

Oral lichen planus and associated comorbidities: An approach to holistic health

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ABSTRACT

Lichen planus (LP) is a chronic inflammatory disorder with involvement of skin, oral and genital mucosa, scalp, and nail appendages. Oral lichen planus (OLP) lesions demonstrate a number of morphologic presentations, persist for a long time with rare self-resolution, and undergo malignant changes. OLP has been associated with numerous systemic connotations such as metabolic syndrome, diabetes mellitus, hypertension, thyroid diseases, psychosomatic ailments, chronic liver disease, gastrointestinal diseases, and genetic susceptibility to cancer. The oral health physician should be aware of these systemic associations and should work in close connect with the primary healthcare physicians to rule out the predisposing factors for the associated comorbidities. This article aims to highlight the various systemic associations of OLP and warrants the screening of these ailments in OLP for prevention and effective management.

Keywords: Diabetes mellitus, hepatitis C virus, lichen planus, oral lichen planus, psychosomatic diseases, systemic diseases

Introduction

Lichen planus (LP) is a chronic autoimmune mucocutaneous condition, primarily affecting the oral and genital mucous membrane, skin, nails, and scalp. Although the condition has an obscure etiopathogenesis, an underlying immune dysfunction and multifactorial predisposing factors also play a role.^[1]

Oral lichen planus (OLP) is the mucosal analog of LP of skin, although the two demonstrate marked clinical variability. OLP exhibits a more persistent course, propensity for malignant alterations with seldom undergoing self-remission. Isolated OLP cases are frequently seen in the dental setup,

with only 20% of the OLP cases presenting with cutaneous manifestations.^[2]

OLP has demonstrated numerous systemic connotations such as diabetes mellitus (DM), hypertension, metabolic syndrome (MS), thyroid diseases, psychosomatic ailments, chronic liver disease, gastrointestinal diseases, and genetic susceptibility to cancer.^[3] Therefore, OLP should be regarded as a systemic disorder, and the dental surgeon should be aware of the various systemic associations of LP and should work in close connection with primary healthcare physicians to rule out the predisposing factors for the associated comorbidities.^[1]

Etiopathogenesis

The exact etiology of OLP is not fully elucidated, although recent research suggests a key role of immunological mechanisms that

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Received: 08-09-2019

Revised: 08-09-2019

Accepted: 23-09-2019

Published: 15-11-2019

Access this article online

Quick Response Code:



Website:
www.jfmipc.com

DOI:
10.4103/jfmipc.jfmipc_749_19

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How to cite this article: Hasan S, Ahmed S, Kiran R, Panigrahi R, Thachil JM, Saeed S. Oral lichen planus and associated comorbidities: An approach to holistic health. J Family Med Prim Care 2019;8:3504-17.

may be implicated. LP is an autoimmune disease, mediated by T CD 8+ cells, macrophages, and Langerhan's cells. Immune mechanisms trigger apoptosis resulting in cell destruction and the appearance of characteristic histological changes.^[2]

Systemic associations

Hepatitis C virus (HCV) infection: Prevalence of HCV infection in patients with OLP varies between 0.5% and 35% as reported by multiple authors for distinguished geographical areas.^[4] Ulcerative/erosive OLP is most frequently seen in patients with chronic liver diseases.^[5] Mokni *et al.*^[6] were the first to suggest a possible link between chronic liver diseases and OLP.

A recent meta-analysis by Alaizari *et al.* ascertained the association between OLP and HCV infection and further necessitated the screening of patients with OLP for the timely diagnosis of HCV infection [Table 1].^[7]

LP has a long-established relationship with a multitude of comorbidities including MS, DM, thyroid dysfunction (hypothyroidism), and dyslipidemia (a risk factor for cardiovascular diseases).^[1] The association of LP with one or two of these comorbidities has been published in the literature.^[8-12] Current published literature has emphasized that chronic inflammation, endocrine dysfunction, and oxidative stress, frequently associated with mucocutaneous disorders, may serve as potential predisposing risk factors for the development of the MS.^[13] According to a recent study by Sadr Eshkevari *et al.*, a majority of patients with LP presented with features of DM, hypertension, MS, and dyslipidemia [Table 2].^[14]

