. The clinical and histopathological characteristics were tabulated and analyzed using statistical methods. This study was conducted in Oral Medicine clinic and Oral Pathology Diagnostic and Research Laboratory (OPDRL), Faculty of Dentistry, University of Malaya.

This study was approved by the Medical Ethics Committee at the Faculty of Dentistry, University of Malaya with Ethics Committee/ IRB reference number of DF OS1819/0068(P).

3.2 Sample size

Sample size calculation was performed using G*Power software version 3.1.9.7. Based on the effect size of 0.321 and power of 0.8, the estimated sample size was at least 106 (Mravak-Stipetić et al., 2014).

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3.3 Cases and tissue samples

3.3.1 Search strategy

Clinical folders of patients seen between the year 2010 and 2020 were obtained from the Oral Medicine clinic. Histopathology records of the Oral Pathology Diagnostic and Research Laboratory, Faculty of Dentistry were retrieved from the database with the search terms as follows: oral lichen planus, oral lichen planus/ oral lichenoid reactions and oral lichenoid reactions/ lesions.

3.3.2 Sample selection

Selection of cases and samples for this study was based on the inclusion and exclusion criteria.

The inclusion criteria were:

1. Cases that were clinically diagnosed as oral lichen planus and oral lichenoid reaction/ lesions.
2. Cases that were histologically diagnosed as oral lichen planus and oral lichenoid reactions/ lesions.

The exclusion criteria were:

1. Cases with inadequate clinical information for assessment of clinical features.
2. Cases with presence of epithelial dysplasia.
3. Cases with missing tissue slides and formalin fixed paraffin embedded blocks.

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3.4 Clinical data collection

Sociodemographic, clinical information and follow up data were extracted from patients' case notes and clinical description provided by the clinician in the histopathological request forms. The sociodemographic and clinical data extracted include:

- Age, gender, race
- Medical and drug history
- Social history
- Dental history
- Clinical presentation
    - extraoral involvement
    - site of lesions
    - clinical type of disease
    - restorations adjacent to lesions

3.5 Histopathological data collection

3.5.1 Histopathological evaluation

Hematoxylin and eosin [H&E] stained tissue slides of oral lichen planus and oral lichenoid reaction/lesions cases from year 2010 to 2020 were retrieved from the archive of OPDRL. Screening was done for each tissue slide to ensure that these samples fulfill the inclusion criteria. The selected tissue slides were scanned with 3DHistech scanner.

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All H&E tissue slides were evaluated in duplicate by one observer on 3DHistech panoramic viewer software. The observer was blinded to the clinical details of each case. The histological parameters were modified from a study by Thornhill et al. (2006).

The histological parameters evaluated were:

i) Epithelium features

- Keratinization (presence and type of keratinization)
- Thickness and configuration
- Results of direct immunofluoresence test

ii) Connective tissue features, which include:

- Depth of the inflammatory infiltrate
- Perivascular infiltrate
- Types of cells present in the inflammatory infiltrate

iii) Plasma cells to lymphocytes ratio

For the evaluation of epithelial thickness and configuration, the features evaluated were presence of acanthosis, atrophy, hyperplasia, and rete ridges. These were adapted from studies by Thornhill et al. (2006) and Schiødt (1984). Acanthosis refers to broadening of rete ridges more than 1/3 of normal area (Thornhill et al., 2006). Atrophy refers to reduction in thickness more than 1/3 of normal area, and hyperplasia refers to thickness more than 1.5 times normal thickness for area, excluding the stratum corneum (Thornhill et al., 2006). Sawtooth rete ridges is characterized by jagged or pointed appearance of the rete ridges (Tamgadge & Tamgadge, 2019).

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3.5.2 Quantification of plasma cells and lymphocytes

Scoring of plasma cells and lymphocytes were performed in duplicate by one observer in a period of after 2 weeks. The observer was blinded to the details of the samples.

3.5.2.1 Selection of representative areas

For each sample, six representative fields were selected at magnification of 400x. The selected fields were at the epithelial-connective tissue interface [zone A] and their respective subjacent regions [zone B], as seen in Fig 3.1. The field columns were separated laterally from each other by two 400x fields. Selection of the fields was done from the right side of the slides. The method of selecting representative fields was modified according to studies by Javvadi et al. (2016) and Javvadi et al. (2018). This was to ensure standardization of field selections in all samples.

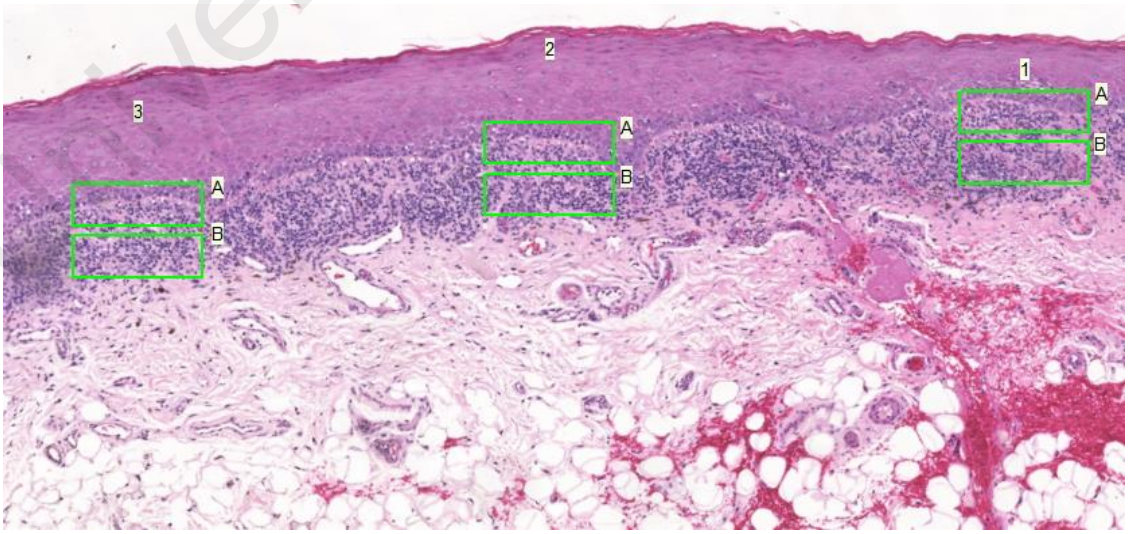

Figure 3.1 Six representative areas selected for plasma cells and lymphocytes scoring

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3.5.2.2 Quantification of plasma cells to lymphocytes ratio

The total number of lymphocytes and plasma cells within each representative area were counted using the open source software QuPath (Bankhead et al., 2017). Scoring for each representative field was done in duplicate. Average scores were obtained and the plasma cells to lymphocytes ratio for each slide was calculated.

3.6 Statistical analysis

Statistical analysis was performed by using SPSS software [version 26, IBM]. P value of 0.05 was considered as significant level.

Intraclass correlation coefficient [ICC] test was performed to observe intraobserver variability in plasma cells and lymphocytes scoring. This is carried out by using SPSS utilizing data from the first and second round count of the lymphocytes and plasma cells. Based on the analysis, the intraobserver agreement for scoring of lymphocytes and plasma cells were 0.999 and 0.975 respectively, which indicated excellent level of reliability (Koo & Li, 2006).

For the purpose of comparisons and associations, the subjects were divided into three groups, which were:

- No exposure: subjects were not taking any drugs and with no presence of dental restorative materials adjacent to lesions.
- Drugs: subjects taking drugs that were associated with oral lichenoid reaction/ lesions, and with no presence of dental restorative materials adjacent to lesions.

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- Restorations: subjects with presence of dental restorative materials adjacent to lesions and not taking drugs that were associated with oral lichenoid reactions/ lesions.

In this study, subjects or patients with exposure to causative factors refers to subjects in the Drugs and Restorations group.

