Histopathology of oral lichen planus and oral lichenoid lesions: An exploratory cross-sectional study

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Abstract

Objective: To better characterize the histopathology of oral lichen planus and oral lichenoid lesions and to highlight the differences between them in order to support the clinician in the diagnostic and therapeutic management of such conditions.

Subjects and Methods: Fifty-five patients, clinically diagnosed with oral lichen planus ($n = 25$) or oral lichenoid lesions ($n = 30$), were consecutively enrolled in the present study. Subsequently, one blind pathologist reviewed all the biopsy specimens of enrolled subjects following a specific protocol to provide a detailed histopathological description. Demographic, anamnestic, and clinical data were also recorded from all the participants. Patients' data were analysed and compared using the chi-squared test, to provide distinguishing features between the studied conditions.

Results: We found a higher and statistically significant number of eosinophils in the oral lichenoid lesions compared with the oral lichen planus group ($p < 0.01$), an equally promising result was seen regarding plasma cells, which were more represented ($p = 0.05$) in the oral lichenoid lesions than in the oral lichen planus cases. No statistically significant differences were detected in demographic, anamnestic and clinical data.

Conclusion: A mixed lichenoid inflammatory infiltrate, consisting of eosinophils and plasma cells, could be used as reliable histological features for the diagnosis of oral lichenoid lesions, as long as compared with findings obtained from the patients' history and clinical examination.

KEYWORDS
eosinophils, histopathology, oral lichen planus, oral lichenoid lesion, plasma cells

1 | INTRODUCTION

Oral lichen planus (OLP) is a chronic, non-infectious, inflammatory condition affecting the oral mucosa, characterized by T-cell mediated immunological dysfunction leading to basal keratinocyte destruction (Lodi et al., 2005). The initial event conducing to T-cell activation and OLP lesion formation is thought to be the expression or unmasking of a basal cell antigen induced by a single (or multiple) initiating factor in genetically susceptible patients (Kurago, 2016). However, both the target antigen and the trigger(s) driving this immune response have not yet been fully identified. A number of potential exogenous triggers have been proposed, including systemic drugs, dental restoration materials, flavouring agents, viral infection and mechanical trauma (Koebner phenomenon) (Van Der Waal, 2009; Rotaru et al., 2020; Schmidt-Westhausen, 2020).

The term 'oral lichenoid lesions' (OLLs) is usually adopted by the scientific community to describe those lesions in which the association with a specific trigger(s) or systemic condition is known (or suspected). The spectrum of OLLs includes 'oral lichenoid contact lesions' (OLCLs), 'oral lichenoid drug reactions' (OLDRs), and the

ones associated with Graft versus Host Disease (GvHD) or Discoid/Systemic Lupus Erythematosus (DLE/SLE). On the other hand, when the causative factor cannot be identified and the condition is idiopathic, the denomination 'oral lichen planus' (OLP) is usually considered the more suitable diagnosis, following clinical and histopathological criteria (Carrozzo et al., 2019).

There has always been a considerable ambiguity on whether to consider OLP and OLLs as two separate entities with a common pathway of tissue reaction or as the same condition triggered by different possible agents or systemic conditions. At present, most experts tend to consider OLP and OLLs as two distinct conditions sharing some clinical, histopathological and immunological overlapping features (Burket et al., 2014; Van der Meij & Van der Waal, 2003). However, when these overlapping features are too numerous, a differential diagnosis between these conditions can be challenging to achieve (Müller, 2011). From a histological perspective, some authors even consider the two conditions indistinguishable (Van Der Waal, 2009; Burket et al., 2014; Woo, 2014). Nevertheless, data from the literature indicates that some histological clues might sometimes favour one diagnosis over the other. For example, a more diffuse and deeper mixed inflammatory infiltrate containing conspicuous eosinophils and/or plasma cells, focal parakeratosis and a higher number of Civatte bodies have been described as distinctive features of OLLs (McCartan, & McCreary, 1997; Mravak-Stipetić et al., 2014; Thornhill et al., 2006). However, definitive and validated histopathological criteria to differentiate these conditions are still lacking (Sugerman et al., 2000). The present study aims at better characterizing the histopathology of OLP and OLLs and at highlighting the differences between them in order to support the clinicians in the diagnostic and therapeutic management of such conditions.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study was conducted on Caucasian patients over 18 years clinically diagnosed with OLP or OLLs at the Oral Medicine and Pathology Unit, Department of Medical, Surgical and Health Sciences, at the University of Trieste between October 2018 and September 2020. Clinical diagnosis was achieved according to the modified WHO diagnostic criteria proposed by Van der Meij and van der Waal (2003). Specifically, participants were suspected of having OLP if they had bilateral white reticular patches on either the buccal mucosa and/or the tongue, regardless of whether erythema and ulcers were present; gingival involvement was also considered. Patients were clinically considered to have OLLs if one or more Van der Waals criteria were missing. All patients underwent an oral mucosal biopsy to confirm the clinical diagnosis.