Hence, patients with OLP entail exceptional surveillance from skilled health professionals and should be meticulously investigated to rule out the predisposing factors for cardiovascular diseases. This will aid to avert the possible complications and the associated comorbidities.^[15]

The linkage between DM and OLP was first reported by Grinspan *et al.*^[16] This association of DM and OLP may be highlighted by two facts: (a) impaired endocrine function in DM may result in immune dysregulation which may predispose to the development of OLP lesions^[17] and (b) few antidiabetic medications in patients with DM may evoke an allergic reaction and result in an oral lichenoid lesion.^[18] A meta-analysis study by Mozaffari *et al.* showed a statistically significant difference between the occurrences of OLP in patients with DM when compared with the controls (1.37% in patients with DM and 0.75% in the control population).^[19] Otero Rey *et al.* conducted a recent systematic review with a two-fold objective, wherein they demonstrated the prevalence of DM in patients with OLP (1.6%–37.7% DM in OLP) and also the prevalence of OLP in DM (0.5%–6.1% OLP in DM) [Table 3].^[20]

The association of thyroid disease and OLP was first reported in 1994, and the published literature has strengthened this

association.^[21] The possible association of OLP and thyroid gland diseases (TGDs) can be partly strengthened by the fact that numerous autoimmune conditions tend to congregate with autoimmune TGDs.^[10,22,23] A meta-analysis study by Li *et al.* showed a statistically significant difference in the prevalence of TGD between the OLP and the control population. The study showed that hypothyroidism and Hashimoto thyroiditis were the most common associated thyroid diseases with OLP [Table 4].^[24]

A study by Dreier *et al.* demonstrated that a majority of patients with OLP presented with dyslipidemia.^[9] Studies by Arias-Santiago *et al.*^[25] and Aniyan *et al.*^[26] demonstrated a higher prevalence of dyslipidemia in both skin and oral LP patients. Chronic inflammatory components result in uncontrolled dyslipidemia, and thus, augment the atherosclerotic plaque formation and other predisposing factors for cardiovascular diseases [Table 5].

Bowel diseases occasionally described concomitant with OLP including celiac disease, ulcerative colitis, and Crohn's disease.^[27] The relationship between *Helicobacter pylori* and OLP has been suggested by various studies. A statistically significant difference in *Helicobacter pylori* infection between patients with LP and control groups has been observed according to studies by Morravvej *et al.*^[28] and Vainio *et al.*^[29]

Psychological stress and anxiety

OLP is regarded as a psychosomatic disorder,^[30] and an increased rate of depression, anxiety, and psychic ailments has been associated with patients with OLP.^[31] Stress accounts as the major attribute to the acute exacerbations in patients with OLP.^[32] The relationship between OLP and stress is well-documented by frequent depressive and anxiety episodes and an elevated salivary cortisol level in patients with OLP.^[33] Elevated salivary/urinary cortisol levels correspond to increased anxiety and depressive states.^[34] A recent study by Radwan-Oczko *et al.* assessed the psychological and psychopathological aspects of patients with OLP. The study confirmed the interrelationship between OLP and stress, depression, anxiety, and the resultant compromised quality of patient's life.^[30] Another systematic review by Cerqueira *et al.* strengthened the linkage between the prevalence of OLP in patients with psychological disorders [Table 6].^[35]

Pharmacological and/or psychotherapeutic stress management may prove as a valuable additional approach in OLP therapy. Psychological assessment of patients should be an integral approach in the comprehensive OLP diagnosis.^[30]

Oral lichenoid reactions

Lichenoid reactions have a recognizable etiology, and clinically and histopathologically mimic OLP. Lichenoid lesions are characteristically unilateral^[36] and erosive.^[37] The inflammatory infiltrate is primarily composed of plasma cells, eosinophils, and neutrophils, and with numerous Civatte bodies.^[36,38]