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CHAPTER 4 : RESULTS

4.1 Socio-demographic data

A total of 122 cases of oral lichen planus and oral lichenoid reactions/ lesions were included. The mean age of the subjects were 51.48 years. Of the 122 patients, 41(33.6%) were males, and 81(66.4%) were females, with male to female ratio of 1:2. The mean age the patients were 51.48 years with age range of 17 to 78 years. Majority (39.3%) of the patients were of Chinese ethnic origin. Table 4.1 demonstrates the distribution of patients according to age, gender, ethnicity respectively.

Table 4.1: Distribution of socio-demographic data

Characteristics		Frequency	%
Age (years)	<55	65	53.3
Mean ± standard deviation, range: 51.48 ± 14.796, 17-78	≥ 55	57	46.7
Gender	Male	41	33.6
	Female	81	66.4
Ethnicity	Malay	24	19.7
	Chinese	48	39.3
	Indian	44	36.1
	Others	6	4.9

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4.2 Clinical data

The clinical findings in this study are tabulated in table 4.2. The most common symptom reported by patients was burning sensation (50.8%). This was followed by pain (13.9%). Majority of the patients, 75 (61.5%) complaint that symptoms affected their buccal mucosa. Most of the patients were hypertensive and diabetic. The most common comorbidities noted were hypertension with 38 (35.2%) cases; followed by diabetes mellitus (DM), 28 (25.9%); and dyslipidemia, 17 (15.7%). Antihypertensives were the most commonly consumed drugs, 34 (35.1%); this was followed by antidiabetics, 20 (20.6%); and statin, 17 (17.5%).

On clinical presentations, 12 (9.8%) patient were recorded with extraoral involvement of the disease. Intraorally, approximately half, 64 (52.5%) of the patients reported involvement of the buccal mucosa only. A high proportion of the cases, 109 (89.3%) involved multiple sites. Majority, 47 (38.5%) patients showed reticular pattern involvement alone. The clinical presentations showed a mixture of patterns, with reticular pattern recorded the highest occurrence among subjects, which were 53.3% of total occurrence of patterns recorded. There were 17 (14.0%) cases recorded presence of restorations adjacent to lesions.

Overall, it was noted that 53 (43.4%) patients were not taking medications and no filling adjacent to lesions; 52 (42.6%) were taking medications and with no filling adjacent to lesions, and 17 (14.0%) with presence of filling adjacent to lesion and not taking medications. These were designated as No Exposure, Drugs, and Restorations groups respectively.

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Table 4.2: Distribution of clinical data

	Characteristics	Frequency	%
Symptoms	Burning	62	50.8
	Pain	17	13.9
	Discomfort	9	7.4
	Burning, discomfort	4	7.4
	Burning, pain	17	13.9
	Discomfort, pain	1	0.8
	Burning, discomfort, pain	3	2.5
	None	9	7.4
Sites of complaint	Buccal mucosa	75	61.5
	Gingiva	7	5.7
	Tongue	9	7.4
	Lip	3	2.5
	Buccal mucosa, floor of mouth	1	0.8
	Buccal mucosa, gingiva	4	3.3
	Buccal mucosa, tongue	5	4.1
	Gingiva, tongue	2	1.6
	Tongue, floor of mouth	1	0.8
	Tongue, lip	1	0.8
	Buccal mucosa, gingiva, tongue	1	0.8
	Whole mouth	5	4.1
	Mouth, not specified	8	6.6
Comorbidities	HPT[1], DM[2]	13	10.7
	HPT	11	9.0
	DM	8	6.6
	Dyslipidemia	7	5.7
	HPT, dyslipidemia	5	4.1
	HPT, DM, dyslipidemia	3	2.5
	Breast cancer	2	1.6
	Gastritis	2	1.6
	Hypothyroidism	2	1.6
	Anemia	1	0.8
	Asthma	1	0.8
	Atypical odontalgia	1	0.8
	Depression	1	0.8
	DM, dyslipidemia	1	0.8
	DM, dyslipidemia, hypothyroidism	1	0.8

[1] Hypertension
[2] Diabetes mellitus

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Table 4.2: continued

Characteristics		Frequency	%
Comorbidities	Epilepsy	1	0.8
	Erythema dyschromium perstans	1	0.8
	Gout	1	0.8
	HPT, asthma	1	0.8
	HPT, DM, asthma	1	0.8
	HPT, DM, gout	1	0.8
	HPT, gout, depression	1	0.8
	HPT, hypothyroidism	1	0.8
	HPT, osteoporosis	1	0.8
	Osteoporosis	1	0.8
	Thalassemia	1	0.8
Frequency of comorbidities	HPT	38	35.2
	DM	28	25.9
	Dyslidemia	17	15.7
	Erythema dyschromium perstans	1	0.9
	Asthma	3	2.8
	Osteoporosis	2	1.9
	Epilepsy	1	0.9
	Gout	3	2.8
	Hypothyroid	4	3.7
	Anemia	1	0.9
	Breast ca	3	2.8
	Thalassemia	1	0.9
	Atypical odontalgia	1	0.9
	Depression	2	1.9
	Gastritis	3	2.8
Frequency of medications taken by patients	Anti-HPT	34	35.1
	Anti DM	20	20.6
	Statin	17	17.5
	Anti-platelet	8	8.2
	Thyroxine	4	4.1
	Anti-seizure	4	4.1
	Allopurinol	3	3.1
	Antidepressant	3	3.1
	Proton pump inhibitor	2	2.1
	Letrozole	1	1.0
	Insulin	1	1.0

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Table 4.2: continued

Characteristics		Frequency	%
Extraoral involvement	No	110	90.2
	Yes	12	9.8
Sites involved	Buccal mucosa	64	52.5
	Buccal mucosa, tongue	19	15.6
	Buccal mucosa, gingiva	18	14.8
	Buccal mucosa, lip	4	3.3
	Tongue	3	2.5
	Buccal mucosa, palate	2	1.6
	Buccal mucosa, tongue, floor of mouth	2	1.6
	Buccal mucosa, tongue, lip	2	1.6
	Gingiva	2	1.6
	Buccal mucosa, floor of mouth	1	0.8
	Buccal mucosa, gingiva, floor of mouth	1	0.8
	Buccal mucosa, palate, gingiva	1	0.8
	Buccal mucosa, tongue, gingiva	1	0.8
	Buccal mucosa, tongue, lip, gingiva	1	0.8
	Gingiva, tongue	1	0.8
Cumulative for each site involved	Buccal mucosa	116	63.4
	Tongue	29	15.8
	Gingiva	24	13.1
	Lip	7	3.8
	Floor of mouth	4	2.2
	Palate	3	13.1
Involve multiple sites	No	13	10.7
	Yes	109	89.3
Clinical presentation	reticular	47	38.5
	reticular, erythema	23	18.9
	reticular, plaque	9	7.4

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Table 4.2: continued

Characteristics		Frequency	%
Clinical presentation	Reticular, erosive, erythema	7	5.7
	Reticular, erosive	6	4.9
	Reticular, erythema, DG [3]	5	4.1
	Reticular, DG	4	3.3
	Erythema	3	2.5
	Reticular, erosive, erythema,	3	2.5
	Erosive	2	1.6
	Erosive, erythema	2	1.6
	Reticular, papular	2	1.6
	Reticular, patch	2	1.6
	Erythema, plaque	1	0.8
	Papular	1	0.8
	Patch	1	0.8
	Reticular, DG, plaque	1	0.8
	Reticular, erosive, DG	1	0.8
	Reticular, erosive, patch	1	0.8
	Reticular, papular, plaque	1	0.8
Frequent clinical presentation	Reticular	113	53.3
	Erythematous	44	20.8
	Erosive	22	10.4
	Desquamative gingivitis	12	5.7
	Plaque	13	6.1
	Papular	4	1.9
Frequent clinical presentation	Patch	3	1.4
	Bullous	1	0.5
Cases with restorations adjacent to lesions	No	105	86.1
	Yes	17	13.9
Subjects groups	No exposure	53	43.4
	Drugs	52	42.6
	Restorations	17	14.0

