ORIGINAL ARTICLE

Cellular and Architectural Differentiation between Oral Lichen Planus and Oral Lichenoid Reaction

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ABSTRACT

Introduction: Oral lichen planus (OLP) and oral lichenoid reaction (OLR) are two very similar diseases clinically and histopathology. OLP is a chronic systemic disease of established immune-mediated pathogenesis while OLR is considered a variant of OLP caused by the presence of medication or dental materials or a manifestation of diseases. To date, there's no agreement on the microscopic diagnosis of OLR and OLP. **Materials and methods:** 20 slides (n=12 OLP cases and n=8 OLR cases) were observed under digital or conventional light microscope for mast cell and eosinophils counting and architectural characteristics of the specimens. Clinical parameters were retrieved from patients' medical files. **Results:** Clinically, patients with OLP significantly presented with bilateral lesions against the unilateral OLR (p=0.000) in Fisher's exact test. Architecturally, Fisher's exact test showed the presence of irregular rete ridges was more prominent in OLP (p=0.042). Cellularly, the Mann-U Whitney test showed a significant difference in the number of mast cell counts (p=0.047) between OLP and OLR which is higher in OLP. No significant difference was noted in the eosinophil count. **Conclusion:** Mast cells count, and certain architectural patterns can be used as histological parameters to differentiate OLP from OLR.

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Keywords: oral lichen planus; oral lichenoid reaction; histopathology; mast cells; eosinophils.

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INTRODUCTION

Oral lichen planus (OLP) is a chronic systemic disease of unknown etiology (1, 2). It commonly involves the mucosa of the oral cavity but can also comprise other sites like skin, vulvar and vaginal mucosa, glans of the penis, scalp, and nails (1). OLP is a relatively uncommon mucosal disease in Malaysia, affecting 0.38% of the population (3). While a recent systematic review stated that in the general population, the estimated pooled prevalence of OLP was 0.89%, and in clinical patients it was 0.98%. OLP was shown to be more prevalent in non-Asian nations, in women, and in people aged 40 and over (1, 4). Roopashree et al. review discussed the numerous theories put up for the pathophysiology of OLP (2). It is thought to involve both antigen-specific and non-specific processes. Basal keratinocytes present the antigen in OLP, and CD8(+) cytotoxic T lymphocytes destroy keratinocytes specifically in response to the antigen. The non-specific processes include mast cells degranulation and matrix metalloproteinase activation that contribute to this lesion. These processes might interact to result in keratinocyte apoptosis in OLP, basement membrane rupture, intraepithelial T cell migration, and T cell accumulation in the superficial lamina propria (2, 5, 6).

Intraoral clinical presentation of OLP usually presents with symmetrical and bilateral white striae which commonly affects the buccal mucosa, followed by the tongue, gingiva, vestibulum, or multiple lesions at once but manifestation on the palate is rare (7). There are six intraoral manifestations of OLP which are reticular, papular, plaque-like, erosive, atrophic, and bullous type

(8). In addition, OLP is characteristically symmetrical in position and usually with the presence of cutaneous lesions (9). Skin lesions will appear in 5% of OLP patients. Forearm flexors are the most typical lesion sites, followed by the legs, back, and chest. These lesions, known as Wickham's striae, are polygonal, violaceous, flat-topped, erythematous papules that typically appear months after the oral lesions (10, 11).

The first histopathological criterias of OLP were proposed by the World Health Organisation (WHO) in 1978 (12), which then undergone significant changes over the years. Initially, OLP described as exhibiting thickened ortho- or parakeratinised epithelium, liquefaction generation or necrosis of the basal cell layer, well-defined juxta epithelial lymphocytic infiltration and Civatte bodies at the basal of the epithelium and lamina propria regions (12). Later, Van der Meiji et al. (13) made a modification as in Table I. The most recent description was by the American Academy of Oral and Maxillofacial Pathology in 2016 which explained the OLP as comprising a band-like or patchy lymphocytic infiltrate in the epithelium-lamina propria interface, basal cell liquefactive degeneration, lymphocytic exocytosis, absence of epithelial dysplasia and absence of verrucous epithelial architectural change (14). Fig. 1 depicted our findings for diagnosis of OLP.