Subsequently, one experienced pathologist, who was blinded to the patients' clinical diagnoses, analysed all samples and filled a specific protocol (Table 1) to assess the detailed histopathological features of both conditions with extensive analysis. The protocol was designed using those histological findings that, based on the literature, might favour the diagnosis of OLLs over OLP and vice versa (Al-Hashimi et al., 2007; Müller, 2011; Van Der Waal, 2009). Histopathological confirmation of OLP or OLL diagnosis, always using the criteria proposed by Van der Meij and van der Waal, was the fundamental entry criterion. Hence, a final OLP diagnosis was considered only if the patient fulfilled all clinical and histopathological criteria. When one or more clinical and/or histopathologic criteria were lacking, the patients were considered an OLL case.

Patients' demographic (age and gender), anamnestic (systemic diseases and current medication/s intake) and clinical data (clinical pattern, location, and distribution of the lesions) were obtained from the official database currently employed at the Oral Medicine and Pathology Unit. Regarding anamnestic information, particular attention was focused on systemic diseases (hypertension, diabetes, hypothyroidism and hepatitis C) and medications (antihypertensive agents, oral hypoglycaemic drugs, antianxiety/psychotropic agents, sulfasalazine, levothyroxine, anticonvulsants, nonsteroidal anti-inflammatory drugs and antibiotics), which are commonly associated with OLLs (McCartan, & McCreary, 1997). Smokers, heavy alcohol consumers and patients who had received steroid therapy (topical or systemic) within the previous month were excluded from the study.

The presence of concomitant cutaneous lesions was registered both in Lichen Planus (LP) and Lichenoid Lesions (LLs) patients. Patients' oral lesions were clinically classified as papular, reticular, plaque-like, erythematous or ulcerative, based on the most predominant clinical pattern. Topographically, the lesions were grouped into four categories: buccal mucosa, tongue, gingiva and palate.

All the patients had provided written informed consent for the analysis of their medical records. The study was approved by the ethical committee of the University of Trieste, Italy (Decreto rettorale n. 846/2017 dd. 24.11.2017, verbale n.107, adunanza 21/09/2020).

2.2 | Statistical analysis

A descriptive statistical analysis was performed, presenting the qualitative variables as frequencies and percentages, and the quantitative as mean ± standard deviation (SD). Demographic, anamnestic, clinical and histological variables were compared between patients with OLP and OLLs to identify associations between the different parameters and diagnoses. The chi-squared test was used in the analysis and a p-value < 0.05 was regarded as statistically significant. The statistical analysis was performed using the R Statistical Software (version 3.1.0, 2014).

3 | RESULTS

Between October 2018 and September 2020, 55 consecutive patients were included in the present study. Patients' baseline demographics and clinical features are presented in Table 2a and b.

TABLE 1 Study protocol for histopathological examination

Parakeratosis				
☐ Absent	☐ Focal	☐ Multifocal	☐ Diffuse	
Orthokeratosis				
☐ Absent	☐ Focal	☐ Multifocal	☐ Diffuse	
Epithelial hyperplasia				
Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Quantitative evaluation				
☐ Absent	☐ Focal	☐ Multifocal	☐ Diffuse	
Acanthosis				
☐ Absent	☐ Focal	☐ Multifocal	☐ Diffuse	
Epithelial atrophy				
Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Quantitative evaluation				
☐ Absent	☐ Focal	☐ Multifocal	☐ Diffuse	
Spongiosis				
☐ Absent	☐ Focal	☐ Multifocal	☐ Diffuse	
Subepithelial cleft				
☐ Absent	☐ Focal	☐ Multifocal	☐ Diffuse	
Increased basal membrane				
☐ Present	☐ Absent			
Basal cell degeneration				
☐ Present	☐ Absent			
Fibrosis				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Lymphocytic inflammatory infiltrate				
Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Distribution				
☐ Interface	☐ Supra-basal	☐ Epithelium	☐ Superficial lamina propria	☐ Deep lamina propria
Lymphocytic exocytosis				
Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Distribution				
☐ Interface	☐ Supra-basal	☐ Epithelium	☐ Superficial lamina propria	☐ Deep lamina propria
Band-like inflammatory infiltrate				
☐ Present	☐ Absent			
Neutrophilic exocytosis				
☐ Present	☐ Absent			
Eosinophils				
Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Distribution				
☐ Interface	☐ Supra-basal	☐ Epithelium	☐ Superficial lamina propria	☐ Deep lamina propria
Colloid bodies				

(Continues)

TABLE 1 (Continued)

Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Distribution				
☐ Interface	☐ Supra-basal	☐ Epithelium	☐ Superficial lamina propria	☐ Deep lamina propria
Plasma cells				
Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Distribution				
☐ Interface	☐ Supra-basal	☐ Epithelium	☐ Superficial lamina propria	☐ Deep lamina propria
Mast cells				
Qualitative evaluation				
☐ Absent	☐ Mild	☐ Moderate	☐ Severe	
Distribution				
☐ Interface	☐ Supra-basal	☐ Epithelium	☐ Superficial lamina propria	☐ Deep lamina propria
A perivascular pattern of the inflammatory infiltrate				
☐ Present	☐ Absent			
Diffuse lymphocytes				
☐ Present	☐ Absent			

The two groups were balanced with respect to age, gender, clinical pattern, location and distribution of the lesions. The mean age for the OLP and OLLs group was 59.7 ± 17.3 (range 25–85) and 64.6 ± 13.7 years (range 34–86) respectively. The gender distribution at baseline was similar in the two groups; a total of 10 men (40.0%) and 15 (60.0%) women were diagnosed with OLP ($n = 25$), and 13 men (43.3%) and 17 (56.7%) women with OLLs ($n = 30$). The buccal mucosa was the most commonly involved site in over half of the patients in both groups. Gingival involvement was more frequent in OLLs (Figure 1a) than in OLP cases (16.6% vs. 4.0%). When considering the clinical pattern, reticular lesions were reported in 19 (76.0%) and 17 (56.7%) patients in the OLP and OLLs groups respectively (Figure 1b and c). The ulcerative pattern appeared to be more frequently observed in OLLs (Figure 1d) than in OLP cases (23.3% vs. 8.0%). Since being an essential diagnostic criterion of OLP, 100% of OLP cases showed a bilateral distribution of the lesions. Among patients with OLLs, 10 (33.3%) exhibited lesions distributed unilaterally instead. No significant differences were detected between the two groups in terms of all the variables listed above.

The distribution of patients' systemic disease and current medications are listed in Table 3. Hypertension was the most frequent systemic condition affecting both the OLP and OLLs patients (36.0% vs. 40.0%), followed by hypothyroidism (24.0% vs. 20.0%) and diabetes (16.0% vs. 6.7%). Only a single case of C hepatitis was reported in the OLP group. Cutaneous involvements were reported in 4 (16.0%) and 5 (16.6%) patients with OLP and OLLs respectively.

Antihypertensives were the most commonly used class of drugs in both the OLP and OLLs groups (36.0% vs. 40.0%). The second and third most frequent medications taken by the two groups were levothyroxine and antianxiety/psychotropic agents. No statistically significant differences were detected in terms of systemic diseases' and current medication intake's distribution.

Concerning the histological features (Figure 2), the presence and distribution of parakeratosis, orthokeratosis, spongiosis and epithelial hyperplasia were similar between the two groups. However, focal parakeratosis and epithelial hyperplasia appeared to be more frequently observed in OLP than in OLLs cases (40.0% vs. 16.7% and 36.0% vs. 13.3% respectively). Acanthosis and epithelial atrophy were seen slightly more in the OLLs compared with OLP cases (46.7% vs. 20.0% and 70.0% vs. 48.0% respectively). Subepithelial clefting was found in 8 (26.7%) and 3 (12.0%) patients in the OLLs and OLP groups respectively. Fibrosis was seen in all patients with OLLs and in 22 (88.0%) OLP cases. The thickening of the basement membrane zone was more frequently seen in OLP than in OLLs cases (16.6% vs. 4.0%). All patients with OLP showed basal cell layer liquefactive degeneration and a band-like lymphocytic inflammatory infiltrate at the epithelium-lamina propria interface. Among OLLs patients, 20 (66.7%) exhibited hydropic degeneration of the basal cell layer and all presented a lymphocytic inflammatory infiltrate, of which 53.3% ($n = 16$) having a band-like pattern. The lymphocytic inflammatory infiltrates in OLLs patients were more diffuse and extended more deeply in the lamina propria (Figure 3a) as compared to OLP cases (Figure 3b). Sawtooth rete ridges were found in 17 (26.7%) and 16 (12.0%) patients in the OLLs and OLP groups respectively. A perivascular pattern of the lichenoid infiltrate was found in 8 patients in OLP and OLLs groups respectively (32.0% vs. 26%) (Figure 3c).