[3] Desquamative gingivitis

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4.3 Histopathological data

The histopathological evaluation is shown in Table 4.3. Histopathological evaluation showed 120 (98.4%) cases were parakeratinized. In 51 (41.8%) of the cases, the epithelium shows acanthosis and hyperplasia. There were often mixtures of epithelial configuration and thickness observed across the samples. Epithelial atrophy is observed in 32 (26.2%) of cases. Direct immunofluorescence (DIF) test was conducted in 95 (77.9%) of samples. The DIF test showed positivity of fibrinogen along the basement membrane zone in 73 (76.8%) cases. Epithelial components are illustrated in Figure 4.1

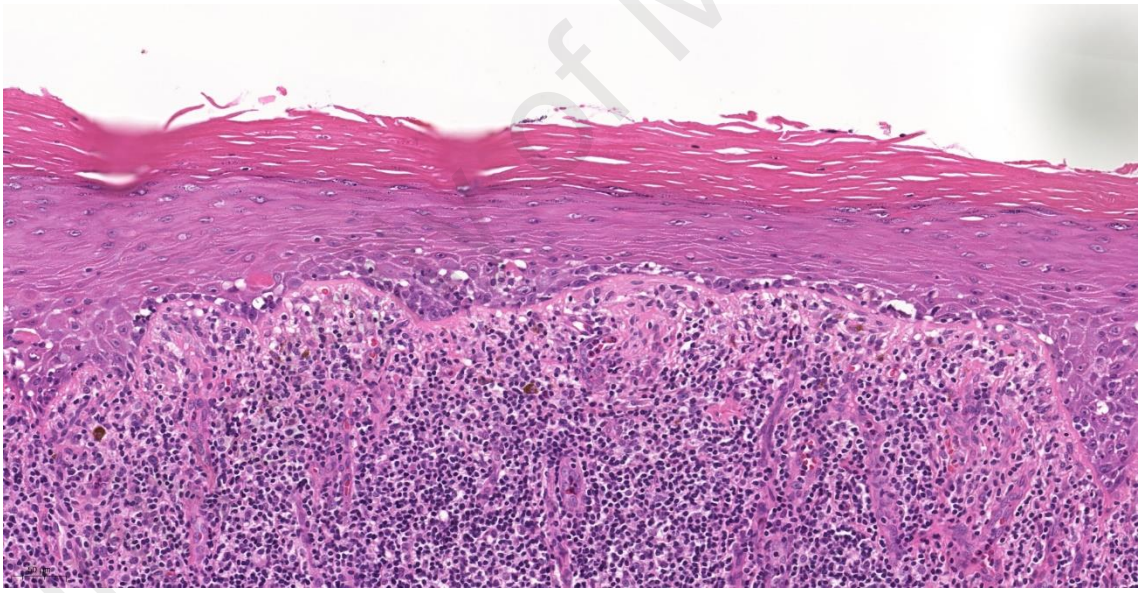

Figure 4.1 Photomicrograph showing epithelial parakeratinization and atrophy

For the evaluation at the connective tissue regions, 75 (61.5%) of cases showed presence of superficial inflammatory infiltrate, while 47 (38.5%) cases showed deep inflammatory infiltrate. Majority of the infiltrate were moderate to heavy, which are seen in 117 (95.9%) of cases. Moreover, 12 (9.8%) of cases showed presence of perivascular infiltrate. Eosinophils are observed in 39 (32%) of cases. Mast cells were present in all

cases. In this study, it was observed that mast cells were mainly found in the deeper layer of the connective tissues. Connective tissue components are illustrated in Figure 4.2

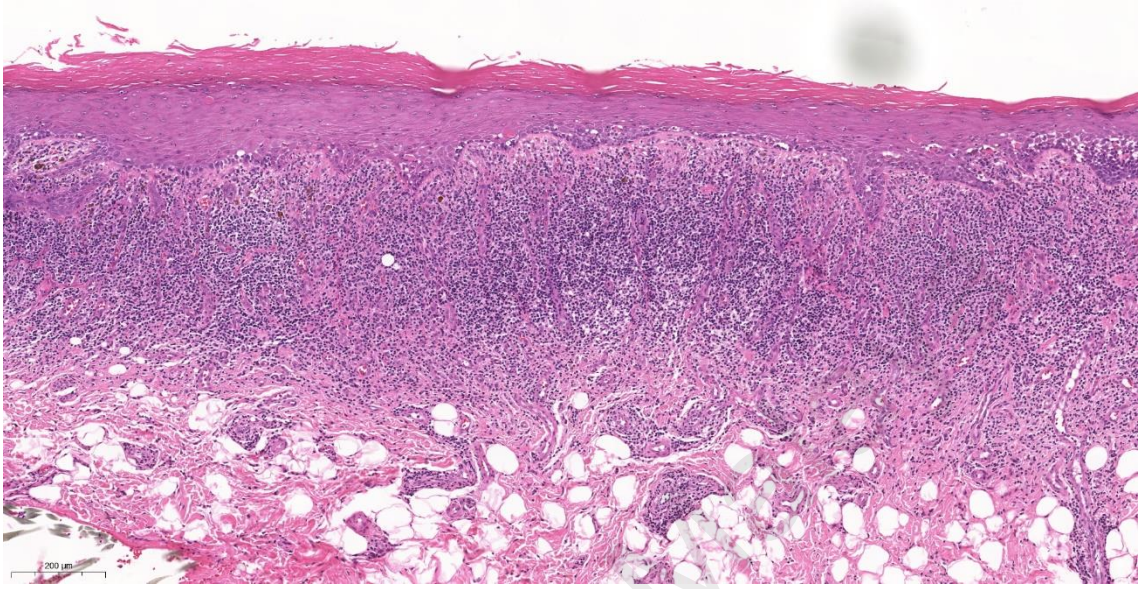

Figure 4.2 Photomicrograph showing heavy inflammatory infiltrate extending into the deeper connective tissue

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Table 4.3: Distribution of Histopathological data

Characteristics		Frequency	%
Epithelium keratinization	Parakeratinized	120	98.4
	Orthokeratinized	2	1.6
Epithelial configuration and thickness	Acanthosis	1	0.8
	Atrophy	7	5.7
	Hyperplasia	9	7.4
	Acanthosis, hyperplasia	51	41.8
	Atrophy, finger-like rete	1	0.8
	Atrophy, hyperplasia	5	4.1
	Hyperplasia, finger-like rete	1	0.8
	Hyperplasia, saw-tooth rete	1	0.8
	Acanthosis, hyperplasia, finger-like rete	7	5.7
	Acanthosis, hyperplasia, sawtooth rete	7	5.7
	Atrophy, acanthosis, hyperplasia	23	18.9
	Atrophy, hyperplasia, sawtooth rete	1	0.8
	Acanthosis, hyperplasia, finger-like rete, saw-tooth rete	1	0.8

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Table 4.3: continued

Characteristics		Frequency	%
Epithelial configuration and thickness (cont.)	Atrophy, acanthosis, hyperplasia, saw-tooth rete	1	0.8
	Atrophy, acanthosis, hyperplasia, finger-like rete	6	4.9
Epithelial atrophy	No	90	73.8
	Yes	32	26.2
DIF test (DIF were not performed in 27 (22.1%) samples)	Negativity for fibrinogen	22	23.2
	Positivity for fibrinogen	73	76.8
Depth of infiltrate	Deep	47	38.5
	Superficial	75	61.5
Intensity of infiltrate	Mild	5	4.1
	Moderate/heavy	117	95.9
Perivascular infiltrate	No	110	90.2
	Yes	12	9.8
Eosinophils presence	No	83	68
	Yes	39	32
Mast cell presence	No	0	0
	Yes	122	100

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4.4 Comparisons of plasma cells to lymphocytes ratio between No exposure, Drugs, and Restorations categories

Cell count to determine the plasma cells to lymphocytes ratio were conducted for each sample. The number of plasma cells and lymphocytes within each representative area (Figure 4.3) were determined. The scoring process are shown in Appendix A. The overall

mean ratio of plasma cells to lymphocytes were 0.011023 ± 0.0228025. The ratio of plasma cells to lymphocytes for the designated group of No Exposure, Drugs, and Restorations were also calculated and shown in the table 4.4.