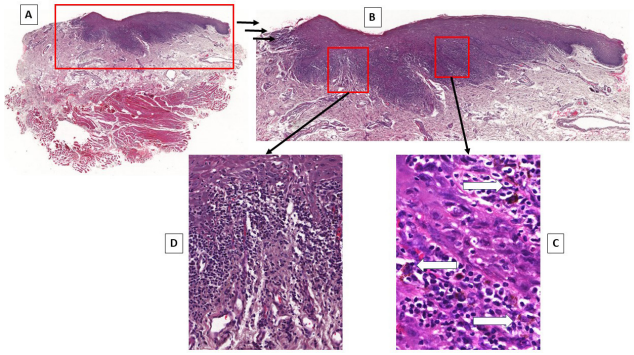

Figure 1: Histopathological features of a case of OLP/OLR. H&E slide from the archive showing (A) parakeratinized stratified squamous epithelium surfaced the fibrofatty connective tissue stroma. The deeper structure consists of skeletal muscle fibres within a fibrous connective tissue. (B) Higher magnification of the epithelium exhibiting a prominent 'saw-tooth' appearance of rete ridges and a band-like subepithelial lymphocytic infiltration. (C) Subepithelial (white arrow) showing pigmentary incontinence. (D) is showing an area of liquefactive degeneration of the basal region. (H&E staining; objective magnification 4 to 20x).

Oral lichenoid reaction (OLR) is a lesion considered as a variant to OLP which is caused by the presence of medication or dental materials or even a manifestation of other diseases such as lupus erythematosus or graft-vs-host disease. It has been associated with numerous commonly used drugs such as beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antihypertensives, diuretics and antimalarials (15).

The typical sites for OLR include lateral borders of the tongue, buccal mucosa, and any oral mucosa that have direct contact with dental restorations (amalgam or composite) or another offending contact agent such as cinnamon (16). The atypical localization against the causal factor and the unilateral positioning for the oral lichenoid reaction were thought to be its characteristics (17).

Microscopic diagnosis of OLP and OLR lacks consensus. They also exhibit some clinical similarities thus difficult to differentiate (18). Example of variable histopathological features include differences in the secretion of mast cells as well as the mixed inflammatory infiltration including plasma cells, neutrophils, and eosinophils between OLP and OLR, but the findings were inconsistent (14, 19-21).

MATERIALS AND METHODS

Study Design and Population

This is a retrospective observational study of patients' clinical files and respective specimen slides. Data of these subjects were collected from November 2020 to March 2021. All HPE slides were examined, and the diagnoses were verified by two oral pathologists (the corresponding author – NI and co-author - ZMZ).

Data Collection and Quality Assurance

The Hematoxylin and Eosin (H&E) slides were collected from the archives of the Oral Pathology Laboratory, Faculty of Dentistry, National University of Malaysia, and the University of Malaya. Clinical parameters of the respected patients include gender, age, chief complaint, past medical history, habits (alcohol and cigarette smoking), uni/bilateral lesion, and clinical appearance of the lesions, were retrieved from their medical records.

Cellular counts and architecture patterns were assessed where for cellular counts, the number of mast cells and the number of eosinophils were counted. As for the architecture, the diffuse infiltration of lymphocytes, presence of saw-tooth appearance, presence of irregularity of the rete ridge, presence of liquefactive degeneration and pigmentary incontinence of each sample were evaluated. Initially, these slides were observed using a light microscope under low magnification (10x objective magnification) for architecture observation of both the pattern of the epithelium and the lamina propria region. Then at higher magnification (40x objective magnification) cellular counting was done to include 10 high power fields (hpf) chosen randomly.

Inter-examiner observation was done between the two students and the two oral pathologists with kappa value of 88.3% for mast cell and 82.7% for eosinophils count. While for the architectural pattern, four of the researchers were sitting together to get the consensus.

