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Clinical Behavior of Oral Lichen Planus in Association with Candidiasis

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Abstract

Background: Both Oral Lichen Planus (OLP) and oral candidiasis may have a polymorphic clinical appearance, but they have different etiologies; the former is classified as an immune-mediated inflammatory disease, whereas the latter is a condition of infectious origin frequently caused by the fungus Candida spp.

Objective: To assess whether candidiasis infection influences the clinical behavior of OLP lesions.

Methods: We selected photographic findings and cytopathological exam results from 281 visits of 32 participants diagnosed with OLP at the oral diagnostic outpatient clinic. All the images were strictly analyzed, and the results were recorded in an Excel spreadsheet for subsequent statistical analysis using the SPSS 21.0 software.

Results: The correlation between exacerbation of OLP lesions and candida infection of the oral mucosa was confirmed. Correlation analysis showed that candidiasis alters the patterns of OLP lesions. Clinical exacerbation of the areas involved, greater extension, and greater clinical evidence were associated with the presence of candidiasis. Furthermore, the lesions tended to diminish after candidiasis was controlled, with more evidence of the reticular pattern of OLP.

Conclusion: Candidiasis infection alters the pattern of OLP lesions.

Keywords: Autoimmunity; Candidiasis; Infection Disease; Mucocutaneous Disorders; Mucosal Immunity; Oral Diagnosis

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Introduction

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disease, which etiology has not been completely clarified. It presents characteristics of an immune-mediated multifactorial disease involving T lymphocytes. OLP lesions may appear in several different forms and are classified as bullous, plaque-like, papular, atrophic, erosive/ulcerative, or reticular.The most common clinical appearances of OLP are the reticular and erosive types. However, it may have a modified clinical appearance in the presence of candidiasis [1,2].

The reticular pattern exhibits an interlacing of fine white lines (Wickham´s striae) or white papules [1,2]. The erosive/ulcerative pattern depicts atrophic erythematous areas with different degrees of ulceration, but fine white radiating striae are always present along the borders of these lesions. The bullous pattern exhibits a single or multiple bullous lesions, which increase in size and tend to rupture, leading to an ulcerated surface, and the borders of these lesions are generally surrounded by fine keratinized striae. The plaque-like or papular pattern shows

a white homogeneous and irregular surface, which may be multifocal and its appearance may become raised and/or rough [3]. The papules are usually followed by another pattern and the size of the lesions range from 0.5 to 1.0 mm with fine striations along the borders [4,5].

OLP is usually asymptomatic, but the erosive pattern causes symptoms, such as pain, stinging, and burning. This OLP type is often associated with fungal infections, such as candidiasis, which may cause exacerbation of symptoms [1,2,6]. Erythematous OLP variants (atrophic, erosive, and ulcerative) are more frequently associated with malignant transformation [7].

Candidiasis is an infectious disease, which may present several clinical features in the oral mucosa and is usually caused by Candida spp. In many cases, it is associated with symptoms, such as pain, stinging, and burning [8,9]. The clinical manifestations of candidiasis in the oral mucosa can be classified as pseudomembranous, erythematous, hyperplastic, rhomboid glossitis, and angular cheilitis [10,11].

The prevalence of oral candidiasis in patients with OLP ranges from 7.7% to 16.6% in biopsy findings and from 37% to 50% in culture findings, regardless of any treatment with antifungal drugs or corticosteroids. However, there is no data on the prevalence of candidiasis through cytopathological exam in patients with OLP and with regard to the association between candidiasis and the clinical behavior of OLP [12].

C. albicans can adhere to the surface of the oral mucosa, triggering an increase in inflammation in the local mucosa and exacerbating OLP, especially the erosive type. This has been associated with the enzymatic virulence factor of activated phospholipase, which in turn is associated with greater toxicity and aggressiveness of C. albicans [13].

Therefore, this study hypothesized that the clinical appearances of OLP lesions are influenced by candidiasis and aimed to assess the association between them.

