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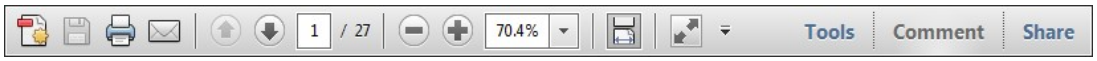


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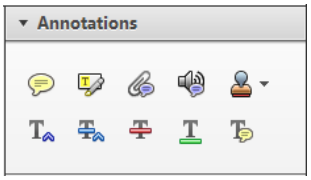


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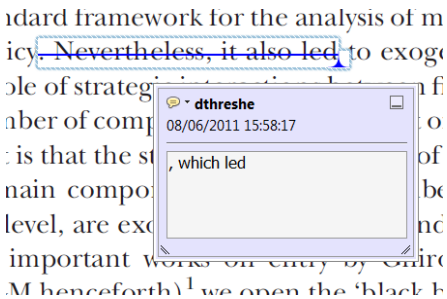


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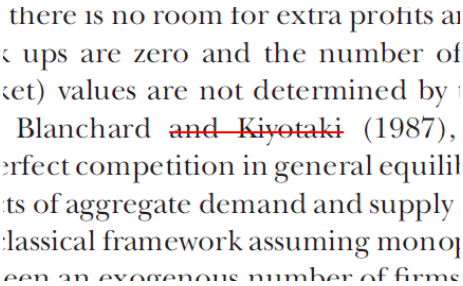

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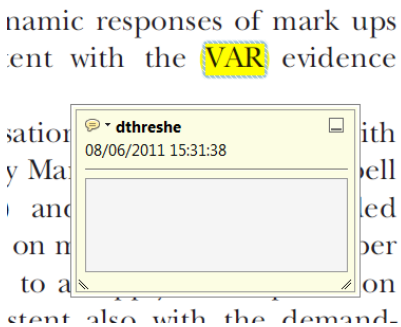


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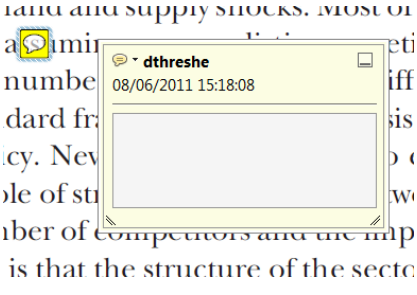

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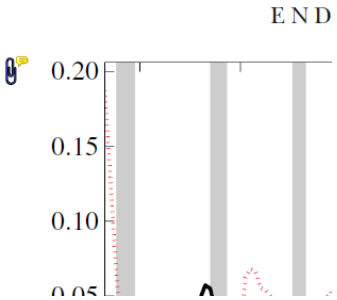


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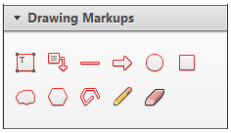


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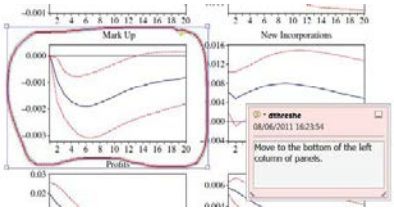

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ORIGINAL ARTICLE

WILEY Journal of Oral Pathology & Medicine

# Psychological profiles in patients with symptomatic reticular forms of oral lichen planus: A prospective cohort study

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**Objectives:** To analyze intra, extra-oral symptoms and psychological profiles in symptomatic patients with reticular (R) forms of oral lichen planus (OLP).

**Materials and Methods:** Thirty symptomatic R-OLP (sR-OLP) patients were compared with an equal number of non-symptomatic R-OLP (nsR-OLP) patients, burning mouth syndrome (BMS) patients, and healthy subjects (HS). The Numeric Rating Scale (NRS), the Total Pain Rating Index (T-PRI), and the Hamilton Rating Scales for Depression (HAM-D) and Anxiety (HAM-A) were administered. Descriptive statistics, the non-parametric ANOVA procedure by Kruskal-Wallis, the exact Fisher test, and the multiple comparison test by the Mann-Whitney *U* test were performed.

