Medication use and medical history of 155 patients with oral lichenoid lesions: a retrospective study

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Several medications have been reported as possible etiologic factors for oral lichen planus (OLP) and oral lichenoid lesions (OLLs). This study investigated the medication profile and medical history of patients with biopsy-proven OLP or OLLs, also classified by the clinically nonspecific term *oral lichenoid mucositis* (OLM), in a busy oral medicine clinic. The University of Florida College of Dentistry records from 2009 to 2014 were searched retrospectively for all patients with a biopsy-proven diagnosis of OLP, OLLs, or OLM. Patients were excluded if dysplasia or carcinoma was diagnosed concurrently at the same biopsy site. The demographics, clinical parameters, systemic diseases, histologic diagnosis, and direct immunofluorescence testing results were recorded. Medication category use was recorded based on both commonly used medications and those that have been reportedly linked to lichenoid disease in the literature. A total of 155 patients with an average age of 63.6 years were included. The majority of patients were women (76.8%) and Caucasian (91.8%). Most of the lesions were multifocal and mixed (white-red) in appearance. The most common systemic conditions were hypertension (n = 80; 51.6%) followed by thyroid disease (n = 52; 33.5%) and diabetes (n = 26; 16.8%). Antihypertensives were the most common medication category followed by, in descending order, nonsteroidal anti-inflammatory drugs, cholesterol-lowering medications, psychiatric medications, and thyroid replacement drugs. The records revealed that 87.7% of the patients took at least 1 medication from 1 of the categories studied. Medication use is common in patients with biopsy-proven OLP or OLLs. Although causation cannot be assessed from the results of this study, the clinician should consider the possibility of medication as a complicating factor in patients with OLP or OLLs.

Received: May 30, 2017
Accepted: July 11, 2017

Key words: medications, oral lichen planus, oral lichenoid drug reaction, oral lichenoid lesion, systemic disease

GENERAL DENTISTRY SELF-INSTRUCTION CE CREDIT
Exercise No. 418, p. 46
Subject code: Oral Medicine, Oral Diagnosis, Oral Pathology (730)

Oral lichenoid disease encompasses a variety of clinical and histologic presentations, including classic oral lichen planus (OLP), which generally appears as symmetric white striated lesions or atrophic or ulcerated lesions with accompanying white striae (Figure).[1] In addition, oral lichenoid lesions (OLLs) may arise in reaction to systemic medications (also known as *oral lichenoid drug reactions* [OLDRs]) or localized irritants or allergens such as dental restorative materials or flavoring agents (also known as *oral lichenoid contact reactions* [OLCRs]).[1] OLLs often appear as unilateral or solitary lesions that may not fulfill all of the clinical or histopathologic features of OLP.[1,2] In many cases, the difference between OLP and OLLs cannot be determined with certainty either clinically or histologically.