Table 1: Studies showing LP association with hepatitis C virus infection

Authors(s)	Year	Title of study	Type of study	Outcome
Moknim <i>et al.</i>	1991	LP and hepatitis C virus	Prospective case study	Suggested association between OLP and HCV infection
Sebastian <i>et al.</i>	1992	A clinical study of 205 patients with OLP	Case-control study	Focused on the relationship between OLP and HCV infection
Bagan <i>et al.</i>	1994	OLP and chronic liver disease: A clinical and morphometric study of the oral lesions in relation to transaminase elevation	Prospective case study	No significant association between LP and HCV antibody
Criber <i>et al.</i>	1994	LP and HCV: An epidemiologic study	Epidemiologic study	HCV infection has an etiological role for OLP
Tanei <i>et al.</i>	1995	Clinical and histopathologic analysis of the relationship between LP and chronic hepatitis	Prospective clinical study	LP may be associated with chronic liver diseases (HCV infection)
Pervez <i>et al.</i>	1996	LP and HCV prevalence and clinical presentation of patients with LP and HCV infection	Case-control study	Statistically significant association between erosive OLP and HCV infection
Nago <i>et al.</i>	1997	High incidence of oral precancerous lesions in a hyper-endemic area of HCV infection	Prospective case study	Higher prevalence of OLP, leukoplakia, and leukoedema (62%) in HCV seropositive patients
Imhof <i>et al.</i>	1997	Prevalence of HCV antibodies and evaluation of HCV genotypes in patients with LP	Case-control study	Statistically significant high prevalence of HCV RNA in OLP patients: suggest an additional role of HCV in LP pathogenesis
Dupin <i>et al.</i>	1997	OLP and HCV infection: A fortuitous association	Case-control study	Mucosal erosions were more common in HCV patients ($P<0.001$)
Bagan <i>et al.</i>	1998	Preliminary investigation of the association of OLP and hepatitis C	Case-control study	Higher prevalence of HCV infection in OLP patients
Chuang <i>et al.</i>	1999	HCV and LP: A case control study of 34 patients	Case-control study	Small but significant % of patients with cutaneous LP had HCV antibodies; clinicians should actively look for HCV infection as LP may be the first presentation of HCV infection
Tucker <i>et al.</i>	1999	Lichen planus is not associated with HCV infection in patients from North-West England	Prospective epidemiological study	HCV infection is not associated with OLP
Grote <i>et al.</i>	1999	Increased occurrence of OLP in HCV infection	Case-control study	The study did not show an increased prevalence of OLP in HCV patients
Mignogna <i>et al.</i>	2000	OLP: Different clinical features in HCV +ve and HCV -ve patients	Prospective case-control study	Statistically significant difference between OLP in HCV+ve and HCV-ve groups for reticular and plaque clinical form
Kirtak <i>et al.</i>	2000	Prevalence of HCV infection in patients with LP in Gazian region of Turkey	Case-control study	The study suggested that the coexistence of LP and HCV infection is coincidental
Erkik <i>et al.</i>	2001	HCV infection prevalence in LP: Examination of lesional and normal skin of hepatitis C virus infected patients with LP for the presence of HCV RNA	Case-control study	The prevalence of HCV infection is not increased in Turkish population with LP. Virus may play a potential pathogenic role by replicating in the cutaneous tissues and triggering LP
Figueredo <i>et al.</i>	2002	OLP and HCV infection	Case-control study	Significantly higher frequency of HCV in OLP patients
Prabhu <i>et al.</i>	2002	LP and HCV - Is there any association? A serological study of 65 patients	Serological study	HCV infection is not associated with OLP
Daramolan <i>et al.</i>	2002	HCV and LP in Nigerians: Any relationship?	Case-control study	Higher prevalence of HCV in Nigerians and not necessarily in LP as a specific entity
Garavir <i>et al.</i>	2002	A study from Nepal showing no correlation between LP and HBV/HCV	Case control study	In Nepal, HBV/HCV does not play a role in the etiopathogenesis of OLP
Friedrich <i>et al.</i>	2003	OLP in patients with chronic liver diseases: A case control study	Case-control study	The study did not show an increased prevalence of HCV in OLP patients
Karavelioglu <i>et al.</i>	2004	Lichen planus and HCV infection in Turkish patients	Case-control study	No significant association between LP and HCV among Turkish population
Campisi <i>et al.</i>	2004	OLP, HCV and HIV: No association in a cohort study from any area of high HCV endemicity	Case-control study	Low OLP prevalence in HCV-infected patients; absence of OLP in HIV-coinfected patients suggest immunosuppression secondary to defective CD4 function

Contd...