Inclusion Criteria and Exclusion Criteria

Inclusion criteria include lesions diagnosed as OLP and/or OLR with complete information on social history, clinical appearance, location, and symptoms. Exclusion criteria comprise dysplastic changes seen in the samples and incomplete clinical information.

Sample Size

Accordingly, 20 subjects with the clinical diagnosis of OLP (n=12) and OLR (n=8) based on the modified WHO diagnostic criteria of OLP and OLR (Table 1) (13), satisfied the inclusion criteria and were included in the study. An online calculation of G*Power software was used for sample size estimation and based on a study by Balci and Ercin 2016 (5), for statistical test between two independent means (two groups). An α value was set as 0.05; the value of β was considered as 0.4 and the effect size was 0.8 in the formula. The required sample size for the OLP group and OLR group was 11, respectively, with the total sample size of 22. Hence, this study almost fulfilled the sample size requirement.

Table I: WHO clinical and histological modified diagnostic criteria of OLP and OLR.

Clinical criteria
1) Presence of bilateral, more or less symmetrical lesions
2) Presence of a lacelike network of slightly raised gray-white lines (reticular pattern)
3) Erosive, atrophic, bullous and plaque-type lesions are accepted only as a subtype in the presence of reticular lesions elsewhere in the oral mucosa. In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term ''clinically compatible with'' should be used.
Histopathologic criteria
1) Presence of a well-defined band like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
2) Signs of liquefaction degeneration in the basal cell layer
3) Absence of epithelial dysplasia
**When the histopathologic features are less obvious, the term ''histopathologically compatible with'' should be used
**Final diagnosis criteria OLP or OLR
- OLP – a diagnosis of OLP requires fulfillment of both clinical and histopathologic criteria
- OLR – the term OLR will be used under the following conditions:
(1) Clinically typical of OLP but histopathologically only compatible with OLP
(2) Histopathologically typical of OLP but clinically only compatible with OLP
(3) Clinically compatible with OLP and histopathologically compatible OLP

WHO: World Health Organization; OLP: oral lichen planus; OLR: oral lichenoid lesion

Statistical Analysis

Descriptive statistics for the clinical data were calculated using frequencies. Fisher's exact test was used for the small sample size and analytical statistics was used for the counts of mast cells and eosinophils. Additionally, the Mann-Whitney U test was used since it was a non-parametric test with only two groups (OLP and OLR). All the differences in which the value of P was less than or equal to 0.05 were considered statistically significant.

Ethical Considerations

This study was approved by the Research Ethics Committee, the National University of Malaysia, reference number UKM PPI/111/8/JEP-2020-496.

RESULTS

Fisher's exact test was used for the analysis of socio-clinical feature distributions between OLP and OLR. In Table II, patients with OLP significantly presented with bilateral lesions (p=0.000) against the unilateral OLR. OLP and OLR lesions were not statistically related to gender, age, chief complaint, past medical history, social history, and clinical appearance. However, Chi-square tests were also conducted within the dependent variables but without predetermined diagnosis of the two oral conditions where they showed significant differences for age (p=0.000), chief complaints of burning sensations (p=0.002) and social history with

Table II: Socio-clinical feature distributions between OLP and OLR.

Socio-clinical variable	OLP (n=12)	OLR (n=8)	p-Value (Fisher's Exact test)
Gender			
Male	5 (41.7%)	3 (37.5%)	p=1.000
Female	7 (58.3%)	5 (62.5%)	
Age			
Below 40	1 (8.3%)	1 (12.5%)	p=1.000
Above 40	11 (91.7%)	7 (87.5%)	
Chief Complaint			
Painless	2 (16.7%)	1 (12.5%)	p=1.000
Burning sensation	10 (83.3%)	7 (87.5%)	
Past Medical History			
Patient without medication	7 (58.3%)	6 (75%)	p=0.642
Patient on medication	5 (41.7%)	2 (25%)	
Risk Factor			
No Risk Factor	11 (91.7%)	7 (87.5%)	p=1.000
With Risk Factor	1 (8.3%)	1 (12.5%)	
Uni/bilateral Lesion			
Bilateral	12 (100%)	0	p=0.000
Unilateral	0	8 (100%)	
Clinical Appearance			
Red Lesion	4 (33.3%)	2 (25%)	p=1.000
White Lesion	8 (66.7%)	6 (75%)	