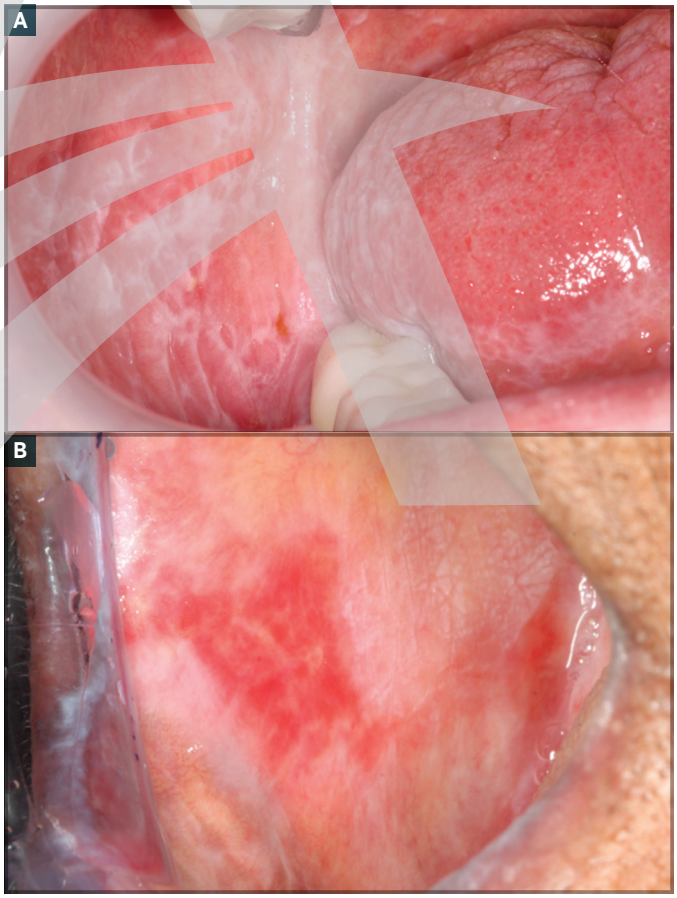


Figure. A. Clinical appearance of reticular lichen planus affecting the buccal mucosa and lateral tongue. B. Erosive lichen planus affecting the buccal mucosa.

Chart 1. Frequency of systemic medical conditions in patients with oral lichenoid disease (N = 155).

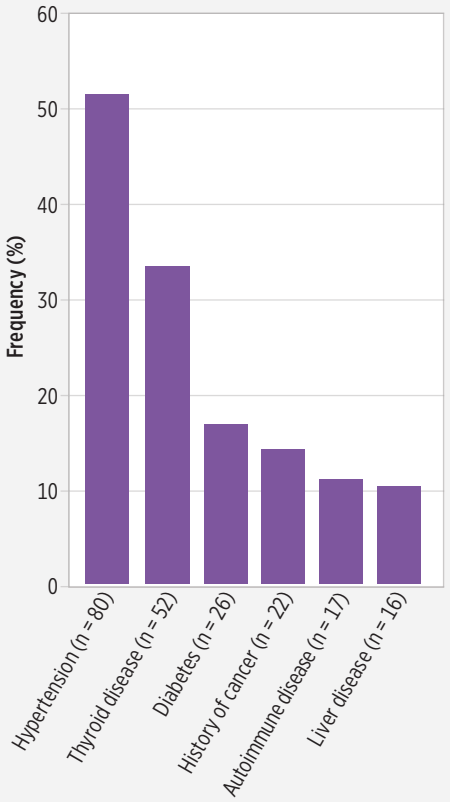
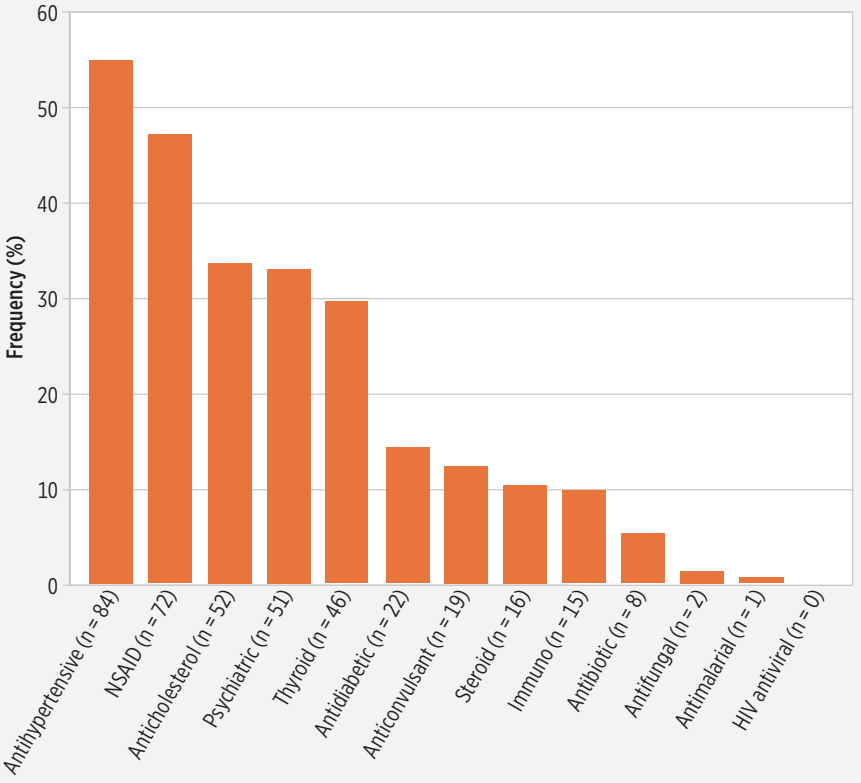


Chart 2. Classes of medications taken by study patients (N = 155).



Abbreviations: HIV, human immunodeficiency virus; Immuno, immunomodulator; NSAID, nonsteroidal anti-inflammatory drug.