Mann-Whitney U test was used to analyze the mean plasma cells to lymphocytes ratio as the data were not normally distributed. There were significant difference when comparing No exposure to Drug and No exposure to Restorations categories as shown in table 4.5.

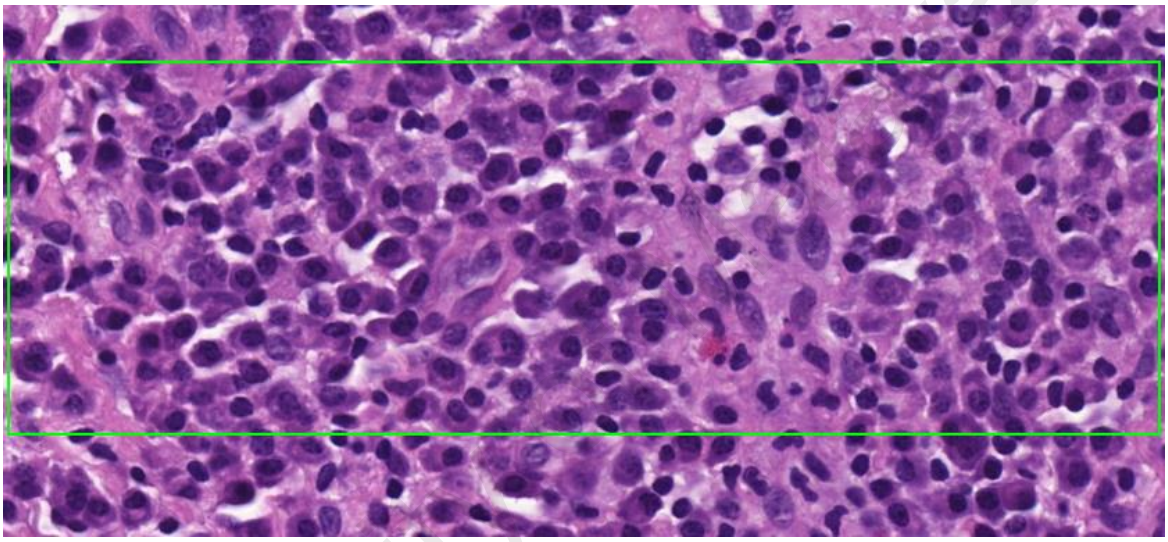

Figure 4.3 Representative area for plasma cells and lymphocytes count

Table 4.4: Plasma cells and lymphocytes cell count

Characteristics		**Mean ± sd[4]**	**95% CI[5]**
Overall Plasma cells to lymphocytes ratio		0.011023 ± 0.0228025	0.006935, 0.015110
Plasma cells to lymphocytes ratio in groups	No Exposure	0.005068 ± 0.0082618	0.002791, 0.007346
	Drugs	0.013798 ± 0.0189939	0.008510, 0.019086
	Restorations	0.021095 ± 0.0480635	0.003617, 0.045807

[4] Standard deviation
[5] Confidence interval

Table 4.5 Comparison of mean plasma cells to lymphocytes ratios between groups

Groups compared	Mean ± sd	95% CI	p value
No exposure	0.005068 ± 0.008262	0.002791, 0.007346	**0.043**
Drugs	0.013798 ± 0.018994	0.008510, 0.019086	
No exposure	0.005068 ± 0.008262	0.002791, 0.007346	**0.031**
Restorations	0.021095 ± 0.048064	-0.003617, 0.045807	
Drugs	0.013798 ± 0.018994	0.008510, 0.019086	0.558
Restorations	0.021095 ± 0.048064	-0.003617, 0.045807	

4.5 Receiver operating curve analysis for plasma cells to lymphocytes ratio

Receiver operating curve (ROC) analysis was carried out for plasma cells to lymphocytes ratio for all No exposure, Drugs, and Restorations groups. The plasma cell to lymphocytes ratio was able to discriminate between No exposure and Drug group with sensitivity of 34.6% and specificity of 92.5%. Moreover, plasma cells to lymphocytes ratio were also able to discriminate between No exposure and Restorations group with a sensitivity of 64% and specificity of 69.8%. However, ROC analysis showed that plasma cells to lymphocytes ratio were unable to discriminate between Drugs and Restorations group. The results are shown in table 4.6.

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Table 4.6: ROC analysis for subject groups

Characteristics	Area under the curve	Cut-off value	*p* value	Sensitivity/specificity
No exposure Drug (1)	0.612	0.12105	**0.048**	34.6% / 92.5%
No exposure Restorations (1)	0.674	0.004829	**0.032**	64.7% / 69.8%
Drug Restoration (1)	0.548	0.004895	0.559	64.7% / 53.8%

4.6 Associations between socio-demographic characteristics and subject categories

The socio-demographic data were statistically analyzed using Chi-square tests [Pearson Chi-square test or Fisher's Exact test, whichever applicable] to determine the association between these characteristics and the samples categories. There were significant association observed between age of patients and subject categories ($p<0.001$). The test showed that higher number of subjects aged 55 and above were using medications. A significant association were also noted between ethnicity and subject categories ($p=0.035$). There were no significant associations observed between gender and the subject categories. These results are shown in Table 4.7.

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Table 4.7: Associations between socio-demographic characteristics and subject categories

Characteristics		No exposure n (%)	Drugs n (%)	Restorations n (%)	*p* value
Age	< 55	41 (63.1)	18 (27.7)	6 (9.2)	**0.000**
	≥55	12 (21.1)	34 (59.6)	11 (19.3)	
Gender	Male	18 (43.9)	16 (39.0)	7 (17.1)	0.731
	Female	35 (43.2)	36 (44.4)	10 (12.3)	
Ethnicity	Malay	14 (26.4)	5 (9.6)	5 (29.4)	
	Chinese	19 (35.8)	19 (36.5)	10 (58.8)	**0.035**
	Indian	17 (32.1)	25 (48.1)	2 (11.8)	
	Others	3 (5.7)	3 (5.8)	0 (0)	

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4.7 Associations between clinical characteristics and subject categories

The association between clinical characteristics and subject categories were also studied. There were no significant associations observed between clinical characteristics and the subject groups. The results are shown in Table 4.8.

Table 4.8: Associations between clinical characteristics and subject categories

Characteristics		No exposure n(%)	Drugs n(%)	Restorations n(%)	*p* value
Extraoral involvement	No	47 (42.7)	46 (41.8)	17 (15.5)	0.340
	Yes	6 (50)	6 (50)	0 (0)	
Involved multiple oral sites	No	4 (30.8)	5 (38.5)	4 (30.8)	0.169
	Yes	49 (45.0)	47 (43.1)	13 (11.9)	
Clinical variant					
Reticular	No	6 (66.7)	2 (22.2)	1 (11.1)	0.331
	Yes	47 (41.6)	50 (44.2)	16 (14.2)	
Erosive	No	45 (45)	40 (40)	15 (15)	0.437
	Yes	8 (36.4)	12 (54.5)	2 (9.1)	
Erythematous	No	35 (44.9)	32 (41)	11 (14.1)	0.889
	Yes	18 (40.9)	20 (45.5)	6 (13.6)	
Desquamative gingivitis	No	47 (42.7)	48 (43.5)	15 (13.6)	0.790
	Yes	6 (50)	4 (33.3)	2 (16.7)	
Papular	No	49 (41.5)	52 (44.1)	17 (14.4)	0.068
	Yes	4 (100)	0 (0)	0 (0)	
Patch	No	52 (43.7)	50 (42)	17 (14.3)	0.632
	Yes	1 (33.3)	2 (66.7)	0 (0)	
Plaque	No	48 (44)	48 (44)	13 (11.9)	0.172
	Yes	5 (38.5)	4 (30.8)	4 (30.8)	
Bullous	No	53 (43.8)	51 (42.1)	17 (14)	0.507
	Yes	0 (0)	1 (100)	0 (0)	

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4.8 Associations between histopathological characteristics and subject categories

The analysis of histopathological characteristics showed that there were significant associations between subject categories and epithelial atrophy (p=0.006), where there was significantly higher presence of epithelial atrophy in the Drugs group. Moreover, there was significant association between subject groups and presence of eosinophils (p=0.002), with more eosinophils seen in the Drugs category. There were no significant association noted between subject categories and types of epithelial keratinization, DIF positivity for Fibrinogen depth of infiltrate, intensity of infiltrate, and perivascular infiltrate. These results are shown in table 4.9.