Eosinophils were present in 5 (20.0%) and 17 (56.7%) patients with OLP and OLLs respectively. The number of eosinophils was

TABLE 2 Baseline demographics and clinical characteristics

(a)			
Variable	**OLP group ($n = 25$)**	**OLLs group ($n = 30$)**	***p*-value (< 0.05)**
Mean age ± SD (years)	59.7 ± 17.3	64.6 ± 13.7	0.2463*
Sex – *n*. (%)			
Female	15 (60.0)	17 (56.7)	0.8066
Male	10 (40.0)	13 (43.3)	0.8066
Location of biopsy– *n*. (%)			
Buccal mucosa	21 (84.0)	21 (70.0)	0.2279
Tongue	1 (4.0)	1 (3.3)	0.8909
Gingiva	1 (4.0)	5 (16.7)	0.1364
Palate	2 (8.0)	3 (10.0)	0.7991
Clinical pattern – *n*. (%)			
Papular	0	0	
Reticular	19 (76.0)	17 (56.7)	0.1375
Plaque-like	3 (12.0)	3 (10.0)	0.8144
Erythematous	1 (4.0)	3 (10.0)	0.3979
Ulcerative	2 (8.0)	7 (23.3)	0.1300
Distribution – *n*. (%)			
Monolateral	0	10 (33.3)	
Bilateral	25 (100.0)**	20 (66.7)	

(b)								
OLP vs OLLs *n*. (%)	**Buccal mucosa**		**Tongue**		**Gingiva**		**Palate**	
Papular	0	0	0	0	0	0	0	0
Reticular	17 (68)	14 (46.7)	1 (4)	1 (3.3)	0	1 (3.3)	1 (4)	1 (3.3)
Plaque-like	2 (8)	1 (3.3)	0	0	1 (4)	2 (6.7)	0	0
Erythematous	1 (4)	2 (6.7)	0	0	0	1 (3.3)	0	0
Ulcerative	1 (4)	4 (13.3)	0	0	0	1 (3.3)	1 (4)	2 (6.7)

Abbrevation: SD, standard deviation.

Note: Quantitative variables are presented as 'mean ± standard deviation'. *p-value was calculated using the t test. A p-value less than 0.05 was used in the rejection of the null hypothesis.

Qualitative variables are presented as 'number of patients (percentages).' p-value was calculated using the chi-squared test. A p-value less than 0.05 was used in the rejection of the null hypothesis.

**Since being an essential diagnostic criterion of OLP, the bilateral distribution of the lesion was present in 100% of OLP cases; as a result, the difference with OLLs cases cannot be evaluated from a statistical perspective.

significantly different between the two groups ($p < 0.01$) based on chi-squared test results. Among OLLs patients, eosinophils were located in the superficial lamina propria (36.7%), between the epithelium-lamina propria interface and the superficial lamina propria (16.7%), and between the superficial and the deep lamina propria (3.3%). In OLP cases, most eosinophils were also found in the superficial lamina propria (12.0%) while the remaining were located at the epithelium-lamina propria interface (4.0%) and between the epithelium-lamina propria interface and the superficial lamina propria (4.0%). A p-value of 0.05 (chi-squared test) was obtained when comparing the number of plasma cells between the two groups, indicating that there was a trend towards a statistically significant difference between the two groups (73.3% vs. 48.0).

All the plasma cells were detected in the superficial lamina propria in both groups (Figure 4a,b). Civatte bodies were found in 6 (24.0%) and 11 (36.7%) patients with OLP and OLLs respectively. Regarding the distribution, Civatte bodies of OLLs patients were located in the supra-basal (45.4%), superficial (36.4%) (Figure 5) and between the supra-basal and the superficial (18.2%) layers of the epithelium. Among OLP patients, Civatte bodies were found in the supra-basal (83.3%) and the superficial (16.7%) layers of the epithelium. No statistically significant differences either in the distribution or the number of Civatte bodies were seen between the OLLs and OLP groups. Only three patients (10.0%) in the OLLs group evidenced the presence of mast cells.