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Authors(s)	Year	Title of study	Type of study	Outcome
Ghodsí <i>et al.</i>	2004	LP and HCV: A case control study	Case-control study	HCV seem to play an important etiologic role in OLP patients in Iran
Asaad <i>et al.</i>	2005	Association of LP and HCV	Case-control study	High prevalence of HCV infection in LP patients
Shengyuono <i>et al.</i>	2009	HCV and LP: A reciprocal association determined by a meta analysis	Meta-analysis of observational studies	HCV infection is associated with a statistically significant risk of OLP development
Lodi <i>et al.</i>	2010	HCV infection in OLP: A systemic review and meta-analysis	Systemic review and meta-analysis	LP patients have significantly high risk of HCV seropositivity; HCV seropositive patients have significantly higher risk for OLP occurrence
Taghavi <i>et al.</i>	2010	Evaluation of relationship between LP and HCV antibody	Descriptive analytical study	No significant association between LP and HCV antibody
Lin <i>et al.</i>	2010	Sero-prevalence of anti-HCV among patients with OLP in Southern Taiwan	Case-control study	Possible association between HCV and OLP suggest screening of OLP patients for HCV
Petti <i>et al.</i>	2011	The magnitude of the association between HCV infection and OLP: Meta analysis of case control study	Meta-analysis of case-control study	Although HCV and OLP were significantly associated, a majority of OLP patients were not affected by HCV
Konidena <i>et al.</i>	2011	HCV manifestations in patients with OLP	Cross-sectional case-control study	Statistically significant high prevalence of HCV in OLP patients: possible etiologic association between OLP and HCV
Alves <i>et al.</i>	2011	Association between HCV and OLP	Cross-sectional case-control study	Statistically significant high prevalence of HCV in OLP patients: possible etiologic association between OLP and HCV
Bob <i>et al.</i>	2012	The prevalence of HCV among LP patients and its clinical pattern at the university of Abuja Teaching Hospital, Gwagwalada, Abiya, Nigeria	Case-control study	Statistically significant difference between HCV antibody among OLP patients, suggesting strong association between HCV infection and OLP
Patil <i>et al.</i>	2012	Epidemiologic relation of OLP to HCV infection in an Indian population	Case-control study	OLP patients did not have any evidence of chronic liver diseases/ HBV/HCV infection
Tovara <i>et al.</i>	2013	OLP: A retrospective study of 633 patients from Bucharest, Romania	Retrospective study	Anti-HCV circulating Abs were more common in OLP patients in contrast to normal populations
Kumar <i>et al.</i>	2013	OLP as an extra hepatic manifestation of viral hepatitis - Evaluation in Indian Sub-continent	Case-control study	No association between OLP and viral hepatitis
Corrozzo <i>et al.</i>	2014	Oral manifestations of HCV infection	Evidence-based literature review	Strong association of OLP in HCV seropositive patients
Kamath <i>et al.</i>	2015	Oral lichenoid lesions - A review and update	Literature review	Focused on the relationship between OLP and HCV infection
Alizari <i>et al.</i>	2016	HCV infection in OLP: A systemic review and meta-analysis	Systemic review and meta-analysis	Statistically significant difference in HCV seropositivity in OLP patients in contrast to control group
Carli <i>et al.</i>	2016	HCV and OLP: Evaluation of their correlation and risk factors in a longitudinal clinical study	Longitudinal clinical study	OLP could serve as an indicator of HCV infection in asymptomatic patients, thus enabling early diagnosis and treatment of hepatitis and better prognosis
Vanzela <i>et al.</i>	2017	Mucosal erosive LP is associated with HCV: Analysis of 104 patients with LP in two decades	Case-control study	Strong association of mucosal erosive OLP in HCV seropositive patients
Manomaivat <i>et al.</i>	2018	Association of HCV infection in Thai patients with OLP: A case control study	Case-control study	Statistically significant high prevalence of HCV in OLP patients: the study warranted the screening of HCV-infected patients with OLP
Gheorge <i>et al.</i>	2018	Potential pathogenic mechanisms involved in the association between LP and HCV infection	Literature review	The study summarized the main potential pathogenic mechanism involved in the association between OLP and HCV
Nosratzahi <i>et al.</i>	2018	Lack of association between oral lichen planus and hepatitis B and C virus infection - A report from Southeast Iran	Case-control study	No association between OLP and viral hepatitis