Material and Methods

The sample initially consisted of 32 individuals with OLP diagnosed between 2004 and 2015, and the data were obtained from the archive of Hospital Universitário Antônio Pedro-Universidade Federal Fluminense (HUAP-UFF). Then, we selected 25 individuals with OLP and candidiasis at some point during the follow-up period (candidiasis group; CG), with a total of 228 clinical follow-ups. All participants had a clinical and histopathological diagnosis of OLP, with at least one positive result for oral candidiasis, two or more cytopathological results on different dates, and photographic documentation of all the lesion sites. Cases with corticosteroid administration during the last 3 months of assessment were excluded.

The subjects were divided into two groups for analysis: the first group consisted of individuals with a response to antifungal therapy at follow-ups (responding group; RG) and the second group included individuals without a response to antifungal therapy at follow-ups (non-responding group; NRG). The interval between the control visits for cytopathological exam ranged from 7 to 15 days. Individuals treated for candidiasis and managed for OLP lesions returned every 120 days for the follow-up of OLP lesions. Oral scraping for cytopathology, photographic documentation, and a description of all the lesions and affected areas were included in the subsequent follow-up visits as part of the protocol for patients with OLP. Patients who had no initial response to antifungal treatment were only on 120 days return appointment after they responded to the antifungal treatment.

It was obtained clinical and demographic data from the participants' electronic records, images, and cytopathological results at each follow-up. All the images were included in the Microsoft PowerPoint program and organized according to participants, with the respective registration dates. A notepad with descriptive information about the participant's clinical progress according to the electronic medical record was attached to the file, as well as the corresponding cytopathological exam results. The analysis of cytopathological results along with a record of images of the oral mucosa on the same day as the clinical follow-up enabled us to evaluate different patterns of OLP lesions associated with the presence or absence of candidiasis. Hence, the study included only cases with cytopathological exam results with photographic records of the same day for all the follow-ups, which were recorded in an Excel 2013 spreadsheet.

The images were obtained from the digital archive using a Canon EOS Rebel professional digital camera, which reproduces the actual size of the recorded object. Descriptions of the lesions were based on the concepts described by Neville and definitions by Houaiss [14,15].

We found and analyzed four OLP patterns and they were the atrophic, reticular, plaque-like, and ulcerative patterns. Also, 17 oral mucosa sites were considered for the localization description of the lesions and they were right and left buccal mucosa, ventral surface of the tongue, dorsum of the tongue, right and left lateral borders of the tongue, upper and lower lips, upper and lower gingiva, floor of the mouth, hard palate, soft palate, upper and lower vestibule, and upper and lower alveolar ridges.

The lesions were analyzed by comparing the photographs. The changes in OLP lesions were classified by two stomatologists as improvement, worsening, and no change. The criteria used to evaluate lesion changes were as follows: improvement, when a decrease in the area(s) affected by the OLP lesion was observed, which may or may not be associated with a decrease in or disappearance of other clinical patterns present in the reticular pattern; worsening, when an increase in the area(s) affected by the OLP lesion was observed, which may or may not be associated with an increase in or appearance of other clinical patterns present in the reticular pattern; and no change, when it was not possible to observe any change in the OLP lesions in the affected areas or in the patterns.

Statistical analysis

The study variables were sex, age, smoking, alcoholism, prosthesis use, hypertension, diabetes, recurrence of candidiasis, clinical alteration, clinical improvement, and clinical worsening.

For the statistical analysis of correlation and comparison of clinical changes of OLP with recurrence of oral candidiasis, it was quantified the number of times each participant presented changes, improvement, and clinical worsening was correlated with the number of recurrences of oral candidiasis.