**Results:** The median and IQR of the HAM-D and HAM-A were 16.0 (11.7-24.0) and 17.5 (13.7-27.2) for the BMS, 13.5 (12.0-15.0) and 15.5 (10.7-18.0) for the sR-OLP patients, 2.0 (2.0-3.2) and 2.0 (2.0-4.0) for the nsR-OLP patients, and 3.0 (2.0-4.0) and 3.0 (2.0-4.0) for the HS, respectively. The median and IQR of the NRS and T-PRI were 9.0 (7.7-10.0) and 11.0 (9.0-12.2) for the BMS and 9.0 (7.7-10.0) and 11.5 (7.0-13.0) for the sR-OLP patients, respectively. Comparison analysis between the BMS and sR-OLP patients revealed a non-significant difference between the medians of the psychological profile and pain in the two groups ($P$-value>.05).

**Conclusions:** The oral complaints are correlated with anxious and depressive symptoms in sR-OLP patients. Mood disorders could modulate the pain perception or that patients could develop two different associated oral diseases, OLP and BMS.

KEYWORDS
anxiety, burning mouth syndrome, depression, oral burning, oral lichen planus, pain

## 1 | INTRODUCTION

Lichen planus (LP) is a mucocutaneous inflammatory disease of unknown etiology.[1] Its oral variant, oral lichen planus (OLP) has a reported prevalence ranging from 0.5% to 2.2% of the general population, and the typical age of presentation is between 30 and 60 years.[2] Although the pathogenic mechanism and triggering factor remain unknown, an immune-mediated pathogenesis has been hypothesized.[3,4]

OLP typically presents with six clinical forms, classified as reticular, erosive, atrophic, plaque-like, papular, and bullous. The various patterns may coexist in a single patient and may change in time.[2]

Approximately two-thirds of OLP patients report oral symptoms that may vary from oral discomfort to continuous debilitating pain. Oral pain is associated in most cases with atrophic or erosive lesions,[5] whereas other oral symptoms, such as discomfort, xerostomia, and taste disturbance, could be exacerbated by the changes in the surface of the oral mucosa at the site of the OLP lesions.[6]

OLP lesions usually persist for many years with periods of quiescence and exacerbation with increasing erythema or ulcerations and

The study has been performed in the University "Federico II" Department of Neurosciences, Reproductive and Odontostomatological Sciences of Naples, Oro-facial pain Unit.

subsequently pain and sensitivity. Instead, patients with quiescent OLP present typically faint white striations, papules, or plaques without pain. An exacerbation of OLP has been linked to periods of psychological stress and anxiety, a predictable correlation with any condition that is related to an immune system imbalance.[5] Patients with OLP are often emotionally unstable and anxious and may develop concomitant systemic disorders.[7]

Some authors have shown high levels of depression and/or anxiety in patients with OLP,[7,8] while others have found these levels to be within the normal range.[9,10] Moreover, Rojo-Moreno reported that patients with erosive OLP were more depressed and/or anxious than patients with non-erosive OLP[11] considering mood alterations as secondary symptoms, in contrast with other studies.[12,13]

OLP has been extensively studied, but little is known about oral discomfort and psychological profiles in the reticular (R) form. Recently, we found a higher level of anxiety and depression and sleep disturbance in asymptomatic patients with reticular form of OLP.[14]

In the last year, we have enrolled, in our outpatient clinic, thirty strongly symptomatic OLP patients with an R form, in which the symptomatology is not related to clinical features and closely resembles BMS. In order to clarify the diagnosis and to better understand this unusual association, we have performed this prospective cohort clinical study.