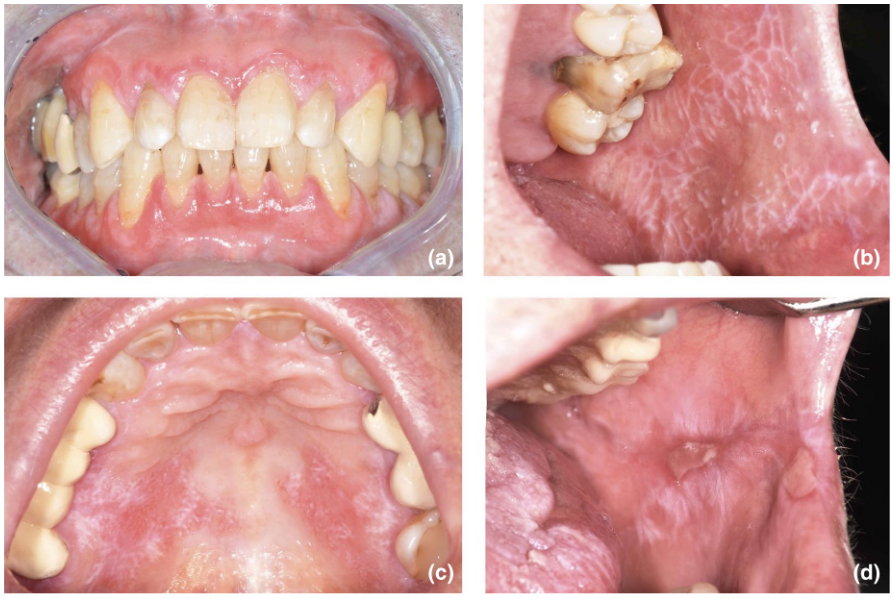

FIGURE 1 (a) Gingival involvement of OLLs presenting as desquamative gingivitis. (b) Reticular pattern of OLP on the buccal mucosa. (c) Reticular pattern of OLLs on the hard palate. (d) Ulcerative pattern of OLLs on the buccal mucosa

TABLE 3 Baseline data regarding systemic diseases and classes of medications

Variable	OLP group ($n = 25$)	OLLs group ($n = 30$)	p-value (< 0.05)
Systemic disease – *n* (%)			
Hypertension	9 (36.0)	12 (40.0)	0.7632
Diabetes	4 (16.0)	2 (6.7)	0.2754
Ipothiroidsm	6 (24.0)	6 (20.0)	0.7231
Hepatitis C	1 (4.0)	0	0.2733
Other autoimmune diseases	2 (8.0)	2 (6.7)	0.8548
Cutaneous involvement (LL or LLs)	4 (16.0)	5 (16.6)	0.9526
Current medication – *n* (%)			
Antihypertensive agents	9 (36.0)	12 (40.0)	0.7632
Oral hypoglycaemic drugs	3 (12.0)	1 (3.3)	0.2197
Antianxiety/psychotropic agents	4 (16.0)	5 (16.7)	0.9448
Sulfasalazine	0	1 (3.3)	0.3638
Levothyroxine	5 (20.0)	6 (20.0)	1.0000
Anticonvulsants	1 (4.0)	2 (6.7)	0.6640
Nonsteroidal anti-inflammatory drugs	2 (8.0)	2 (6.7)	0.8548
Antibiotics	0	0	

Note: Data are presented as 'number of patients (percentages).' p-value was calculated using the chi-squared test. A p-value less than 0.05 was used in the rejection of the null hypothesis.

4 | DISCUSSION

The terminology, diagnosis and classification of OLP and OLLs have been controversial and debated topics for over a decade. By common consensus, it has been agreed that the term OLLs should be used to define either those lesions that, in contrast to OLP, are associated with a specific causative agent or systemic disease or those idiopathic exhibiting an OLP-like aspect but lack one or more typical clinical and/or histopathological OLP features (Carrozzo et al., 2019; Cheng et al., 2016; Van Der Waal, 2009).

While OLP and OLLs tend to be considered as distinct conditions, they do share some overlapping characteristics, which may make it difficult to reach a definite diagnosis (Carrozzo et al., 2019; Müller, 2011). From a histopathological point of view, many authors have demonstrated the presence of some findings that are detected more frequently in OLLs compared with OLP and vice versa.

For example, Mravak-Stipetić and colleagues conducted a retrospective study on 92 patients with OLP and 14 patients with OLLs respectively. Histologically, they found significantly more