Table 4.9: Association between histopathological characteristics and subject categories

Characteristics		No exposure n(%)	Drugs n(%)	Restorations n(%)	*p* value
Epithelium keratinization	Parakeratinized	51 (42.5)	52 (43.3)	17 (14.2)	0.266
	Orthokeratinized	2 (100)	0 (0)	0 (0)	
Epithelial atrophy	No	39 (54.9)	26 (36.6)	6 (8.5)	**0.006**
	Yes	14 (27.5)	26 (51.1)	11 (21.6)	
DIF positivity for Fibrinogen	Negative for Fibrinogen	11 (50)	9 (40.9)	2 (9.1)	0.804
	Positive for Fibrinogen	32 (43.8)	31 (42.5)	10 (13.7)	
Depth of infiltrate	Superficial	39 (52)	27 (36)	9 (12)	0.055
	Deep	14 (29.8)	25 (53.2)	8 (17)	
Intensity of infiltrate	Mild	2 (40)	2 (40)	1 (20)	0.923
	Moderate/ heavy	51 (43.4)	50 (42.7)	16 (13.7)	
Perivascular infiltrate	No	49 (44.5)	48 (43.6)	13 (11.8)	0.124
	Yes	4 (33.3)	4 (33.3)	4 (33.3)	
Eosinophils presence	No	45 (54.2)	30 (36.1)	8 (9.6)	**0.002**
	Yes	8 (20.5)	22 (56.4)	9 (23.1)	

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4.9 Multivariate analysis for significant characteristics

A multivariate analysis utilizing binary logistic regression determined that deeper inflammatory infiltrate, presence of epithelial atrophy, Drugs group, and Restorations group were associated with presence of eosinophils. Moreover, presence of restorations adjacent to lesions was also associated with epithelial atrophy. The results are showed in table 4.10 and 4.11.

Table 4.10: Binary logistic regression showing characteristics, associated p-values, and odds ratio of presence of eosinophils in samples

Characteristics	p-value	Odds ratio [95% CI]
Sex	0.155	2.078 [0.758 – 5.692]
Age group	0.199	0.534 [0.205 – 1.392]
Infiltrate depth	**0.016***	0.335 [0.138 -0.814]
Epithelial atrophy	**0.043***	2.504 [1.029 – 6.093]
Drugs group	**0.016***	3.708 [1.271 – 10.814]
Restorations group	**0.011***	5.984 [1.498-23.898]

Table 4.11: Binary logistic regression showing characteristics, associated p-values, and odds ratio of epithelial atrophy

Characteristics	*p*-value	Odds ratio [95% CI]
Sex	0.084	2.166 [0.901 – 5.208]
Age group	0.768	1.141 [0.475 – 2.744]
Infiltrate depth	0.438	0.716 [0.307 – 1.668]
Eosinophils presence	**0.043***	2.503 [1.027 – 6.100]
Drugs group	0.155	1.994 [0.771 – 5.158]
Restorations group	**0.046***	3.752 [1.024 – 13.753]

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CHAPTER 5 : DISCUSSION

5.1 Socio-demographic evaluations

The socio-demographic parameters included in this study were age, gender and ethnicity. In the present study, the mean age of patients were 51 years old when diagnosed with oral lichen planus or oral lichen planus/ lesions. This characteristic corresponds to description by Li et al. (2020), where oral lichen planus has higher prevalence among individuals aged 40 years and above. Interestingly, the youngest age of patient in our study was 17 years old. Although rare among younger age group, oral lichen planus had been reported to occur in paediatric populations, between age of 8 to 18 (Chatterjee et al., 2012). This study also observed higher incidence of the disease among females, with male to female ratio of 1:2. These observations were also described in a study by Li et al. (2020), where oral lichen planus prevalence was higher among females predominantly aged 40 years and above. Majority of the subjects in this study were from Chinese and Indian origin, which consists of 39.3% and 36.1% of patients respectively. A preliminary study in Malaysian population by Lim et al. (2009) also observed that there were higher occurrence of oral lichen planus among Chinese and Indian populations.

5.2 Clinical evaluations

This study also documented the complaint of patients. The most commonly reported complaints by the patients were burning sensation, which were present in half of the subjects. This was followed by pain. Radwan-Oczko et al. (2018) also noted that the most commonly reported complaint in oral lichen planus was burning sensation. Our study also noted that the most common site of complaint was buccal mucosa. This is consistent with the fact that buccal mucosa is the most common site of involvement for oral lichen planus and oral lichenoid reaction/ lesions (Shen et al., 2012).

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In the study of comorbidity among the subjects, it was observed that hypertension and diabetes mellitus were the most commonly seen comorbidities among subjects. A proportion of our subjects had multiple comorbidities, for example, hypertension accompanied by diabetes mellitus. Hypertension and diabetes mellitus were present in 35.2% and 25.9% of patients respectively. These figures were higher when compared to the prevalence of hypertension and diabetes mellitus in Malaysia, which were 30.3% and 17.5% respectively (Zainal, 2018). This may be because there is an increased probability of patients having concurrent medical problems in a tertiary clinical setting such as in oral medicine clinic. Lichen planus is known to have established relationship with multitude of comorbidities. A study by Cassol-Spanemberg et al. (2019) noted that hypertension and diabetes mellitus were among the systemic disease most commonly associated with lichen planus. The association between diabetes mellitus and oral lichen planus was first reported by Grinspan (1966). Moreover, Kaomongkolgit (2010) also observed that the onset of oral lichenoid reaction appears to correspond to the administration of medications, especially antihypertensive drugs, oral hypoglycaemic drugs, antimalarial drugs, gold salts and penicillamine. In addition, it can also be highlighted that impaired endocrine function in diabetes mellitus can contribute to the development of oral lichen planus (Petrou-Amerikanou et al., 1998). Other than that, there were also increased occurrence of dyslipidemia in the study subjects. This is in concordance to the study by Aniyan et al. (2018), which reported that an association exist between dyslipidaemia and oral lichen planus. An interesting observation in this study was there were four subjects that were also diagnosed with hypothyroidism. Study by Li et al. (2017) demonstrated correlation between oral lichen planus and hypothyroidism. These findings indicated that oral lichen planus, oral lichenoid reaction/ lesions are often associated with systemic disease (Cassol-Spanemberg et al., 2019). An important matter is the risk of cardiovascular disease in patients with dyslipidemia. Dyslipidemia is known to promote

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atherosclerosis, which is a major risk factor for coronary artery disease (Garg et al., 2015; Kopin & Lowenstein, 2017). Oral health physicians should ensure that these patients undergo thorough history taking and examination in order to investigate for possible presence of these disease and their manifestations (Cassol-Spanemberg et al., 2019b). Moreover, oral health physicians should also be aware of these systemic associations and should liaise with primary healthcare physicians to investigate the predisposing factors for associated comorbidities (Hasan et al., 2019).