The aims of the study were to evaluate: (i) the intra-oral and extra-oral symptoms and the psychological profile in a sample of patients with the symptomatic reticular (sR) form of OLP; and (ii) to compare mood disorders and pain in the study groups, namely sR-OLP, non-symptomatic reticular (nsR) OLP, burning mouth syndrome (BMS) patients, and healthy subjects (HS) in order to better understand the relationships between disease, symptoms and emotional status in the sR form of OLP.

## 2 | MATERIALS AND METHODS

The study was a prospective cohort single assessment clinical study performed at the Oral Medicine Unit of the "Federico II University of Naples" between January and July 2015.

Thirty subjects with sR-OLP, thirty subjects with nsR-OLP, thirty patients with BMS, and thirty HS were included in the trial following inclusion/exclusion criteria, undergoing a simple randomization procedure with IBM SPSS software (version 19, IBM Corporation, Armonk, NY, USA).

This study was approved by the Ethics Committee of the University "Federico II of Naples." Every patient underwent a complete clinical interview and examination. The patients diagnosed with BMS and OLP at the time of the enrollment were evaluated a second time by the same clinician after a period of 6 months to confirm the diagnosis. The diagnosis of OLP was determined by clinical examination and confirmed by histology. All groups were matched for sex, age, and educational level.

All patients who reported one or more extra-oral symptoms during the first visit were referred to the relevant specialistic area, that is, ophthalmology, gynecology, otolaryngology, gastroenterology, neurology, cardiology, internal medicine, and dermatology to establish the exact etiology of the symptoms. Each specialist physician gathered, recorded, and analyzed all the extra-oral symptoms in their own area and grouped them into either an "attributable to a medical condition/dysfunction" category or a "functional" category. Every patient who refused a specialist consultation after their first visit or reported having a medically explained symptom was automatically excluded from the study. All specialist physicians made a diagnosis of "functional" based on what is currently reported in the literature, that is, functional or "medically unexplained" symptoms are defined as symptoms for which no appropriate medical diagnosis could be found after a physical examination and adequate laboratory and radiological investigations.[15]

The inclusion criteria for patients with sR-OLP were as follows: (i) either sex, aged eighteen or older; (ii) a reticular keratotic clinical pattern of OLP; (iii) a previous histological and clinical diagnosis of OLP and the absence of epithelial dysplasia; (iv) referred oral symptoms present for at least 3 months; and (v) the absence of any alteration in salivary flow rates and laboratory tests including for levels of $B_1$, $B_2$, folic acid, and iron. The exclusion criteria were as follows: (i) the presence of any other clinically identifiable oral lesion not attributable to OLP; (ii) the presence of any oral erosive lesions; and (iii) any ongoing psychiatric therapy.

The inclusion criteria for patients with nsR-OLP were as follows: (i) either sex, aged eighteen or older; (ii) a reticular keratotic clinical pattern of OLP; (iii) a previous histological and clinical diagnosis of OLP and the absence of epithelial dysplasia; and (iv) the absence of any alteration in salivary flow rates and laboratory tests including for levels of $B_1$, $B_2$, folic acid, and iron. The exclusion criteria were as follows: (i) the presence of any other clinically detectable oral lesion not attributable to OLP; (ii) the presence of any oral erosive lesions; (iii) a complaint of oral symptoms/oral discomfort; and (iv) any ongoing psychiatric therapy.

The inclusion criteria for patients with BMS were as follows: (i) either sex, aged eighteen or older; and (ii) diagnosis of BMS in accordance with the International Classification of Headaches:[16] the presence of continuous symptoms of oral burning or pain recurring daily for more than 2 hours per day, lasting for longer than 3 months, with no paroxysm and not following any unilateral nerve trajectory and the absence of local or systemic factors that could produce the same symptoms.

The exclusion criteria were as follows: (i) any clinically identifiable oral lesion; (ii) organic conditions that could be considered a causative factor; and (iii) any ongoing psychiatric therapy.