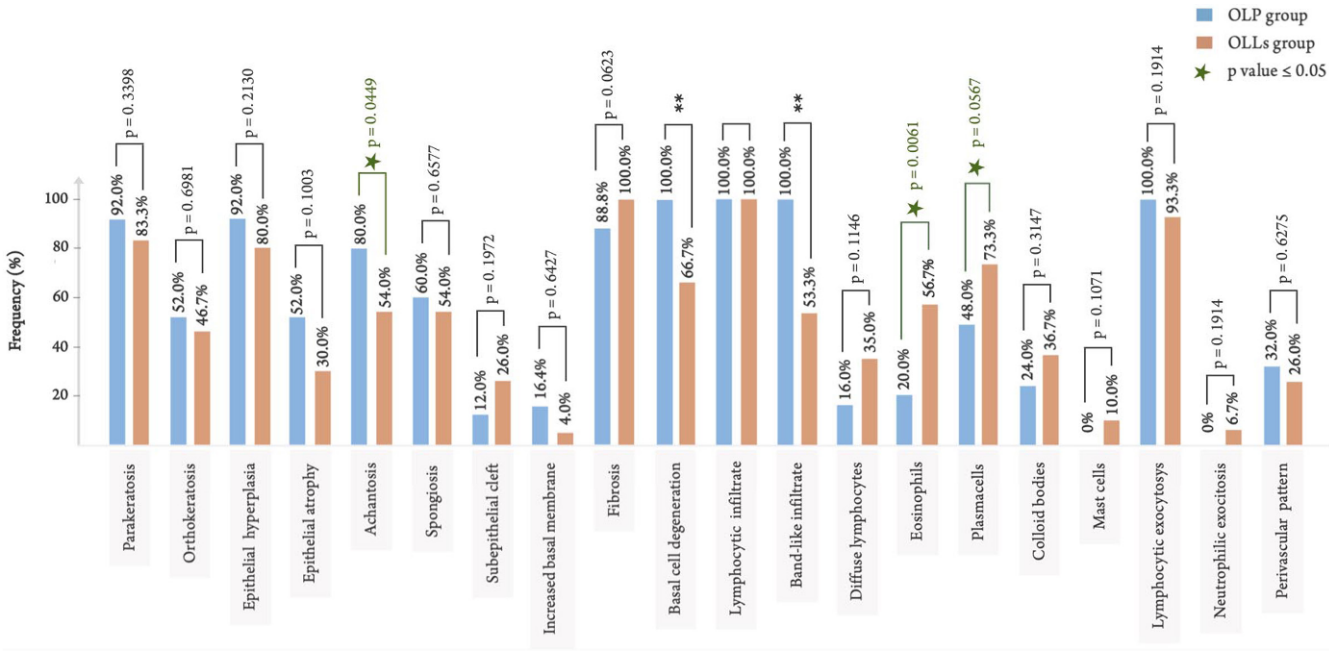

FIGURE 2 Distribution of histopathologic features between OLP and OLLs

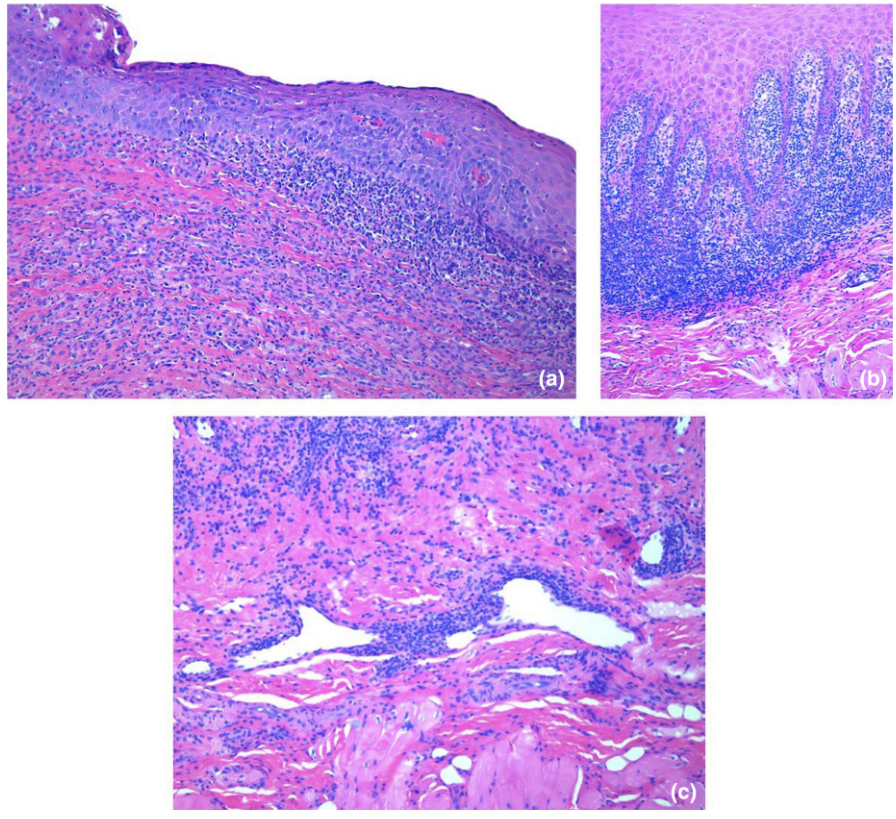

FIGURE 3 (a) Diffuse and sparse lichenoid inflammatory infiltrate extends into deeper stroma from an OLLs biopsy (Haematoxylin and Eosin stain × 10). (b) More localized, band-like infiltrate at the epithelium-lamina propria interface from an OLP biopsy (Haematoxylin and Eosin stain × 10). (c) Perivascular pattern of the lichenoid infiltrate in a patient with OLLs (Haematoxylin and Eosin stain × 10)

eosinophils, plasma cells and granulocytes in OLLs lesions than in OLP (Mravak-Stipetić et al., 2014).