OLP and OLLs are chronic, recurring conditions that vary widely in severity and may cause significant quality of life issues in severely affected patients. Multiple etiologic factors have been proposed, including systemic disease, medications, stress, localized trauma, and irritants/allergens.[3] Treatment, usually with topical corticosteroids, is not universally successful and may involve substantial side effects; therefore, any modifiable etiologic factors that can be identified to minimize disease presentation may help in management of the disease.[3] The purpose of this retrospective study, undertaken at a large oral medicine clinic, was to identify common medical conditions and medications used by patients with OLP or OLLs.

Materials and methods

With Institutional Review Board approval, the clinical records at the University of Florida College of Dentistry (UFCOD) Oral Medicine Clinic were searched. The records from July 1, 2009, to July 1, 2014, were searched to identify patients treated for OLP, OLLs, or *oral lichenoid mucositis* (OLM)—a nonspecific term utilized to label oral lichenoid disease in the absence of sufficient clinical information. The UFCOD biopsy service was then cross searched for initially identified patients, and only patients with biopsy confirmation of their lesions were included in the study. Cases were excluded if a biopsy confirmation of the clinical diagnosis could not be identified, if the patient had a concurrent diagnosis of dysplasia or squamous cell carcinoma of the oral cavity, if the histologic diagnosis was inconclusive, or if insufficient information was available for review. A database was constructed, and the following information was collected: the patient's age, sex, and race; the location of lesions within the mouth; the clinical appearance of lesions; medication usage at the time of presentation; concurrent medical conditions at the time of presentation; the histologic diagnosis from the biopsy; and the results of any direct immunofluorescence (DIF) testing. The resulting data were aggregated and evaluated qualitatively and statistically with Pearson chi-square testing using SPSS (version 23, IBM). Statistical significance was defined as $P < 0.05$.

Results

A total of 155 patients were included in the study. The average age was 63.6 years (range of 27-91 years), and 76.8% (n = 119) of the patients were women. Caucasian patients made up 91.8% (112/122) of the cases in which race was known (when self-identified by patients on medical history questionnaires); African American patients were 5.7% (7/122) of the sample with race reported, and Asian American patients were 2.5% (3/122).

Multifocal or bilateral presentation of lesions was recorded for 94.1% (128) of 136 cases reporting this information, while solitary or unilateral lesions were described in only 5.9% (8) of cases. The majority of the clinicians reported that the patients

Table 1. Use of antihypertensive medications by patients with oral lichen planus.

Category	No. of patients[a]	% of Subsample[b] (n = 84)	% of Total sample (N = 155)
β-Blockers	32	38.1	20.6
Calcium channel blockers	31	36.9	20.0
Diuretics			
Thiazide	19		
Loop	4		
Potassium-sparing	4		
Unspecified	1		
Total	*28*	33.3	18.1
ACE inhibitors	28	33.3	18.1
Angiotensin receptor blockers	17	20.2	11.0
α-Adrenergic blockers	4	4.8	2.6
Direct renin inhibitors	1	1.2	0.6

Abbreviation: ACE, angiotensin-converting enzyme.

[a]Some patients were taking multiple antihypertensive medications.
[b]Patients who were taking antihypertensive medications.

demonstrated either red or mixed red and white lesions (76.4%, n = 113/148 reporting this information), while in 35 patients (23.6%) the clinicians reported only white lesions. All cases had a biopsy-confirmed diagnosis of either OLP or OLM. The diagnoses OLL, OLDR, and OLCR are not commonly used by this particular biopsy service due to the stringent clinical criteria needed for these diagnoses. DIF was performed on 106/155 total lesions, and 90 (84.9%) were positive for fibrinogen deposition at the basement membrane; results were negative in 13 cases and inconclusive in 3 cases. In the 90 fibrinogen-positive lesions, the following staining intensity patterns were observed (scale of 1-4): +1 positivity, n = 11; +2 positivity, n = 28; +3 positivity, n = 43; and +4 positivity, n = 2. In 6 cases, results were marked only as "positive" on the report.