The inclusion criteria for HS were as follows: (i) either sex, aged eighteen or older; (ii) the absence of any clinically identifiable oral lesion; (iii) the absence of any symptom referred in the oral cavity; (iv) the absence of any history of psychiatric disorders; (v) ongoing psychiatric therapy; and (vi) consultation exclusively for a dental disease. The exclusion criteria were (i) subjects with an unstable medical disease or debilitating pathology (e.g, cancer, osteonecrosis, or an immunological disease).

Socio-demographic information, age, sex, education, employment, and marital status, data concerning systemic diseases and drugs, and oral and extra-oral symptoms were all recorded in clinical charts. Any oral symptoms reported were categorized according to the type of sensation referred as burning (localized or diffuse), xerostomia, dysgeusia, itching, sialorrhea, globus pharyngeus, or other. The extra-oral symptoms reported were categorized according to the anatomic district involved as ophthalmological, otholaryngoiatric, urogenital, cardiopulmonary, gastrointestinal, cutaneous-glandular, or neurological. Any oral lesions detected in sR-OLP and nsR-OLP were categorized in relation to their localization.

Upon admission, each patient was assessed in accordance with the following evaluation battery scale: the Hamilton Rating Scale for Depression (HAM-D) and Anxiety (HAM-A) for an evaluation of depression and anxiety, the Total Pain Rating Index (T-PRI) from the short form of the McGill Pain Questionnaire (SF-MPQ) for the assessment of the quality of pain, and the Numeric Rating Scale (NRS) for a quantification of the self-reported oral pain intensity. All these scales were reviewed for completeness before collection and were administered in their Italian version.

The HAM-D is composed of 21 items pertaining to the affective field. Scores can range from 0 to 54. A score >10 indicates impairment. Scores in the 10-17 range indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression.[17]

The HAM-A is composed of 14 items. Scores can range from 0 to 56. A score <17 indicates mild symptoms, scores between 18 and 24 indicate mild-to-moderate severity, and scores >25 indicate moderate-to-severe anxiety.[18]

The T-PRI of the SF-MPQ, a shorter version of the McGill pain questionnaire (MPQ), is a multidimensional pain questionnaire which measures the sensory, affective, and evaluative aspects of the perceived pain. The Pain Rating Index is composed of 15 items from the original MPQ, and each is scored from 0 (none) to 3 (severe). The T-PRI score is obtained by summing the item scores (range 0-45). There are no established critical cut points for the interpretation of the scores, and as for the MPQ, a higher score indicates worse pain.

The NRS (NRS-11) is a well-validated instrument for the evaluation of pain intensity. This scale ranged from 0 to 10 (0=no oral symptoms and 10=the worst imaginable discomfort).

Respondents are asked to report pain intensity in the last 24 hours.[19]

## 2.1 | Statistical analysis

Descriptive statistics, including means, standard deviations, medians, and interquartile ranges, were used to summarize all the variables. We used the exact Fisher test to assess any clinical differences among the variables in the four groups.

The non-parametric ANOVA procedure by Kruskal-Wallis was employed to test for any differences among the recorded medians