All the statistical tests used in this study were performed using the Statistical Package for Social Science (SPSS) program, version 21.0 (IBM, Armonk, NY, USA). The normality test of the quantitative variables was verified by the Shapiro-Wilk test and graphical analysis. In the descriptive statistical analysis, the qualitative variables were expressed as absolute and relative frequency and quantitative variables as mean (standard deviation) and median (minimum–maximum). Pearson's linear correlation and point biserial correlation were used to estimate the coefficients of correlation between two quantitative variables and between dichotomous and quantitative variables, respectively. Individuals with 1–2 recurrences of candidiasis were compared with those presenting ≥3 recurrences using the Mann–Whitney U test. The level of statistical significance was set at 5% ($p<0.05$).

Results

We selected 32 participants with 281 follow-ups, photographic documentation, and cypathological exam results. The follow-ups were divided as follows: 84 (29.9%) with candidiasis and 197 (70.1%) without candidiasis.

The final sample consisted of 25 participants with 228 follow-ups, 84 of which included oral candidiasis diagnosis and 144 did not. Seven participants were excluded because they did not present candidiasis at any time during the follow-up period.

A total of 689 OLP lesions were identified and classified as follows: 244 (35%) atrophic, 223 (32.0%) white plaque-like, 203 (30.0%) reticular, and 19 (2.0%) ulcerative.

According to the lesions evaluated, we observed that the buccal mucosa was the most affected area, with 304 (44.0%) different lesions, followed by the gingiva with 141 (20.0%), palate with 81 (12.0%), tongue with 74 (11.0%), lip and floor of the mouth with 32 (4.5%), and vestibule with 25 (4.0%).

Different patterns observed during the follow-ups of the 25 participants had the following site distribution: the atrophic pattern (244 lesions) was mostly observed in the buccal mucosa (98 lesions; 14.0%), gingiva (56; 8.0%), and palate (34; 5.0%); plaque pattern (223 lesions) in the buccal mucosa (91; 13.0%), gingiva (46; 7.0%), and palate (30; 4.0%); and reticular pattern (203 lesions) in the buccal mucosa (109; 16.0%), gingiva (37; 5.0%), and palate and tongue (17; 2.0%). The ulcerative pattern was the least identified, with six lesions located in the buccal mucosa, five in the lip, and three in the vestibule.

The participants (n=25) with a positive result for oral candidiasis in at least one exam had 84 follow-ups for oral candidiasis during the 11 years of the study. However, oral candidiasis was cured after antifungal treatment in 51 follow-ups, as confirmed by the cytopathological exam (RG). We observed improved clinical appearance in 10 (92.0%) ulcerative, 39 (78.0%) atrophic, 35 (70.0%) reticular, and 34 (68.0%) plaque-like OLP cases. However, there was worsening in one (8.0%) ulcerative, 11 (22.0%) atrophic, 15 (30.0%) reticular, and 16 (32.0%) plaque-like cases (Figure 1).

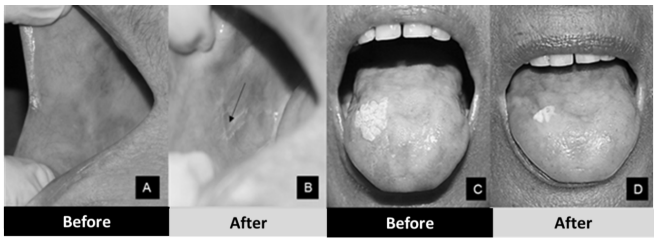

Figure 1 Clinical image of worsening and improvement of oral lichen planus lesion after 2 weeks.

A and B show clinical worsening in the right buccal mucosa after 2 weeks and exacerbation of white striae, with reddish center of atrophy (arrow). C and D show clinical improvement after 2 weeks on the dorsum of the tongue, with decrease in the size of the white lesion.

Candidiasis persisted after antifungal treatment in 29 follow-ups (GSR), as confirmed by the cytopathological exam. We observed worsening of clinical appearance in 20 (69%) reticular, 18 (62%) atrophic, two (100%) ulcerative, and 18 (62%) plaque-like cases. However, there was improvement in eight (27%) reticular, 10 (38%) atrophic, and 10 (38%) plaque-like cases. Four follow-ups of participants with candidiasis were excluded due to the absence of clinical examination after cytopathological diagnosis.