The following were the most commonly reported systemic medical conditions: hypertension (HTN), 51.6% (n = 80); thyroid disease, 33.5% (n = 52); diabetes mellitus (DM), 16.8% (n = 26); history of cancer (including skin cancers), 14.2% (n = 22); autoimmune disorders, 11.0% (n = 17); and liver disease, 10.3% (n = 16) (Chart 1). Of the 22 patients reporting a history of cancer, 6 reported breast cancer; 5, skin cancer (2 squamous cell carcinoma [SCC], 2 basal cell carcinoma, and 1 melanoma); 3, head and neck SCC; 2, prostate cancer; 2, colon cancer; 1, bladder cancer; 1, thyroid cancer; 1, ovarian cancer; and 1, nonspecified cancer. Patients reported the following autoimmune diseases: systemic lupus erythematosus (n = 3); rheumatoid arthritis (n = 2); both systemic lupus erythematosus and rheumatoid arthritis (n = 1); Sjögren syndrome (n = 2); both Behçet diesease and Sjögren syndrome (n = 1); psoriasis (n = 1); psoriatic arthritis (n = 1); polymyalgia rheumatica (n = 1); other dermatologic conditions (n = 4); and unspecified autoimmune disease (n = 1). Of the patients reporting liver disease, 7 reported hepatitis C, 1 reported hepatitis B, and 8 reported either unspecified hepatitis or unspecified liver disorder.

Medication usage was recorded in categories based on types of medications that have been linked to OLP in past studies: antihypertensive drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), cholesterol-lowering medications, psychiatric or antianxiety medications, thyroid replacements, antidiabetics, anticonvulsants, steroids, immunomodulators, antibiotics, antifungals, antimalarials, and human immunodeficiency virus (HIV) medications.[3,4] Only 12.3% of the patients in the present study reported not taking any medications from the aforementioned categories (n = 19), while the remaining 87.7% reported taking at least 1 medication (n = 136). Overall, 446 medications were recorded among the 155 patients in the study, and each patient averaged 3 medications.

Chart 2 shows the frequency of medication use by category among the patients in this study. The most commonly reported medication groups were antihypertensives (n = 84), NSAIDs (n = 72), cholesterol-lowering agents (n = 52), psychiatric or antianxiety medications (n = 51), and thyroid replacement medications (n = 46). Other medication categories were reported less frequently. A subcategorization of antihypertensive medications used by the patients is presented in Table 1.

Statistical analysis with Pearson chi-square (statistical significance $P < 0.05$) was performed for demographic data (age groups: less than 40, 40-60, and more than 60 years of age; and sex), medical conditions (HTN, thyroid disease, DM, history of cancer, autoimmune disease, and liver disease), and the most common 5 medication groups (antihypertensives, NSAIDs, psychiatric/antianxiety medications, thyroid replacements, and cholesterol-lowering agents) for each of the following factors: (1) white versus red or mixed lesions; (2) multifocal versus

Table 2. Pearson chi-square testing of demographic and medical history parameters in terms of clinical measures.

Parameter	Lesion characteristics		
	White vs red or mixed	Unilateral/solitary vs multifocal/diffuse	Negative vs positive DIF
Demographic			
Age (< 40; 40-60; > 60 y)	*P* = 0.195	*P* = 0.358	*P* = 0.691
Sex (male vs female)	*P* = 0.195	*P* = 0.794	*P* = 0.694
Medical condition			
HTN	*P* = 0.863	*P* = 0.493	*P* = 0.019[ab]
Thyroid disease	*P* = 0.562	*P* = 0.558	*P* = 0.679
Diabetes mellitus	*P* = 0.487	*P* = 0.441	*P* = 0.797
History of cancer	*P* = 0.328	*P* = 0.240	*P* = 0.507
Autoimmune disease	*P* = 0.897	*P* = 1.000	*P* = 0.748
Liver disease	*P* = 0.772	*P* = 0.014[ac]	*P* = 0.161
Medication use			
Antihypertensive	*P* = 0.975	*P* = 0.520	*P* = 0.047[ad]
NSAID	*P* = 0.902	*P* = 0.391	*P* = 0.854
Psychiatric	*P* = 0.577	*P* = 0.344	*P* = 0.375
Thyroid replacement	*P* = 0.943	*P* = 0.710	*P* = 0.415
Cholesterol-lowering	*P* = 0.980	*P* = 0.785	*P* = 0.337

Abbreviations: DIF, direct immunofluorescence; HTN, hypertension; NSAID, nonsteroidal anti-inflammatory drug.

[a]Statistically significant (*P* < 0.05).

[b]Positive DIF results were found in 38/48 patients (79%) without HTN vs 52/55 patients (95%) with HTN.