Reddy et al. compared the histopathological characteristics of three groups of patients with OLP (n = 30), OLLs (n = 30), and clinically normal buccal mucosa (control group, n =10) respectively. The study results showed an increased but not statistically significant number of eosinophils in OLLs and OLP compared with the control group and in OLLs compared with OLP cases (Reddy et al., 2012). Firth et al. evaluated and compared the eosinophil densities in 79 patients with OLP and 10 patients with oral lichenoid drug reactions (OLDRs). Conversely, the authors did not find significant differences between the two groups, suggesting that eosinophils' presence in

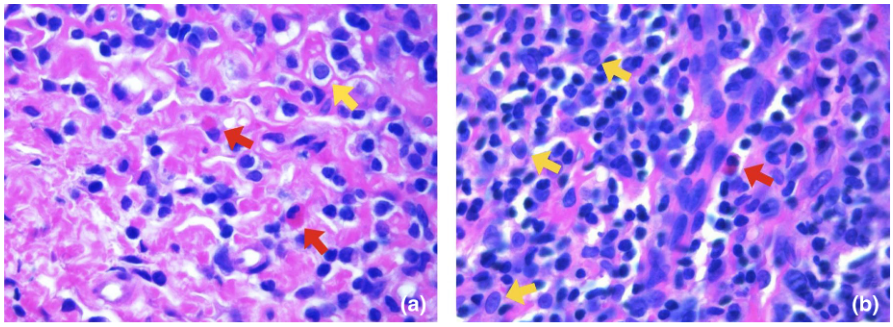

FIGURE 4 (a) Mixed cellular infiltrates consisting of eosinophils (red arrows), plasma cells (yellow arrows) and lymphocytes from OLLs biopsies (haematoxylin and Eosin stain × 63). (b) Mixed cellular infiltrates consisting of eosinophils (red arrows), plasma cells (yellow arrows), and lymphocytes from OLLs biopsies (haematoxylin and Eosin stain × 40)

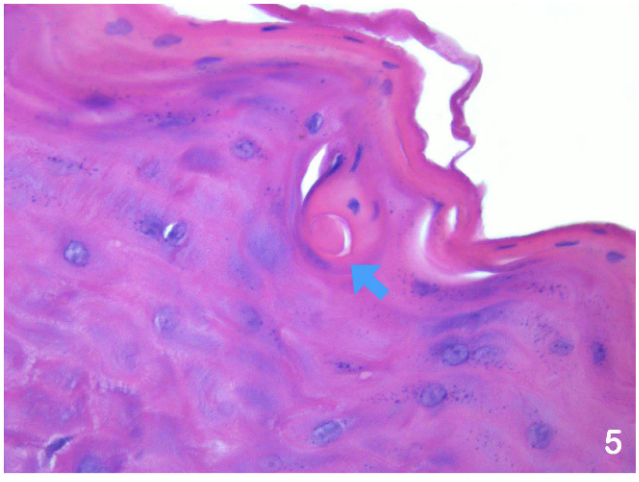

FIGURE 5 Civatte body (light blue arrow) in the cornified layer of the epithelium in a patient with OLLs (Haematoxylin and Eosin stain × 40)

the inflammatory infiltrate cannot be used as a reliable histological criterion for establishing a definite OLDR diagnosis (Anitua et al., 2019; Firth & Reade, 1990). These results appear to align with a study by Hay and Reade in which the authors did not find an infiltrate of eosinophils in any OLDR due to methyldopa biopsies examined (Hay & Reade, 1978).

Ferisse et al. evaluated Langerhans cells density in two groups of patients with OLP ($n = 14$) and OLLs ($n = 15$). The authors discovered a significantly higher amount of Langerhans cells in the OLLs compared with the OLP group. Thus, these cells appeared to be more implicated in OLL immunopathogenesis than in OLP (Ferisse et al., 2021).

In the present study, we compared the histopathology of two groups of patients with OLP ($n = 25$) and OLLs ($n = 30$). Our results highlight similar histological features in OLP and OLL specimens, except for the number of eosinophils and plasma cells in the lichenoid inflammatory infiltrate. We found statistically significant more eosinophils ($p < 0.01$) and plasma cells ($p = 0.05$) in OLLs compared with the OLP group. This result appears to be consistent with that shown by Mravak-Stipetić, although the roles of eosinophils and plasma cells in OLL pathogenesis remain controversial and not widely recognized. Moreover, above all for plasma cell analysis, the statistical significance is slight and near the cut-off level. This data should be confirmed by future studies with increased sample size and statistical power.

Unexpectedly, focal parakeratosis appeared more frequent in OLP than OLLs cases. This result contrasts reports from the literature (Carrozzo et al., 2019; Cheng et al., 2016; Van Der Waal, 2009).