Correlation analyses were performed between the variables "number of clinical alterations of OLP" and all covariates analyzed in this study. A statistically significant moderate positive correlation was observed between clinical alterations of OLP and recurrence of candidiasis ($r=0.68$, $p<0.0001$). However, no significant correlation was found between clinical alterations of OLP and other covariates.

Correlation analysis between the variables "clinical improvement of OLP" and "recurrence of candidiasis" also showed a statistically significant moderate positive correlation ($r=0.75$; $p<0.0001$), similar to that between "clinical worsening" and "recurrence of candidiasis" ($r=0.52$, $p<0.007$).

The participants with a diagnosis of oral candidiasis presented different episodes of candida infections. These recurrences of candidiasis were stratified into two groups: one group of 12 individuals with 1–2 recurrences and another of 13 individuals with≥3 recurrences. The two groups were compared, and statistically significant differences were observed for all comparisons (Table 1).

Table 1: Comparison between clinical changes, clinical improvement, and clinical worsening of OLP in the relapsing candidiasis groups. RC, Recurrence of candidiasis. The data are presented as the mean (standard deviation); median (minimum–maximum). The p-value refers to the Mann–Whitney U test.

Variables	Group 1–2 RC (n = 12)	Group ≥ 3 RC (n = 13)	p-value
Clinical change	3.7 (1.9); 3.5 (1–7)	8.9 (4.2); 9.0 (4–17)	0.001
Clinical improvement	1.7 (0.8); 1.5 (1–3)	4.5 (1.8); 5.0 (1–7)	0.0001
Clinical deterioration	2.0 (1.4); 2.0 (0–4)	4.4 (2.9); 5.0 (1–7)	0.03

Discussion

The frequency of oral candidiasis in the 32 participants with OLP was 78%; however, when analyzed over the 11 years of follow-up, we observed the presence of the condition in 84 (29.9%) of the 281 follow-ups. According to the literature, the prevalence of oral candidiasis associated with OLP ranges from 11% to 47%. We verified that the diagnosis of candidiasis is often established by culture or physical exam [16,17]. Both the methods have limitations for the diagnosis of candidiasis [18,19]. Culture, even in the presence of spores, which represents colonization, may have a positive result, and the clinical appearance is not always characteristic for diagnosis, because some alterations may be misinterpreted as candidiasis. Also, the absence of clinical characteristics may be interpreted as absence of candidiasis, but it may actually be a case of subclinical candidiasis. In our study, the cytopathological exam, which has well-established criteria for the diagnosis of candidiasis, was performed at all the follow-ups. The results of the frequency of candidiasis were comparable with those in the literature, but the frequency was high compared with the total number of patients with OLP. This may be attributed to the fact that OLP has several clinical characteristics, with associated red and white areas; these features can lead the clinician to interpret these characteristics as those associated with OLP and not candidiasis. The cytopathological exam enables us to diagnose candidiasis in the presence or absence of clinical characteristics [20].

The atrophic pattern predominated (35% of cases), followed by the plaque-like (32%), reticular (30%), and ulcerative (2%) patterns. The literature generally describes the reticular pattern as being the most common. This divergence could be explained by the fact that only participants with OLP and oral candidiasis were considered in this study; this result influenced the predominance of the atrophic pattern, which was clearly observed in the evaluation of individuals with oral candidiasis who responded to treatment; these individuals showed a predominance of white lesions (reticular and plaque patterns) compared with red lesions (atrophic and ulcerative patterns) [18,21]. Although it was not the purpose of this study, to confirm the possible influence of candidiasis on OLP pattern, we also conducted an analysis in which we evaluated 32 individuals with OLP, thus including those with and without candidiasis. We observed a predominance of the reticular pattern in this analysis and confirmed the prominence of the atrophic pattern in participants with OLP and oral candidiasis.