In this study we also investigated the type of drugs taken by the patients. Polypharmacy were noted among the subjects in this study. The medications usage in Drugs group were recorded based on types of medications that have been linked to oral lichen planus in past studies, which were antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAID), cholesterol-lowering medications, psychiatric or antianxiety medications, thyroid replacements, antidiabetics, and anticonvulsants. The most commonly taken drugs in this study were antihypertensives, antidiabetics, and cholesterol lowering drugs (statins). The high intake of these drugs was anticipated in this study as there were a high number of cases presenting with diseases such as hypertension, diabetes mellitus, and dyslipidemia. There were several reports on statins causing adverse reactions including lichenoid reactions (Roger et al., 1994), dermatomyositis (Oztas et al., 2017), and skin eruption (Forouzan et al., 2020; Wong et al., 2018). Antihypertensive and antidiabetic drugs had also been reported to be related to oral lichenoid reaction/ lesions (Sonano & Sarrion, 2010). In fact, there were multiple studies showing increased in the incidence and severity of oral lichen planus among patients who were taking medications for cardiovascular disease (Habbab et al., 2010). Moreover, anti-platelet, thyroxine, anti-seizure, allopurinol, proton-pump inhibitor, letrozole, and insulin were also among the medications taken by subjects. These medications were often taken in combination with each other. These medications have been reported to be associated with oral lichenoid

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reaction/ lesions. For example, a study by Robledo-Sierra et al. (2013) found significant association between levothyroxine and oral lichen planus. The authors also suggested possible association between oral lichen planus and hypothyroidism. Moreover, anti-platelet drugs, namely acetylsalicylic acid and clopidogrel had been associated with lichenoid reactions (Guijarro & López, 2003; Ruiz Villaverde et al., 2003). Meanwhile, other studies have also reported association of lichen planus and lichenoid reaction/lesions with carbamazepine (Atkin et al., 1990; Hajnsek et al., 2012), gabapentin (Yuan et al., 2015), proton-pump inhibitors (Bong et al., 2000), letrozole (Öktem et al., 2016; Yuan et al., 2015), and allopurinol (Chau et al., 1984).

Despite the high number of patients taking these implicated medications, drug related oral lichenoid reaction/lesions were difficult to pinpoint, because the presentation of the disease has a wide variation. For example, the onset of the disease can occur from weeks to over a year after initiation of medications (Halevy & Shai, 1993). This latent period appears to be related to the class of drug, the dosage, the individual reaction, and presence or absence of concomitant medications (Halevy & Shai, 1993). Previous exposure to the offending drug may shorten the latent period of drug reaction (Powell et al., 1983).

Moreover, this disease can persist for weeks to months after cessation of the offending medications, some may even remain as milder form of the disease (Schlosser, 2010). Therefore, a definitive and clear temporal relationship between initiation of medications and onset of oral lichenoid reaction may not be easily apparent (Al-Hashimi et al., 2007). Furthermore, the most reliable method of diagnosing oral lichenoid reaction/lesions is by observing the resolution of lesions after withdrawal of the suspected drug, and re-challenge with the same drug. However, this is considered impractical as it is potentially hazardous to the patient, and the reactions may take months to resolve (Al-Hashimi et al., 2007).

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In this study, it was not possible to definitively differentiate between oral lichen planus and oral lichenoid reaction/ lesions for the majority of cases or to pinpoint specific offending drug based on removal or resolution of the lesions after removal of the medications. However, the high percentage of patients in this study taking medications that have be shown to be associated with oral lichenoid reaction/lesions suggested that medication use may be a potentially modifiable factor in our subjects, even if the drug use is not the definite cause of the disease (Alqahtani et al., 2018).

The site of disease most often involved in this study was the buccal mucosa and tongue. 52.5% of patients presented with involvement of the buccal mucosa alone. Involvement of multiple oral sites were also often seen in this study, with 89.3% of subjects exhibiting multiple sites of involvement. Buccal mucosa is well known as the most common site of presentation for oral lichen planus and oral lichenoid reaction/lesions. In fact, a study by Juneja et al. (2006); Xue et al. (2005) also observed that the buccal mucosa the most frequent site of involvement. Other sites that were commonly involved for intraoral lesions are tongue and gingiva (Cassol-Spanemberg et al., 2019; Ingafou et al., 2006; Ismail et al., 2007). Furthermore, an extensive Asian study by Xue et al. (2005) also recorded labial mucosa as one of the sites often affected besides buccal mucosa, tongue, and gingiva. Moreover, the study by Xue et al. (2005) also observed that 90.9% of patients had multiple oral sites of involvement, which closely approximates our study. They observed that less than 10% of patients had single oral site involvement, which often affect the lip and gingiva. In our study, we noted that the lesions occur rarely on the floor of mouth and palate, with 4 cases and 3 cases respectively. The rare occurrence of this disease at the floor of mouth and palate was also described by Krupaa et al. (2015).

Moreover, our study also recorded that 9.8% of subjects presented with extraoral involvement of the disease. Extraoral involvement of lichen planus and oral lichenoid

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reaction/lesions refers to manifestation of lichen planus at sites such as genital mucosa, conjunctiva, skin and nail (Gorouhi et al., 2014). The most common extraoral presentation typically involves the skin, especially flexor surfaces (Cassol-Spanemberg et al., 2019; Gorouhi et al., 2014). We observed that only a small minority of cases presented with extraoral involvement, which is equal amount (6) for both No exposure and Drugs group, while Restorations group recorded no extraoral involvement. This finding is in concordance with a study by Omal et al. (2012) on 18,306 patients, where they recorded very low prevalence of combination of oral and skin lichen planus compared to isolated oral lichen planus alone.

Our study also analyzed the clinical appearance of the disease. The clinical types of oral lichen planus were described by Andreasen (1968), where oral lichen planus was divided into 6 clinical types, which include reticular, papular, plaque, atrophic, ulcerative or erosive, and bullous. Desquamative gingivitis were included in the atrophic type. The clinical evaluation in our study was based on the clinical forms described by Andreasen (1968), however, for the ease of discriminatory and evaluation purpose, we have categorized desquamative gingivitis into a different group. All the clinical appearance of this disease was recorded at first visit presentations. In this study, 38.5% of subjects presented with only reticular white striations unaccompanied by other clinical types. Combinations of multiple of clinical appearance in subjects were often observed in this study, with 68% of our samples exhibits multiple clinical appearance of oral lichen planus and oral lichenoid reaction/lesions. In almost all instances, reticular appearance accompanied erythema, plaque, erosive, papular and desquamative gingivitis. When seen in terms of frequency of each clinical appearance, we observed that the most commonly encountered appearance is the reticular type. This type is present in 113 subjects out of the total of 122 subjects, which occur either in combinations or alone. The second most common presentation is erythematous appearance, which is present in 44 subjects. A large

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clinical study which involved 674 patients by Xue et al. (2005) also observed reticular type being the most commonly encountered. However, a study by Eisen (2002) found that erosive type was slightly more than reticular type. Desquamative gingivitis is a clinical sign in which the gingiva appears reddish, glaze, and friable, along with the destruction of the epithelium (Hasan, 2014). In our study, we noted that half of desquamative gingivitis were accompanied by other clinical types, such as reticular, erosive, and erythema, with reticular being the most common. Another half of desquamative gingivitis in our study were not accompanied by other types. It is important to be aware that although desquamative gingivitis is considered as a presentation of the atrophic type, it is used to describe a specific clinical symptom and is not pathognomonic of atrophic type oral lichen planus and oral lichenoid reaction/lesions (Russo et al., 2009). Desquamative gingivitis can also appear in vesiculo-ulcerative disease such as mucous membrane pemphigoid and pemphigus vulgaris (Russo et al., 2009). The clinical type that was least observed in this study was the bullous type. Bullous lichen planus is the rare variant of lichen planus. It is characterized by vesicles or bullae that develop in pre-existing lichen planus lesions (Liakopoulou & Rallis, 2017). Long term surveillance in cases of oral lichen planus revealed that exacerbations and changes in morphology were common in this disease (Eisen, 2002). For example, reticular lesions may transform into erosive type (Eisen, 2002). Also, in our study, 17 subjects presented with dental restorations adjacent to lesions. The types of restorations include metal and tooth-colored restorations.