LP: Lichen planus; OLP: Oral lichen planus; HCV: Hepatitis C virus

Dental restorative materials: Amalgams, composite resins, cobalt, and gold are the chief contributors to oral lichenoid reaction (OLR). Flavoring agents and plastics also play a role in the pathogenesis and management of patients with OLR.^[39]

Table 2: Studies showing association of LP and comorbidities

Authors(s)	Year	Title of study	Type of study	Outcome
Kurgansky <i>et al.</i>	1994	Wide spread LP in association with Turner's syndrome and multiple endocrinopathies	Case report	Widespread LP was seen along with DM, hypothyroidism, IBD, and Turner's syndrome
Chang <i>et al.</i>	2009	Significantly higher frequency of presence of serum auto antibodies in Chinese patients with OLP	Case-control study	Higher prevalence of serum autoantibodies in OLP patients (60.9%)
Ebrahimi <i>et al.</i>	2012	Mucosal LP: A systemic disease requiring multidisciplinary care: A cross sectional clinical review from a multidisciplinary perspective	A cross-sectional clinical review	A majority of the patients presented with multifocal lesions, and isolated oral lesions were seen in 28% of females and 38% of males: 285 patients had at least one additional autoimmune disease
Munde <i>et al.</i>	2013	Demographics and clinical profile of OLP: A retrospective study	A retrospective study	The most common systemic disease was hypertension followed by DM followed by hypothyroidism; epithelial dysplasia was seen in four cases
Chung <i>et al.</i>	2014	Autoimmune co morbid diseases associated with LP: A nationwide case control study	Case-control study	LP association with varied autoimmune diseases (SS, SLE, dermatomyositis, alopecia areata, and vitiligo)
Jornet	2014	Association of Autoimmune diseases with OLP: A cross sectional clinical study	Cross-sectional clinical study	No significant association of OLP and autoimmune diseases
Baykal <i>et al.</i>	2015	Prevalence of metabolic syndrome in patients with mucosal LP: A case control study	Case-control study	Higher occurrence of metabolic syndrome in mucosal LP; mean fasting blood glucose and diastolic BP were significantly higher in LP patients; no significant difference in the prevalence of dyslipidemia and insulin resistance
Lauritano <i>et al.</i>	2016	OLP clinical characteristics in Italian population: A retrospective study	A retrospective study	The most common systemic disease with OLP: DM>hypertension>Hep C and thyroiditis>malignant transformation: symptomatic OLP in 27% patients
Eshkevari <i>et al.</i>	2016	The association of cutaneous LP and metabolic syndrome: A case control study	Case-control study	Cutaneous LP is associated with significantly higher risk for metabolic syndrome, DM, dyslipidemia, and hypertension
Kurian <i>et al.</i>	2017	Prospective case control study on metabolic syndrome in LP in a tertiary care center	Prospective case-control study	No significant association of MS in LP patients; hypertension, triglycerides, and low HDLC levels were significantly associated with LP
Sponenberg <i>et al.</i>	2018	OLP and its relationship with systemic diseases: A review of evidence	Evidence-based literature review	OLP patients are carriers of a disease with systemic implications and may require a multidisciplinary treatment approach
Hasbah <i>et al.</i>	2018	Prevalence of metabolic syndrome in LP: A cross sectional study from a tertiary care center	Cross-sectional clinical study	A majority of LP patients presented with metabolic syndrome
Bilobol <i>et al.</i>	2019	LP and co morbid conditions.	Literature review	The most common global trends of comorbidities of LP were determined; results can form the basis for updating the clinical guidelines for LP management
Kumar <i>et al.</i>	2019	Co morbidities in LP: A case control study in Indian patients	Case-control study	Strong association of OLP with DM and dyslipidemia and hypothyroidism
Okpala <i>et al.</i>	2019	Metabolic syndrome and dyslipidemia among Nigerian with LP: A cross sectional study	Cross-sectional study	Insignificant association with metabolic syndrome and significant association with dyslipidemia