Our preliminary study offers cause for reflection on clinical implications. First, clinical manifestation is not enough to perform a certainty diagnosis. Second, histological examination is fundamental to distinguish OLP and OLLs, so a biopsy is mandatory in suspected cases. Specifically, to distinguish OLP from OLLs, it should be mandatory to define the cellular composition of the lichenoid inflammatory infiltrate. In the presence of eosinophils and plasma cells, OLLs diagnosis should be considered, and, thus, accurate history-taking and careful physical examination of the oral cavity should be performed to detect a potential exogenous trigger in the pathogenesis of the disease. Eventually, pathological retrieval and general health history should always be considered comprehensively to perform a correct diagnosis. When an exogenous trigger and potential OLLs causative agent (e.g. systemic drugs, dental restoration materials or flavouring agents) is identified, it should be removed whenever possible. However, especially in OLDRs, the causal relationship between the suspected medication involved and the disease's onset is sometimes difficult to ascertain (Fortuna et al., 2017). This happened especially in patients taking medications for long periods of time (Firth & Reade, 1990). The presence of a variable latent period from the drug introduction to the appearance of the OLDRs makes it more difficult to understand if there exists a real causal relationship between the drug and the disease or if this association is merely coincidental. Hence, in these patients, the histological identification of a mixed inflammatory infiltrate, consisting of eosinophils and plasma cells, would help establish a diagnosis of OLDRs and facilitate the decision to consider the oral lesion as drug-induced. However, histopathological results must always be compared with the clinical findings, including the distribution and localization of the lichenoid lesion. In our study, the number of patients taking medications was 11 (44.0%) and 14 (46.6%) in the OLP and OLLs groups respectively. The percentage of patients using antihypertensive drugs, which have been demonstrated to be associated with OLDRs, was 40% and 36% in the OLLs and OLP groups respectively. Nevertheless, no temporal relationship between the medications used and the disease onset was found in these patients. Of course, the limited number of enrolled patients cannot be neglected. These data should

set the basis for further investigation. In any case, when finding oral mucosal lesions compatible with OLP or OLLs, a careful evaluation of the patient's drug history is mandatory (Carrozzo et al., 2019; Fortuna et al., 2017).

Our results could also be useful in managing suspected oral lichenoid contact lesions (OLCLs) to amalgam. Indeed, the presence of a mixed cellular inflammatory infiltrate containing eosinophils and plasma cells in patients with a positive patch test to mercury and clinically objective lesions (direct topographic relationship with an amalgam filling) may support the diagnosis of OLDRs and the need to replace the amalgam filling suspected to cause the delayed hypersensitivity reaction (Koch & Bahmer, 1995; Thornhill et al., 2003).

Moreover, the presence of conspicuous eosinophils and plasma cells in the lichenoid inflammatory infiltrates may sometimes be suggestive of an underlying systemic condition, such as DEL, SLE or GVHD (Carrozzo et al., 2019; Cheng et al., 2016; Van der Meij & Van der Waal, 2003).

However, when considering the cellular disposition of the lichenoid inflammatory infiltrate to distinguish between OLLs and OLP, it is important to exclude the presence of candida and areas of ulceration, both of which may result in accumulations of neutrophils and plasma cells (Thornhill et al., 2006). Further, the histopathological features of OLP or OLLs may potentially be influenced by several factors, such as the stage of the disease activity at the time of the biopsy, the clinical pattern, the anatomic sites and any recent therapy for the condition (Cheng et al., 2016). Nevertheless, we believe that an oral mucosal biopsy with histopathological examination represents a reasonable and prudent clinical practice that should always be considered in the OLP or OLL diagnosis.

However, this study has several limitations. First, the sample size is small and not calculated *a priori*. Second, to increase the statistical power of our findings, we have planned to perform a double-blind study involving more than one pathologist, following the encouraging results obtained in this preliminary analysis. Finally, the biopsy site's influence on the prevalence of eosinophils and plasma cells in the lichenoid infiltrate should be considered to eliminate possible biases correlated to oral biofilm.

In conclusion, despite showing some overlapping features, OLP and OLLs should be considered distinct conditions that may sometimes be distinguished upon histological examination. Our study's results demonstrate how the presence of a mixed lichenoid inflammatory infiltrate, consisting of eosinophils and plasma cells, may become a reliable histological feature for the diagnosis of OLLs, as long as compared with findings obtained from the patients' history and clinical examination.

CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Michele Lodolo: Formal analysis; Investigation; Writing – original draft. **Margherita Gobbo:** Conceptualization; Investigation; Methodology; Writing – original draft. **Rossana Bussani:** Investigation; Methodology. **Lucio Torelli:** Data curation; Formal analysis; Methodology. **Katia Rupel:** Conceptualization; Investigation; Validation. **Giulia Ottaviani:** Investigation; Methodology. **Augusto Poropat:** Investigation. **Matteo Biasotto:** Conceptualization; Methodology; Supervision.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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