5.3 Histopathologic evaluations

5.3.1 Epithelial components

The histological evaluation method of the subject specimens was adopted from a study by Martin H Thornhill et al. (2006) and Schiødt (1984). In this study, we observed that

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98.4% of cases were composed of parakeratinized epithelium. Only 1.6% of cases are composed of orthokeratinizing epithelium. A study by Miyamoto (1989) also shared the same observation, where the author observed that lichen planus is mainly composed of parakeratinized epithelium.

For the evaluation of thickness and configuration of the epithelium, we observed that nearly all cases in our study exhibits variable mixtures of thickness and configuration. The most commonly seen were acanthosis accompanied with hyperplasia, which was seen in 41.8% of cases. The second most common configuration were combination of acanthosis, hyperplasia, and atrophy, which comprises of 24.6% of cases. Hyperplasia in this study referred to increase of thickness of more than 1.5 times normal thickness for an area relative to the normal adjacent epithelium, excluding the stratum corneum (Schiødt, 1984; Thornhill et al., 2006). Acanthosis in this study refers to broadening of rete ridges more than two times normal thickness for area, excluding stratum corneum (Schiødt, 1984; Thornhill et al., 2006). In addition, atrophy in our study refers to reduction in thickness of more than one-third of normal area (Schiødt, 1984; Thornhill et al., 2006). A study by Mravak-Stipetić et al. (2014) demonstrated that acanthosis is commonly seen in oral lichen planus and oral lichenoid reaction/ lesions. Epithelial hyperplasia is also commonly seen in oral lichen planus (Fernández-González et al., 2011). Our findings on the occurrence of epithelial atrophy however was higher than the study by Srivani et al. (2017), where they observed that epithelial atrophy was only present in 10% of their subjects, while our study observed that epithelial atrophy was present in 26.2% of cases.

We have also evaluated direct immunofluorescence (DIF) test in this study. For our study, we noted that DIF were performed in 95 cases. Out of these cases, 76.8% showed positivity for fibrinogen at the basement membrane. This observation was in agreement with study by Buajeeb et al. (2015); Firth et al. (1990) and Kulthanan et al. (2007), where

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the observed positivity of DIF in oral lichen planus ranged between 75% to 82.9%. One particular study by Laskaris et al. (1982) however recorded 100% positivity of fibrinogen deposition along the basement membrane.

5.3.2 Connective tissue components

Other than the epithelium, the connective tissue components were also studied. One of them is the depth of inflammatory infiltrate. In the studies by Schiødt (1984) Thornhill et al. (2006), deep inflammatory infiltrate was considered as inflammatory infiltrate that is located deep to the superficial infiltrate, in some or all areas. We observed in our study that deep inflammatory infiltrate was present in 38.5% of cases, and 61.5% of cases exhibits superficial infiltrate. According to the Modified WHO diagnostic criteria of oral lichen planus and oral lichenoid reaction, presence of well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes is one of the histopathologic criteria for the diagnosis of oral lichen planus (Van der Meij & Van der Waal, 2003). This criterion was also mentioned by Cheng et al. (2016).

Majority (95.5%) of cases in our study exhibits moderate to heavy intensity of inflammatory infiltrate. In this study, moderate and heavy intensity of inflammatory infiltrate were grouped together for the ease of classifications. Heavy to moderate intensity of inflammatory infiltrate are often linked to oral lichen planus and oral lichenoid reaction/lesions, while mild infiltrate was often associated with mucous membrane pemphigoid and graft versus host disease (Cheng et al., 2016).

Perivascular infiltrate was present in 9.8% of our study samples. The presence of perivascular infiltrate is considered as one of the criteria of oral lichenoid reaction (Cheng

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et al., 2016; Ismail et al., 2007; Rice & Hamburger, 2002; Thornhill et al., 2006). However, this feature is not specific and requires clinical correlation of drug used (Müller, 2011).

Presence of eosinophils were also evaluated in this study. Eosinophils are a minority circulating granulocyte which functions to regulate local immune and inflammatory responses (Fulkerson & Rothenberg, 2013). Their accumulation in the tissue and blood is associated with several inflammatory and infectious disease (Fulkerson & Rothenberg, 2013). The presence of eosinophils is usually related to allergy, which include allergic drug eruption, urticaria, allergic contact dermatitis, atopic dermatitis, eczema. Other than that, eosinophilic infiltrate can also be present in parasitic infestations, arthropod bites, and autoimmune blistering disease such as pemphigoid (Long et al., 2016). In our study, we observed that eosinophils were present in 32% of samples. In our context, the presence of eosinophils is often linked to oral lichenoid reaction/lesions (Cheng et al., 2016; Juneja et al., 2006; Rice & Hamburger, 2002). Moreover, a study by Mravak-Stipetić et al. (2014) also documented that eosinophils were present in 62% of their oral lichenoid lesion cases.

Mast cells are immune cells of the myeloid lineage which originates from pluripotent progenitor cells of the bone marrow. These cells are found in epithelial and connective tissues throughout the body (Krystel-Whittemore et al., 2016). The cytoplasm of the mast cells contains 50-200 large granules that store inflammatory mediators such as histamine, heparin, cytokines, and neutral proteases. Mast cells regulates vasodilation, vascular homeostasis, angiogenesis, and innate and adaptive immune responses. Moreover, mast cells are also involved in the process of many diseases such as allergy, asthma, anaphylaxis, and gastrointestinal disorders (Krystel-Whittemore et al., 2016). In our study, it was observed that mast cells were present in all samples being studied. In the

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context of oral lichen planus and oral lichenoid reaction/ lesions, the role of mast cells in the pathogenesis of oral lichen planus and oral lichenoid reaction/lesions had been given tremendous attention. Mast cells are responsible for trafficking inflammatory cells into the connective tissue which in turn helps in the progression and maintenance of chronicity of oral lichen planus (Sharma et al., 2011). There had been extensive studies of mast cells expression in oral lichen planus. A study by (Juneja et al., 2006) found that the number of mast cells was significantly higher in oral lichen planus and oral lichenoid lesion compared to control. Another study by Reddy et al. (2012) observed significant increase in number of mast cells in oral lichen planus and oral lichenoid reaction compared to normal buccal mucosa. In fact, a systematic review by Vadivel et al. (2019) recorded increase in mast cells numbers in oral lichen planus compared to normal tissues. Our study results showed agreement with these past studies. In addition to the presence of mast cells, this study also observed that mast cells were mainly seen in the deeper connective tissues. Studies by Reddy et al. (2012) and Balci et al. (2015) also observed that mast cells in oral lichen planus mainly present in the deeper connective tissue.

5.4 Categories of subjects

In this study, we divided our subjects into three categories or groups, which comprised of No exposure, Drugs, and Restorations. We had separated No exposure group from Drugs and Restorations group in order to exclude the likelihood of oral lichenoid reaction/ lesions caused by drugs and dental restorations. Patients exposed to causative factors refer to the Drugs and Restorations group, and patients not exposed to causative factors refers to the No exposure group. Our study also separated Drugs and Restorations groups, this is mainly because if these two groups are mixed together, it is not possible to point out which is the causative factors.