OLP: oral lichen planus; OLR: oral lichenoid reaction

risk factors (p=0.000). Histopathological aspects based on Fisher's exact test showed that there was significant difference in the presence of irregular rete ridges (p=0.042) in which it is more predominantly presence in OLP. Cellular presentation of the lesions shown in Fig. 2. We displayed that there was a significant difference in the number of mast cell counts (p=0.047) between OLP and OLR with a mean of 6.92 cells in OLP (Table III). In addition, the Mann–Whitney U test showed that there was no significant difference in the number of eosinophils between OLP and OLR.

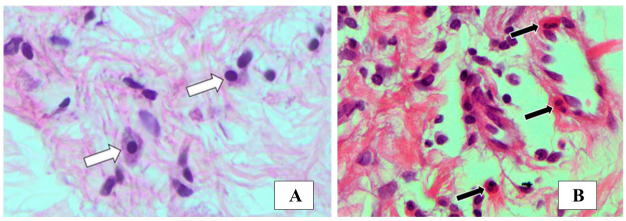

Figure 2: A high magnification of mast cells and eosinophils presentation in OLP/OLR. Mast cells (white arrows) are found within the lamina propria of loose fibrous connective tissue, and they are surrounded by lymphocytes (A). Mast cell is a large cell (15-30 µm) with rounded nuclear and the cytoplasmic granules partially obscure the nucleus while the cell border appears uneven (H&E staining; objective magnification 40x). Eosinophils exhibited bilobed nucleus and appears 'brick-red' in color due to acidophilic granules (black arrows) (B). They are usually found in the deeper section of the lamina propria, often near the skeletal muscle fibers. These cells are 12-17 µm in diameter. (H&E staining; objective magnification 20x).

Table III: Statistical analysis of histopathological features associated with OLP and OLR.

Histopathological Variable	OLP (n=12)	OLR (n=8)	p-value
Diffuse Infiltration			
Yes	6(50%)	3 (37.5%)	Fisher's Exact Test p=0.670
No	6(50%)	5 (62.5%)	
Saw Tooth Rete Pegs			
Yes	5 (41.7%)	2 (25.0%)	Fisher's Exact Test p=0.642
No	7 (58.3%)	6 (75.0%)	
Irregular Rete Ridge			
Yes	6 (50%)	0	Fisher's Exact Test p=0.042
No	6 (50%)	8 (100%)	
Liquefactive Degeneration			
Yes	5 (41.7%)	5 (62.5%)	Fisher's Exact Test p=0.650
No	7 (58.3%)	3 (37.5%)	
Pigmentary Incontinence			
Yes	9 (75.0%)	4 (50%)	Fisher's Exact Test p=0.356
No	3 (25%)	4 (50%)	
Mast cells			
Mean value	6.92	2.5	Mann-Whitney U Test p= 0.047
Eosinophils			
Mean Value	2.75	4.5	Mann-Whitney U Test p= 0.980

OLP: oral lichen planus; OLR: oral lichenoid reaction

DISCUSSION

The oral mucous membranes can be affected by oral lichen planus and oral lichenoid responses, two recurrent, chronic inflammatory mucocutaneous diseases that can occur with or without skin lesions. Both disorders' aetiology is still an anonymity. Additionally, because these lesions are so similar, it is challenging to distinguish between them histopathologically and clinically. OLP and OLR can only be diagnosed to a limited extent using immunohistochemistry (IHC). However, IHC plays a significant role in deciphering pathophysiology and predicting a malignant development in a certain lesion. Aisha AH Al-Jamaei et al. in a systematic review found that there are several levels of heterogeneity and few high-caliber research (22). The most often reported proteins were p53, Bcl-2 and Ki-67, though there were disagreements. In addition, PCNA and P21 were found to be potential predictive indicators for assessing the risk of OLP malignancy, although they still need to be further validated (22).