[c]Multifocal lesions were found in 116/121 patients (95%) without liver disease vs 12/15 patients (80%) with liver disease.

[d]Positive DIF results were found in 36/45 patients (80%) who were not using antihypertensives vs 54/58 patients (93%) who were using antihypertensives.

unilateral or solitary lesions; and (3) positivity on DIF testing. There was no statistically significant difference between the color of lesions (white versus red or mixed) and any of the tested variables. A statistically significant difference (*P* = 0.014) was noted between multifocal versus solitary lesion presentation and the presence of liver disease; 95.9% (n = 116/121) of those without liver disease manifested multifocal disease versus 80.0% (n = 12/15) of those reporting liver disease. No other variables were statistically different when multifocal lesion presentation and solitary lesion presentation were compared. In terms of DIF positivity, a statistically significant difference (*P* = 0.019) was noted for patients reporting HTN: While 79.1% (n = 38/48) of patients not reporting HTN showed DIF fibrinogen positivity, 94.5% (n = 52/55) of patients reporting HTN did. In addition, among patients not taking antihypertensive medications, 80.0% (n = 36/45) showed DIF fibrinogen positivity versus 93.1% (54/58) of those taking antihypertensives, a statistically significant difference (*P* = 0.047). No other variables showed a statistically significant difference in terms of DIF positivity. Statistical results are summarized in Table 2.

Discussion

OLP is a T-cell–mediated inflammatory disorder of the skin or mucosa in which activated T cells, usually $CD8^+$ lymphocytes, attack the basal layer of the epidermis or epithelium.[3] Lichen planus of the skin is a rare disorder affecting 0.5%-2.0% of the population, but oral lichenoid disease may commonly affect the mucosa even in the absence of skin lesions.[2,3] It is often difficult to differentiate true OLP from OLLs due to inconsistencies in diagnostic criteria, diversity of clinical presentations, difficulty in correlating medical histories with medication use timelines, and difficulty in the identification of allergens or other irritating factors. It is generally a disease affecting middle-aged patients and is significantly more common in women.[3] The patients in the present study were firmly categorized in an established patient demographic; more than 75% were women, and the average age was in the mid-seventh decade.

OLP may present as a white striated condition that is usually bilateral (reticular form), most commonly affecting the buccal mucosa or lateral tongue. In this state it is usually asymptomatic and may thus be underdiagnosed.[3] Other, more severe forms

include the erythematous atrophic or ulcerated forms, both of which often also show areas of telltale striations elucidating the lichenoid features common to OLP but may require biopsy to confirm the diagnosis.[1] In approximately 10% of cases, the gingiva may be the only site affected; this usually presents as desquamative gingivitis: a red, erosive, generally painful condition that must be differentiated from other vesiculobullous and autoimmune diseases.[3] OLP may increase in severity with advancing age or progression of the disease.[3] Unlike OLP, OLLs are more often isolated or asymmetric.[2]

The majority of the patients in the present study showed multifocal disease that was either atrophic or ulcerated. It is important to note that most of the patients in the present study presented with cases of a symptomatic nature that may have been unsuccessfully treated elsewhere; therefore, a bias toward more severe disease in this patient population is likely.

Symptomatic OLP or OLLs are often confirmed via biopsy. Findings include a bandlike inflammatory infiltrate of mainly lymphocytes in the superficial lamina propria, liquefactive degeneration of the basal layer, and an absence of dysplasia, as outlined in the 2003 modified World Health Organization classification for the diagnosis of OLP/OLLs.[1] Immunohistochemical testing is sometimes performed to differentiate OLP from other autoimmune diseases and usually shows a shaggy, bandlike deposition of fibrinogen along the basement membrane zone.[3]

Previous research has proposed a link between various systemic diseases or medications and OLP. For some diseases where there is little variation in treatment regimens, it has been difficult to determine if a possible association may be due to the underlying medical condition or the medication used to treat it, whereas other diseases and medications have a more clearly linked association.[4-6] An early example of this is the recognition of Grinspan syndrome in 1963, which is classified as OLP along with DM and HTN.[4] Subsequent work has identified that the antihypertensive medications used to treat this condition are most likely to be the etiologic factor of the OLP.[4] An association between DM and OLP has been studied with mixed results, although multiple antidiabetic medications have long been associated with lichenoid lesions.[4-6]

A more recent association between thyroid disease and the medications used to treat thyroid disease has been proposed; several studies have found a significant association between OLP and either thyroid disease, particularly hypothyroidism, or the use of thyroid medications, although other studies have not found such an association.[7-12] However, it is not yet clear whether thyroid disease itself or the medications may be the triggering agent. In 33% of the patients in the present study, a history of thyroid disease was present, suggesting the possibility of this disease as a contributing factor.