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5.4.1 Associations between clinicopathological features and subject groups

Our study demonstrated significant association ($p<0.001$) between age of the subjects and their grouping. This study showed that subjects who were 55 years old and above were more likely to be on medications, which is in the Drugs group. This is in agreement with a Malaysian study, where Hasan et al. (2017) observed that there were high prevalence of elderly populations taking medications for cardiovascular disease and diabetes mellitus, which were 81% and 42% respectively. Moreover, it is well established that hypertension and diabetes mellitus, being the comorbidity most commonly associated in this study, were most prevalent in those aged 50 or over (Letchuman et al., 2010; Mahadir Naidu et al., 2019). Thus, this result may suggest that older age group may be more prone for oral lichenoid reaction/lesions.

This study also found association between ethnicity and subject groups ($p = 0.035$), where it was observed that there were remarkably more patients of Indian origin in the Drugs group. This finding corroborates with a Malaysian study by Wan Nazaimoon et al. (2013) which observed that diabetes was most prevalent among the Indian ethnicity. All three ethnic groups had comparable prevalence of hypertension (Naing et al., 2016) and dyslipidemia (Ambigga et al., 2016).

In our study, we observed significant association between epithelial atrophy and subject groups ($p=0.006$). Binary logistic regression test showed that Restorations group were 3.8 times more likely to have epithelial atrophy as the No exposure group. This is in agreement with a study by Schiødt (1984) which suggested that epithelial atrophy is one of the criteria favoring oral lichenoid reaction compared to typical oral lichen planus. However, a study by Thornhill et al. (2006) concluded that atrophy can be present in both oral lichen planus and oral lichenoid reaction, and is not a criterion used to distinguish oral lichen planus and oral lichenoid reaction.

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Our study found that there is a significant association between presence of eosinophils and subject groups (p=0.002). Binary logistic regression test showed that Drugs and Restorations group were 3.7 and 6.0 times respectively more likely to have the presence of eosinophils as the No exposure group. This result is in agreement with a study by Mravak-Stipetić et al. (2014) where it was observed that there were significantly more eosinophils in oral lichenoid lesion than oral lichen planus. Moreover, a study by Thornhill et al. (2006) also concluded that eosinophils were considered as discriminators of oral lichen planus and oral lichenoid reaction when tested on bivariate analysis. A study by Reddy et al. (2012) also had concluded that there was significant increase in eosinophils density in oral lichenoid mucositis compared to oral lichen planus. However, a study by (Firth et al., 1990) observed that there was no significant difference in eosinophils densities between oral lichen planus and oral lichenoid reaction. The author further suggested that presence of eosinophils in the inflammatory cell infiltrates could not be used as reliable criterion for distinction between oral lichen planus and oral lichenoid reaction.

Our study did not find significant association between positivity of fibrinogen and subject groups. The presence of fibrinogen positivity was observed across all groups. Cases with positivity for fibrinogen were mainly composed of cases from No exposure group (43.8%) and Drugs group (42.5%). Although Restorations group made up 13.7% of the cases with positivity towards fibrinogen, we observed that 10 out of 17 cases in the group yielded positive findings. This suggests that exposure to causative factors do not influence the fibrinogen positivity in a DIF test. This finding is in contrast to a study by Yamanaka et al. (2018), where it was found that positive fibrinogen yield is significantly higher in oral lichen planus compared to oral lichenoid reaction, thus suggesting DIF can be a helpful tool in differential diagnosis of oral lichen planus and oral lichenoid reaction. Also, Buajeeb et al,. (2015) found higher number of positivity for fibrinogen in oral lichen

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planus lesions with white striae than those without white striae. In contrast, Montague et al., (2015) reported positive fibrinogen DIF test in potentially malignant and malignant oral lesions including leukoplakia, verrucous carcinoma, and squamous cell carcinoma. Thus, suggesting that positivity for fibrinogen is not exclusive of oral lichen planus (Montague et al., 2015).

Although it has been mentioned by Cheng et al. (2016) that mixed and deep inflammatory infiltrate, which was described as infiltrate that extend into the deep lamina propria as a feature of oral lichenoid reaction, our study did not find significant association between depth of infiltrate and subject groups. However, our study observed that deep infiltrate is often seen more in Drugs group. Our study also did not find significant association between perivascular infiltrate and subject groups. One needs to be aware that perivascular infiltrate also can present in many diseases, such as lichen simplex chronicus, erythema multiforme, lupus erythematosus and graft versus host disease (Billings, 2019). Moreover, this study found no associations between intensity of infiltrate and subject groups.

5.4.2 Plasma cells to lymphocytes ratio

Plasma cells and lymphocytes count for all cases were performed in this study. Subsequently, plasma cells to lymphocytes ratio for each case in this study were determined. Our study also compared mean ratio of plasma cells to lymphocytes between the groups which showed that there was significant difference in the mean ratio of plasma cells to lymphocytes between the No exposure and Drugs groups, as well as between No exposure and Restorations group. There was no significant difference noted between Drugs and Restorations group. The presence of plasma cells in oral lichen planus and oral lichenoid reaction/ lesions had been described by Mravak-Stipetić et al. (2014),

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where the study observed significantly more plasma cells in oral lichenoid reaction/lesions compared to oral lichen planus.

Receiver operating curve (ROC) analysis were used to determine the discriminative value of plasma cells to lymphocytes ratio in our study. Our ROC analysis showed that plasma cells to lymphocytes ratio was able to discriminate between No exposure and Drugs group with a sensitivity of 34.6% and specificity of 92.5% (p = 0.048). However, the area under the curve is 0.612, which suggests poor accuracy in discriminating between No exposure and Drug group (Streiner & Cairney, 2007). Another ROC test was done between No exposure and Restorations group showed that plasma cells to lymphocytes ratio was also able to discriminate between No exposure and Restorations group with sensitivity of 64.7% and specificity of 69.8% (p = 0.032). However, the area under the curve for this test which is 0.674 also suggests poor accuracy in discriminating between No exposure and Restorations group (Streiner & Cairney, 2007). This may be due to our method of selecting the representative areas for plasma cells and lymphocytes count, which may neglect the areas with highest numbers of plasma cells. However, this finding is in agreement with a study by Mravak-Stipetić et al. (2014), where it was observed that there was significantly more plasma cells in oral lichenoid lesion compared to oral lichen planus. Furthermore, this finding is also shared by Bariş et al. (2014), where the authors concluded that oral lichenoid reaction related to drugs had predominantly mixed inflammatory infiltrate with presence of plasma cells, which is located deeper in the connective tissue. In addition, a study by Thornhill et al. (2006) also observed that presence of plasma cells is one of the features that discriminate between oral lichenoid reaction and oral lichen planus, where presence of plasma cells favors oral lichenoid reaction. Hence it can be postulated that the presence of high numbers of plasma cells in this study were associated with presence of drugs or medications intake and restorations adjacent to lesions.

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5.5 Limitations of study

Due to the relatively modest sample size (n=122), where the number of samples of one of the groups were only 17, the results may not fully represent the study population. Moreover, a number of cases severely lacked clinical data, rendering them unable to be included as study sample. There were some cases with missing formalin fixed paraffin embedded tissue block and histological slides.

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CHAPTER 6 : CONCLUSION

The clinical and histopathological characteristics of patients seen at the Faculty of Dentistry, University of Malaya corroborate with studies in the literature.

Significant association was observed between the presence of eosinophils and exposure to causative factors, which were consumption of medications linked to oral lichenoid reactions, and also presence of restorative materials adjacent to lesions.

The present study was able to show that there was significant difference in the plasma cells to lymphocytes ratio between subjects exposed to causative factors and those who were not. In addition, this study demonstrated higher plasma cells to lymphocytes ratio in patients exposed to causative factors than those who were not.

These findings strongly support the role of causative factors, mainly the drugs and dental restorative materials in the etiology of oral lichenoid reactions/ lesions, although it is difficult to pinpoint. Thus, in clinical settings, together with proper history and clinical findings, these features may facilitate clinicians in planning appropriate management for patients.

We recommend a clinicopathological study of oral lichen planus and oral lichenoid reaction/ lesions with a larger cohort involving multiple centers to obtain larger sample size and results that is more representative of the national populations.

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