**TABLE 1** Socio-demographic and clinical characteristics of the BMS, nsR-OLP, sR-OLP, and HS

| | BMS | nsR-OLP | sR-OLP | HS | *P*-value |
|---|---|---|---|---|---|
| Demographic variables | Frequency (%) | | | | |
| Gender | | | | | |
| Male | 7 (23.3) | 11 (36.7) | 7 (23.3) | 14 (47.7) | |
| Female | 23 (77.7) | 19 (63.3) | 23 (77.7) | 16 (53.3) | |
| Job | | | | | |
| Yes | 6 (20.0) | 10 (33.3) | 10 (33.3) | 10 (33.3) | |
| No | 18 (60.0) | 14 (46.7) | 12 (40.0) | 16 (53.4) | |
| Retired | 6 (20.0) | 6 (20.0) | 8 (26.7) | 4 (13.3) | |
| Family situation | | | | | |
| Single | 4 (13.3) | 5 (16.7) | 1 (3.3) | 5 (16.7) | |
| Not single | 26 (86.7) | 25 (83.3) | 29 (96.7) | 25 (83.3) | |
| | Mean±SD | | | | |
| Age (in years) | 57.9±8.4 | 56.9±13.6 | 65.3±11.3 | 50.5±9.7 | |
| Education (in years) | 8.7±3.6 | 10.3±4.8 | 7.8±3.7 | 10.2±2.8 | |
| Clinical parameters | Median; IQR | | | | |
| HAM-D | 16.0; [11.7-24.0] | 2.0; [2.0-3.2] | 13.5; [12.0-15.0] | 3.0; [2.0-4.0] | <.001** |
| HAM-A | 17.5; [13.7-27.2] | 2.0; [2.0-4.0] | 15.5; [10.7-18.0] | 3.0; [2.0-4.0] | <.001** |
| NRS | 9.0; [7.7-10.0] | 0.0; [0.0-0.0] | 9.0; [7.7-10.0] | 0.0; [0.0-0.0] | <.001** |
| T-PRI | 11.0; [9.0-12.2] | 0.0; [0.0-0.0] | 11.5; [7.0-13.0] | 0.0; [0.0-0.0] | <.001** |

IQR is the interquartile range. The significance difference between medians was measured by the Mann-Whitney *U* test.
*Moderately significant $0.01<P\leq.05$.
**Strongly significant $P\leq.01$.

of the HAM-A, HAM-D, SF-MPQ, and NRS in the four groups. *P*-values<.05 were considered to reflect a statistical significance. The Mann-Whitney *U* test with the Bonferroni correction was performed among the same variables in the four groups in any case in which a significant difference in the former test was found. In this analysis, *P*-values<.008 were considered to represent a statistical significance.

**TABLE 2** Multiple comparison test of HAM-A, HAM-D, NRS, and T-PRI in the BMS, nsR-OLP, sR-OLP, and HS

| | | BMS | nsR-OLP | sR-OLP |
|---|---|---|---|---|
| HAM-D | BMS | - | | |
| | nsR-OLP | **<0.001** | - | |
| | sR-OLP | 0.207 | **<0.001** | - |
| | H | **<0.001** | 0.372 | **<0.001** |
| HAM-A | BMS | - | | |
| | nsR-OLP | **<0.001** | - | |
| | sR-OLP | 0.077 | **<0.001** | - |
| | H | **<0.001** | 0.520 | **<0.001** |
| NRS | BMS | - | | |
| | nsR-OLP | **<0.001** | - | |
| | sR-OLP | 0.516 | **<0.001** | - |
| | H | **<0.001** | 1.000 | **<0.001** |
| T-PRI | BMS | - | | |
| | nsR-OLP | **<0.001** | - | |
| | sR-OLP | 0.766 | **<0.001** | - |
| | H | **<0.001** | 1.000 | **<0.001** |

The significance difference between medians was measured using the Mann-Whitney *U* test with the Bonferroni correction. The test is significant with a *P*-value<.008.

## 3 | RESULTS

Table 1 summarizes the demographic characteristics and clinical parameters of the BMS, nsR-OLP, sR-OLP, and HS. There were 23 female patients (77.7%) and seven male patients (23.3%) with a mean age of 65.3±11.3 and a lower level of education (7.8±3.7) in the sR-OLP patients.

The sRK-OLP patients and BMS patients had a higher median in the HAM-A, HAM-D, NRS, and T-PRI indicating a mild depression and anxiety for these patients compared with the nsR-OLP and HS.

The sR-OLP patients and BMS patients had a higher mean in the NRS and T-PRI indicating a higher intensity of pain perception compared with the nsR-OLP and HS.

As shown in Table 2, the multiple comparison test of HAM-A, HAM-D, NRS, and T-PRI revealed statistically significant different values among the BMS, nsR-OLP, and HS (*P*-value<.001) and among the sR-OLP, nsR-OLP, and HS (*P*-value<.001).