A review of other studies proposed a possible link between certain autoimmune disorders, such as ulcerative colitis and autoimmune dermatologic disease, and lichen planus of the skin.[13] An increase in immune-related autoantibodies—such as antinuclear antibody and certain antithyroid or gastrointestinal tract antibodies—has been found in a recent study, highlighting the possibility that OLP is a manifestation of systemic autoimmune disease in at least a small subset of patients.[14]

Perhaps the best-studied systemic condition in association to OLP is hepatitis C. Hepatitis C infection has been shown to be associated with an increase in OLP in some populations but not universally.[15] In particular, populations in Southern Europe, Japan, and possibly the United States appear to show the highest evidence of hepatitis C–associated OLP, while other populations have not yet shown a link.[16,17] Since some studies have not correlated the highest worldwide hepatitis C–positive populations with increased OLP rates, it is thought that endemic geographic variation alone is not sufficient to explain the differences, and it was found that patients with HLA-DR6^{+} presentation are generally more affected.[3,17] Case reports of approximately 50 patients presenting with OLP within 3-120 days after hepatitis B vaccination have also strengthened this association.[18] Conversely, some medications (such as interferon alfa) that are used to treat active hepatitis C infection have also been associated with OLP reactions.[3] Hepatitis C patients with OLP may also show more severe manifestations of the disease than patients without hepatitis C.[19] In the present study, 10% of the patients reported liver disease, which is within the parameters of previous studies (0.5%-35.0% of OLP associated with chronic hepatitis C).[19] In this study, the presence of liver disease was less commonly associated with multifocal disease (as opposed to solitary lesions) than was the absence of liver disease, though this result may have been influenced by relatively low numbers of both patients with liver disease and patients reporting solitary disease.

Multiple studies have shown an increase in the incidence of OLP and severity of disease in patients taking an increasing number of medications for systemic disease.[7,20,21] The medications most frequently associated with OLP have been antihypertensives (particularly angiotensin-converting enzyme inhibitors, β-blockers, and diuretics) and NSAIDs.[3,4] Other medications that have been associated include antiretroviral medications for the treatment of HIV, antimalarials, antidiabetics, antifungals, antibiotics, antimycobacterials, antidiarrheals, cholesterol-lowering statins, anticonvulsants, psychiatric medications, chemotherapeutics, immunomodulatory medications, and newer biologics such as monocolonal antibodies and tumor necrosis factor α inhibitors.[3,4] This study demonstrated that the presence of HTN or use of antihypertensive medications has an increased association with DIF positivity. However, no association was noted for red versus white disease (the red or ulcerated disease generally is more severe than the white) or multifocal versus solitary lesions for any of the most common medication categories.

Medication-related OLLs may be notoriously difficult to pinpoint, as presentation of the disease may occur from weeks to over a year after the medication is initiated.[2] It may also persist for weeks to months after cessation of the offending medication, and milder persistent disease may remain.[3] It was not possible to definitively differentiate between OLP and OLLs in the majority of the patients in the present study or to pinpoint a specific offending medication based on resolution of lesions after removal of the medication. However, the high percentage of patients in this study taking medications that have been shown to be associated with OLDR—particularly antihypertensives and NSAIDs—is suggestive that medication use may be a potentially modifiable factor in patients with symptomatic oral lichenoid disease, even if the drug is not the sole cause of the disease. In

addition, some prior studies have speculated that OLLs may be more likely to be associated with malignant transformation than traditional OLP, highlighting the importance of differentiating this subset of lesions.[22,23]

Conclusion

In the present study, polypharmacy and multiple medical conditions were noted in a majority of patients being treated for OLP or OLLs in a large oral medicine clinic. Although it is often difficult to pinpoint definitive etiologic factors for OLP, and the disease likely involves multiple variables, careful documentation of a patient's medical and medication history may be helpful in identifying potentially modifiable factors, such as medications or uncontrolled systemic disease. Biopsy may be helpful in confirming oral lichenoid disease, and long-term follow-up is recommended due to the low yet possible association with malignant transformation reported in the literature.[24]