In addition to being the area with greatest involvement, the buccal mucosa was also the most common site for all OLP patterns. The reticular pattern predominated in the buccal mucosa in 16% of the participants, followed by the atrophic pattern in 14% and plaque-like pattern in 13%. The literature showed similar results, with the reticular pattern being most commonly observed in the buccal mucosa. The most common pattern in the gingiva was the atrophic (8%), which was consistent with the literature [18,22,23]. The atrophic pattern predominated in the palate, but we could not perform a comparative analysis because of the difficulty of finding such data in the literature [21,24]. The plaque-like pattern predominated in the tongue; however, the literature reported the atrophic pattern as the most common. Interestingly, the ulcerative pattern at both the bilateral buccal and lower lip mucosal sites represented 57% of the total ulcerative lesions. The difference in the epithelial lining of these regions combined with the propensity to trauma may lead to the development of ulcerative lesions in a mucosa already altered by the OLP-related immune response.

In the analysis of improvement or worsening, RG exhibited greater frequency of clinical improvement in OLP lesions than that of NRG. The most improved patterns included atrophic (78%) and ulcerative (92%), which was consistent with the literature. We believe that candidiasis exerts a strong influence on the appearance of atrophic and ulcerative lesions due to the inflammatory response-related mechanisms as previously mentioned [19]. Once candidiasis is treated, this inflammatory response becomes less intense and more specific to the etiopathogenic mechanism of OLP. Thus, these areas tend to diminish or disappear and may show reticular and plaque-like patterns.

In the analysis of improvement or worsening, NRG exhibited greater frequency of clinical worsening of OLP lesions than that of clinical improvement for all the four patterns (atrophic, reticular, plaque, and ulcerative). The reticular pattern (69%) was most associated with worsening. We could not compare these data with the literature. Some studies reported an improvement in OLP lesions after the treatment of candidiasis, but none included post-antifungal treatment follow-up or demonstrated the outcomes when there was no therapeutic response. In the present study, OLP lesions were monitored through the description of all the clinical features and cytopathological exam over a long period of time [19,25]. This analysis confirmed the influence of candidiasis on the clinical behavior of OLP lesions, with worsening and greater aggressiveness of the lesions. This result reinforces the importance of the diagnosis of candidiasis, its treatment, and the use of cytopathological exams as part of the protocol of individuals with OLP.

The analysis of clinical alterations of the OLP lesions was correlated with all the variables of this study; however, it

showed a statistically significant positive correlation with only oral candidiasis recurrence. We observed correlations of clinical improvement and worsening with recurrence of oral candidiasis. Worsening of OLP may be associated with relapsing candidiasis, considering that aggressiveness and worsening of OLP symptoms were observed in the presence of candidiasis. Furthermore, an improvement in OLP was observed in cases with recurrence of candidiasis, which was evident in NRG. In NRG, we observed several episodes of recurrence and persistence of candidiasis, along with several episodes of clinical improvement of OLP after antifungal responded treatment.

We compared clinical improvement, worsening, and no change in OLP pattern with the number of recurrences of oral candidiasis. All the variables were significantly enhanced with an increase in the number of recurrences of candidiasis. This has not been previously reported in the literature and thus provides important evidence that the clinical alterations in OLP become greater and more aggressive with increasing number of oral candidiasis recurrences.

Conclusion

OLP lesions most commonly affect the buccal mucosa, gingiva, and palate, with a predominance of the reticular pattern in the buccal mucosa and atrophic pattern in the gingiva and palate. Candidiasis is common in patients with OLP, increasing its frequency according to the number of follow-ups. Clinical lesions of OLP in the presence of candidiasis have a more aggressive and heterogeneous appearance, with more evident red areas. OLP tends to be exacerbated in the presence of candidiasis. There is a correlation between change in the clinical behavior of OLP and presence of candidiasis; the number of changes in OLP lesions is associated with increasing number of candidiasis recurrences.

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Conflict of Interest

This study does not have any conflict of interest.

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