A comparison analysis between the BMS and sR-OLP patients and between the nsR-OLP and HS revealed a non-significant difference between the medians of the psychological profile and pain in the two groups (*P*-value>.05).

**TABLE 3** Frequency of oral and extra-oral symptoms in the BMS, nsR-OLP, sR-OLP, and HS

| | BMS (%) | nsR-OLP (%) | sR-OLP (%) | HS (%) | *P*-value |
|---|---|---|---|---|---|
| Oral symptoms | | | | | |
| Burning | 30 (100.0) | 0 (0) | 30 (100.0) | - | <.001** |
| Localized on tongue | 10 (33.3) | 0 (0) | 5 (16.7) | - | .002* |
| Diffuse | 14 (46.7) | 0 (0) | 25 (83.3) | - | <.001** |
| Other symptoms | 25 (83.3) | 0 (0) | 29 (96.7) | - | <.001** |
| Xerostomia | 19 (63.3) | 0 (0) | 14 (46.7) | - | <.001** |
| Dysgeusia | 17 (56.7) | 0 (0) | 17 (56.7) | - | <.001** |
| Itching | 10 (33.3) | 5 (16.7) | 7 (23.3) | - | <.001** |
| Sialorrhea | 6 (20.0) | 0 (0) | 5 (16.7) | - | .040* |
| Globus pharyngeus | 7 (23.3) | 0 (0) | 7 (23.3) | - | .016* |
| Extra-oral symptoms | 29 (96.7) | 10 (33.3) | 27 (90.0) | 10 (33.3) | <.001** |
| Ophthalmological | 18 (60.0) | 1 (3.3) | 8 (26.7) | 1 (3.3) | <.001** |
| Otholaryngoiatric | 21 (70.0) | 0 (0) | 21 (70.0) | 2 (6.7) | <.001** |
| Urogenital | 10 (33.3) | 1 (3.3) | 9 (30.0) | 1 (3.3) | <.001** |
| Cardiopulmonary | 10 (33.3) | 1 (3.3) | 8 (26.7) | 0 (0) | <.001** |
| Gastrointestinal | 19 (63.3) | 3 (10.0) | 17 (56.7) | 3 (10.0) | <.001** |
| Cutaneous/glandular | 8 (26.7) | 2 (6.7) | 0 (0) | 0 (0) | <.001** |
| Neurological | 3 (10.0) | 3 (10.0) | 12 (40.0) | 1 (3.3) | <.001** |
| Others | 6 (20.0) | 1 (3.3) | 9 (30.0) | 0 (0) | .002* |

*Moderately significant 0.01<*P*≤.05.
**Strongly significant *P*≤.01.

Table 3 shows the frequency of oral and extra-oral symptoms in the BMS, nsR-OLP, sR-OLP, and HS. Oral burning was present in all the patients with BMS and sR-OLP, 83.3% (25 patients) of the sR-OLP patients having diffuse burning. The NRS is higher and equal in the two groups (9.0; [7.7-10.0]). 96.7% (29 patients) and 83.3% (25 patients) of the BMS and sR-OLP, respectively, showed other oral symptoms, among these the most frequent being dysgeusia (56.7%) in the sR-OLP group. 90% (27 patients) of the sR-OLP and 96.7% (29 patients) of the BMS patients had extra-oral symptoms, with otholaryngoiatric and gastrointestinal being the most frequent.

As shown in Table 4, there was the frequency of the oral sites involved in relation to the nsR-OLP and sR-OLP patients. The sR-OLP patients had less frequent lesions on the margins of the tongue than the nsR-OLP patients (*P*-value .005).