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References

1. van der Meij EH, van der Waal I. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. *J Oral Pathol Med*. 2003;32(9):507-512.
2. Müller S. Oral manifestations of dermatologic diseases: a focus on lichenoid lesions. *Head Neck Pathol*. 2011;5(1):36-40.
3. Schlosser BJ. Lichen planus and lichenoid reactions of the oral mucosa. *Dermatol Ther*. 2010;23(3):251-267.
4. Yuan A, Woo SB. Adverse drug events in the oral cavity. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;119(1):35-47.
5. Van Dis ML, Parks ET. Prevalence of oral lichen planus in patients with diabetes mellitus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;79(6):696-700.
6. Ali AA, Suresh CS. Oral lichen planus in relation to transaminase levels and hepatitis C virus. *J Oral Pathol Med*. 2007;36(10):604-608.
7. Robledo-Sierra J, Mattsson U, Jontell M. Use of systemic medications in patients with oral lichen planus – a possible association with hypothyroidism. *Oral Dis*. 2013;19(3):313-319.
8. Siponen M, Huuskonen L, Läärä E, Salo T. Association of oral lichen planus with thyroid disease in a Finnish population: a retrospective case-controlled study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2010;110(3):319-324.
9. Hirota SK, Moreno PA, dos Santos CH, Seo J, Migliari DA. Analysis of a possible association between oral lichen planus and drug intake. A controlled study. *Med Oral Patol Oral Cir Bucal*. 2011;16(6):e750-e756.
10. Kragelund C, Tomsen CE, Bardow A, et al. Oral lichen planus and intake of drugs metabolized by polymorphic cytochrome P450 enzymes. *Oral Dis*. 2003;9(4):177-187.
11. Compilato D, Paderni C, Di Fede O, Gulotta G, Campisi G. Association of oral lichen planus with thyroid disease in a Finnish population: a retrospective case-control study: "A different finding from a Mediterranean area". *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111(1):12-13; author reply 13-14.
12. Robledo-Sierra J, Landin-Wilhelmsen K, Nyström HF, Mattsson U, Jontell M. Clinical characteristics of patients with concomitant oral lichen planus and thyroid disease. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;120(5):602-608.
13. Epidemiological evidence of the association between lichen planus and two immune-related diseases. Alopecia areata and ulcerative colitis. Gruppo Italiano Studi Epidemiologici in Dermatologia. *Arch Dermatol*. 1991;127(5):688-691.
14. Chang JY, Chiang CP, Hsiao CK, Sun A. Significantly higher frequencies of presence of serum autoantibodies in Chinese patients with oral lichen planus. *J Oral Pathol Med*. 2009;38(1):48-54.
15. Carrozzo M, Scally K. Oral manifestations of hepatitis C virus infection. *World J Gastroenterol*. 2014;20(24):7534-7543.
16. Carrozzo M. Oral diseases associated with hepatitis C virus infection, 2: lichen planus and other diseases. *Oral Dis*. 2008;14(3):217-228.
17. Lodi G, Pellicano R, Carrozzo M. Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. *Oral Dis*. 2010;16(7):601-612.
18. Tarakji B, Ashok N, Alakeel R, et al. Hepatitis B vaccination and associated oral manifestation: a non-systematic review of literature and case reports. *Ann Med Heath Sci Res*. 2014;4(6):829-836.
19. Gheorghe C, Mihai L, Parlatescu I, Tovaru S. Association of oral lichen planus with chronic C hepatitis. Review of the data in literature. *Maedica (Buchar).* 2014;9(1):98-103.
20. Habbab KM, Moles DR, Porter SR. Potential oral manifestations of cardiovascular drugs. *Oral Dis*. 2010;16(8):769-773.
21. Potts AJ, Hamburger J, Scully C. The medication of patients with oral lichen planus and the association of nonsteroidal anti-inflammatory drugs with erosive lesions. *Oral Surg Oral Med Oral Pathol*. 1987;64(5):541-543.
22. van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. *Oral Oncol*. 2007;43(8):742-748.
23. Rotim Z, Bolanca Z, Roguli AA, Andabak M, Boras VV, Vrdoljak DV. Oral lichen planus and oral lichenoid reaction – an update. *Acta Clin Croat*. 2015;54(4):516-520.
24. Fitzpatrick SG, Hirsch SA, Gordon SC. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. *J Am Dent Assoc*. 2014;145(1):45-56.