Like IHC, the direct immunofluorescence (DIF) assay alone cannot be regarded as sufficient evidence for OLP, and OLR differentiation (23). Both OLP and OLR had fibrinogen accumulated at the basement membrane zone, although the fluorescence in the OLR was either less intense (24) or show no difference (25).

In our research we can conclude that OLP and OLR were predominant in females and above 40 years old which is concurrent with other findings (14, 26). However, younger patients in their 30s were not uncommon (14). It is rare to see OLP among the children, but a recent report (14) described 316 pediatric patients with OLP. Interestingly, a slight male predominance was noted in pediatric OLP cases. Approximately two-thirds of patients with OLP experience discomfort with variable intensity and expressed in some cases only upon contact with spicy or acidic food (14).

Smoking and alcohol consumption were risk factors that helped to improve distinction between the OLP and OLR (27). However, this was not true in our finding. There was no significant difference in either OLP and OLR patients, with or without these factors.

On different note, without predetermination of the clinical diagnosis using the WHO diagnostic criteria (13), both OLP and OLR in our study did show significant differences from the normal oral mucosa, which were influenced by the patient's risk factors of habit, age, and presence of burning sensation.

Among our 20 patients, 85% of them complained of burning sensation at the site of the lesion, in contrast to a Malaysian study (3) which showed that the onset of OLP in many patients are insidious and some patients are unaware of their oral condition. Asymptomatic

lesion makes them unaware of their oral lesion and they do not seek treatment because most of them were symptomatic dental attendees. There is a need to do a national study on the Malaysian patients with OLP/OLR since the findings were inconsistent. In a study by Javier Alberdi-Navarro et al. only 1.8% out of total 217 patients with OLP/OLR presented with burning sensation (28). Malaysian study showed a few clinical features suggestive of OLR to include the preference location on the palate and presence of unilateral white striae and erosions (3).

Other studies proposed some clinical differentiations for example the atypical localization against the causal factor and unilateral positioning for the lichenoid reaction, symmetrical positioning, and presence of cutaneous lesions in case of lichen planus (16, 18, 20, 29). There are six types of clinical appearances (8) indicate that the whitish lesions such as the reticular, papular and plaque-like lesions are considered to have lower tendency of malignant transformation compared to the reddish lesions like the erosive, atrophic, and bullous type. Moreover, OLP usually appears on the buccal mucosa bilaterally and symmetrically, then on the tongue, gingiva, vestibulum, or multiple lesions and manifestation on the palate is rare. The reticular pattern is the most common type which presents as Wickham's striae (fine white striae) and often asymptomatic. The article also mentioned that OLR is always described as having the same clinical features as OLP. However, there are a few clinical features suggestive of OLR including the atypical sites, unilaterality, and erosions, although only a few data to support this possibility. The diagnosis of OLR is done by excluding the 'idiopathic OLP' because the causes of most of the cases in OLR cannot be identified (3, 7, 16).

Medications such as non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensive drugs, anti-malarial drugs, angiotensin-converting enzyme inhibitors, diuretics, oral hypoglycemic agents, penicillamine and beta-blockers and antiretroviral drugs have been reported to have an association with oral lichenoid reactions (3, 15). Comparably, in our research, 25% of OLP patients who have bilateral and symmetrical white striae were on medication for hypertension, dyslipidemia, idiopathic heart disease and diabetes mellitus. A larger sample size may show association with the type of diseases and medications taken by the patients.