**TABLE 4** Frequency of oral sites involved in nsR-OLP and sR-OLP patients

| | nsR-OLP (%) | sR-OLP (%) | *P*-value |
|---|---|---|---|
| Oral lesions | 30 (100.0) | 30 (100.0) | 1.000 |
| Buccal mucosa | 26 (86.7) | 25 (83.3) | .937 |
| Gingivae | 20 (66.7) | 14 (46.7) | .295 |
| Dorsum of the tongue | 6 (20.0) | 2 (6.7) | .315 |
| Margins of the tongue | 11 (36.7) | 1 (3.3) | .005* |
| Palate | 2 (6.7) | 1 (3.3) | .839 |
| Lips | 1 (3.3) | 0 (0) | .601 |
| Floor of mouth | 1 (3.3) | 0 (0) | .601 |

Test is significant with *P*-value<.05.

As shown in Table 5, we did not find any statistically significant differences in terms of systemic diseases and drug use among the four groups.

## 4 | DISCUSSION

The pathogenesis of OLP is complex, with genetic, environmental, and lifestyle factors reported.[1,5] Several previous studies have established a concomitance of OLP, mood disorders such as anxiety and depression, and an increased vulnerability to psychiatric disorders, while other studies have categorized OLP as a psychosomatic disease.[9,20-23]

Psychological alterations are able to modify and promote a dysregulation of immune functions with an alteration of the imbalance of the Th1/Th2 cytokines with a close relationship between this imbalance and the pathogenesis of a series of autoimmune disorders, and OLP is considered an immunological disease with a predominance of the Th2 response.[8]

However, any relationship between mood alterations and inflammation may be considered bidirectional: depression increases inflammation and inflammation promotes depression. Cytokines can access the central nervous system and interact with the cytokine network of the brain with a deep influence on its function;[24] in addition, the cytokines administration can promote depression, while anti-inflammatory medications may decrease depressive symptoms, and depression interventions may be able to reduce inflammation.[25] Peripherally, the local inflammatory response vs an unknown antigen may be responsible for the peripheral neuropathy in OLP.[26]

**TABLE 5** Frequency of systemic diseases and medications received in the BMS, nsR-OLP, sR-OLP, and H groups

| Disease | BMS (%) | nsR-OLP (%) | sR-OLP (%) | HS (%) | *P*-value |
|---|---|---|---|---|---|
| Hyperthyroidism | 4 (13.3) | 6 (20.0) | 6 (20.0) | 4 (13.3) | .811 |
| Hypertension | 9 (30.0) | 12 (40.0) | 11 (36.7) | 8 (26.7) | .682 |
| Hypercholesterolemia | 8 (26.7) | 9 (30.0) | 5 (16.7) | 3 (10.0) | .204 |
| Previous acute myocardial infarction | 4 (13.3) | 1 (3.3) | 3 (10.0) | 2 (6.7) | .535 |
| Infection by HCV | 2 (6.7) | 1 (3.3) | 1 (3.3) | 1 (3.3) | .890 |
| Diabetes | 4 (13.3) | 4 (13.3) | 1 (3.3) | 1 (3.3) | .269 |
| Previous neoplasm | 5 (16.7) | 1 (3.3) | 2 (6.7) | 0 (0) | .058 |
| Others | 8 (26.7) | 6 (20.0) | 2 (6.7) | 2 (6.7) | .070 |
| Medication | | | | | |
| Levotiroxina | 5 (16.7) | 6 (20.0) | 6 (20.0) | 4 (13.3) | .889 |
| Antiplatelet | 8 (26.7) | 7 (23.3) | 7 (23.3) | 3 (10.0) | .395 |
| B-blockers | 2 (6.7) | 3 (10.0) | 2 (6.7) | 2 (6.7) | .948 |
| Diuretics | 3 (10.0) | 3 (10.0) | 2 (6.7) | 1 (3.3) | .724 |
| ACE-inhibitors | 4 (13.3) | 5 (16.7) | 8 (26.7) | 5 (16.7) | .572 |
| Calcium-antagonists | 0 (0) | 1 (3.3) | 2 (6.7) | 3 (10.0) | .319 |
| Statins | 7 (23.3) | 6 (20.0) | 3 (10.0) | 3 (10.0) | .363 |
| Oral hypoglycemics | 3 (10.0) | 1 (3.3) | 1 (3.3) | 1 (3.3) | .551 |

Test is significant with *P*-value<.05.