OLR can be differentiated from OLP by using the Modified WHO diagnostic criteria of OLP and OLR (2003) (13) in Table 1. However, detailed criteria were not given for OLR, and it was diagnosed if it is "only compatible" either clinically or histopathologically with OLP. Hence, there is an uncertainty about diagnostic histological differences between OLR and OLR (27).
Consistent with our findings, histological differentiations observed for OLP were thickened epithelium, liquefaction degeneration or necrosis basal cell layer, well-defined juxta epithelial lymphocytic infiltration, and presence of Civatte bodies in basal epithelium and lamina propria (7, 8, 15, 16, 29). Current findings by Suzuki, 2021 revealed that melanin pigment and melanophores are scattered in OLP; but in OLR only mixed inflammatory cells are infiltrated, but no melanophores. Additionally, they found no basal cells were noted in the prominent area in OLP (30).

Previous studies have shown that antigen-specific and nonspecific underlying mechanisms of basal cell apoptosis and destruction of basal lamina in OLP and OLR have been shown to be responsible for the recruitment of T-cells to the lesion sites (5, 6).

Our study was focusing on the nonspecific mechanism of the mast cells and eosinophils. Our results showed that the number of mast cells counted in OLP was significantly higher than in OLR, which was consistent to a study by Ramalingam S et al. (2018) (6, 20). Mast cells may have assisted in attracting T lymphocytes to subepithelial infiltration, which has been linked to an increase in the total mast cell count in OLP as they have the capacity to affect the permeability of the endothelium. This process was done through the release of mast cell derived mediators, especially mast cell proteases (6). Inconsistent findings were noted regarding the presence of degranulation of the mast cells in OLP/OLR (31, 32).

There could be a functional connection between the number of mast cells and eosinophils. However, focusing studies on this matter are scarce. When mast cells are activated, a late-phase response begins, drawing eosinophils and other inflammatory cells from the blood circulation to the inflamed site. Tryptase and chymase are two mast cell-specific granule mediators, can promote eosinophil activation and degranulation (33). Additionally, infiltrating eosinophils have been found near mast cells in allergic inflamed tissues as well as in several other conditions, such as pemphigoid (34) and cancer (35). Nevertheless, our study did not prove that both mast cells and eosinophils count rise together in the OLP/OLR lesions. If a higher sample size is used, there can be a statistically significant difference in these cells' densities.

The architecture observed in all 20 slides to include the presence of diffuse infiltration of lymphocytes, presence of irregularity of rete ridge, presence of saw-tooth shaped rete pegs, presence of liquefactive degeneration and pigmentary incontinence.

Our study includes the architectural evaluation of the presence of diffuse lymphocytic infiltration, irregularity of rete ridges, the saw-tooth appearance of rete pegs, and the presence of liquefactive degeneration. Conversely, there was no significant difference in these architectural

features except for the presence of irregular rete ridges. Irregular rete ridges were observed to have an equal possibility of being present or absent in OLP, while in OLR they are absent. In addition to the architecture of the epithelium, a study stated that among the main histopathological features typical of a lichenoid reaction is the absence of liquefactive necrosis in the basal layer (36). In another study, it was stated that this basal liquefaction degeneration was more prominent in OLP (37). Consistent with our finding, a Malaysian study (3) showed that the "saw-tooth" appearance of the rete pegs was not routinely observed in OLP/OLR lesion, unlike other studies (38). To come to a point, the pattern of the epithelial rete ridges and the degeneration of the basal cell region were unhelpful in differentiating between OLP and OLR.

This study was conducted by two elective undergraduate students who had limited time to perform large-scale research. Consequently, the sample collection period was restricted to November 2020 to March 2021, leading to a small sample size. It was challenging to train inexperienced undergraduate students to use a microscope and to identify microscopic structures, such as cells and other relevant features within a limited time. In addition, the use of old slides with faded microscopic features made it difficult to visualize the structures clearly, and the re-staining process was both labour-intensive and time-consuming.

CONCLUSION

Our study suggested that some histological criteria are crucial for distinguishing between OLP and OLR. The mast cells count, and the pattern of the rete ridges are two microscopic features that may help the diagnosis. Differentiating OLP from OLR is important for better implementation of treatment strategies.

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