Furthermore, structural and functional changes in the peripheral nerve fibers may sustain the OLP chronic inflammation (the theory of neurogenic inflammation)[27] and be responsible for the oral discomfort. For other authors, any oral discomfort in OLP may be due to a more intense peripheral neuropathy and not related to psychological factors.[10,12]

In this complex picture, we considered that a missing factor is an analysis of the psychological profile of sR-OLP patients supported by a controlled comparison with an analysis of the psychological profiles of nsR-OLP patients, BMS patients, and HS.

In our study, we found higher level of anxiety and depression in patients with sR-OLP and with BMS compared to patients with nsR-OLP and HS. The qualitative characteristics of pain in patients with BMS and with sR-OLP were the same because the oral burning was continuous, spontaneous, and bilateral alleviating during meals, increasing in severity during the late afternoon and during stressful life events, and not strictly correlated to the site of the lesions. Oral burning was present in all the patients with BMS and sR-OLP, and diffuse burning was revealed in 25 sR-OLP patients (83.3%); the NRS is higher and equal in the two groups. Similarly, we found many other oral symptoms and extra-oral symptoms not related to OLP and considered "medically unexplained" by appropriate specialist physicians who examined the patients, as in BMS. In addition, we did not find any differences relating to systemic diseases and the consumption of medications between the four groups.

It is certainly possible that mood disorders could modulate the perception of oral and extra-oral symptoms in many diseases as is suggested by the fact that we found statistically significant differences in the values of HAM-D and HAM-A between the four groups.

Furthermore, these data were significant in relation to BMS vs nsR-OLP and HS, and in relation to sR-OLP vs nsR-OLP and HS. On the other hand, no significant differences were found between BMS and sR-OLP or between nsR-OLP and HS, founding that significant differences exist in the psychological profiles between the nsR-OLP and sR-OLP patients, and that the sR-OLP and the BMS patients are similar to each other and completely different from the nsR-OLP and HS. We are not be able to establish if the oral symptoms are primary or secondary to the mood disorders, but the absence of anxiety and depression in the nsR-OLP and HS highlights that among our sR-OLP patients, pain and mood disorders are clearly relevant.

These results lead us to formulate two different possible conclusions.

The first is that mood disorders could modulate the perception of oral and extra-oral symptoms in a subset of patients with R-OLP, amplifying the peripheral neuropathy; in turn, the peripheral neuropathy through the access of pro-inflammatory cytokines to the brain could worsen the psychological profile and make the symptoms chronic. The second, and no less probable, is to consider that two different diseases, such as BMS and OLP, could develop at different times in the same patient. Until now, the definition of BMS excludes the possibility of its diagnosis in cases where we find oral lesions, but in our study, the symptomatology was exactly the same in the two groups. In this perspective, it could prove necessary to re-evaluate the parameters for the diagnosis of BMS in order to give more weight to symptoms in particular when the patient has associated comorbidities.

In summary, the present results have highlighted the contemporary presence of unusual oral and extra-oral symptoms and mood disorders in a subset of patients with R-OLP, demonstrating that anxiety and depression are common problems in OLP.

We suggest screening for mood disorders in OLP, in particular, when the oral symptomatology cannot be correlated with the clinical morphology of lesions (the absence of atrophic, erythematosus, bullous, and erosive lesions). Moreover, we suggest a multidisciplinary evaluation and management of these patients, treating anxiety and depression to improve the prognosis and quality of life. Future prospective research will be necessary to confirm our hypothesis.

There are several limitations to the study. First, the small size of the sample, analyzed in a tertiary center, means that the results may not be generalizable. Secondly, this was a case-control study unsuitable for an evaluation of the prospective relationships between pain, mood disorders and peripheral neuropathy in OLP.

## CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

## ETHICAL APPROVAL

This study has been carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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