LP: Lichen planus; OLP: Oral lichen planus; DM: Diabetes mellitus; IBD: Inflammatory bowel disease; SS: Sjogren's syndrome; SLE: Systemic lupus erythematosus; BP: Blood pressure; MS: Metabolic syndrome; HDLC: High density lipoprotein cholesterol

Drug-induced OLR: The most common drugs associated with OLR are nonsteroidal anti-inflammatory agents (NSAIDs) and angiotensin-converting enzyme inhibitors (captopril, enalapril).^[37] In 1994, Thompson and Skaehill showed strong evidence that drugs such as beta-blockers, methyl dopa, penicillamine, and NSAIDs are linked with lichenoid eruptions.^[40] Withdrawing the offending drugs results in the resolution of the lichenoid reaction and this aids the diagnosis of OLR.

Genetic predisposition: Documentation of several familial cases have suggested genetic predisposition in the pathogenesis

of OLP.^[41] Lowe *et al.* were the first to report a significantly higher HLA-A3 frequency in a British family with cutaneous LP.^[42]

Predisposing factors

Mechanical trauma

Dental procedures, sharp cusps, uncountoured dental restorations, ill-fitting prosthesis, and deleterious oral habits are the possible predisposing factors.^[43] Koebner's phenomenon refers to the development of lesions at sites subjected to trauma. This suggests a possible explanation for erosive lesions being more

Table 3: Studies showing association of LP with DM

Authors(s)	Year	Title of study	Type of study	Outcome
Grinspan <i>et al.</i>	1966	Lichen rubber planus de la muquase puccale bone associated un diabete	Retrospective study	38% of OLP patients had DM
Jolly <i>et al.</i>	1972	LP and its associations with DM	Case-control study	Strong association between LP and DM
Howell <i>et al.</i>	1973	OLP and DM: A potential syndrome	Case-control study	Strong association between LP and DM (13% OLP patients had diabetes)
Powel <i>et al.</i>	1974	Glucose tolerance in LP	Case-control study	Study suggested a controversial link between OLP and DM; an altered response to the oral administration of glucose exists in LP patients
Lowe <i>et al.</i>	1976	Carbohydrate metabolism in LP	Case-control study	Impaired carbohydrate metabolism and higher prevalence of DM than in general population
Christensen <i>et al.</i>	1977	Glucose tolerance in patients with OLP	Case-control study	Impaired carbohydrate metabolism and higher prevalence of DM than in general population
Haley <i>et al.</i>	1979	Abnormal glucose tolerance associated with LP	Case-control study	A majority of OLP patients showed abnormal glucose tolerance
Bussel <i>et al.</i>	1979	Glucose tolerance in patients with lesions of the oral mucosa	Case-control study	12.8% of OLP patients had abnormality in carbohydrate metabolism (abnormal glucose tolerance test)
Lundstrom <i>et al.</i>	1983	Incidence of DM in OLP patients	Case-control study	High incidence of DM in OLP patients (28%) suggests the hypothesis that DM may be related to the pathogenesis of OLP
Lozarda-Nur <i>et al.</i>	1985	Assessment of plasma glucose in 99 patients with OLP	Case-control study	OLP patients had abnormality in carbohydrate metabolism (abnormal glucose tolerance test)
Nigam <i>et al.</i>	1987	Glucose tolerance study in LP	Prospective study	Results reinforce the possibility of glucose intolerance in LP patients
Borghelli <i>et al.</i>	1987	OLP and DM: A preliminary epidemiological study	Case-control study	No statistically significant difference between OLP in diabetic/nondiabetic group
Saleem <i>et al.</i>	1989	OLP among 4277 patients from Giza, Saudi Arabia	Case-control study	OLP patients had abnormality in carbohydrate metabolism (abnormal glucose tolerance test)
Silver <i>et al.</i>	1991	A prospective study of findings and management in 24 patients with OLP	Prospective study	No significant association between OLP and DM
Albrecht <i>et al.</i>	1992	Occurrence of oral leukoplakia and LP in DM	Prospective case study	Significantly higher prevalence of oral leukoplakia and LP in DM patients
Bagan	1993	OLP and DM: A clinico-pathologic study	Case-control study	Strong association between OLP and DM
Borghelli <i>et al.</i>	1993	OLP in patients with diabetes: An epidemiologic study	Case-control study	No statistically significant difference between OLP in diabetic/nondiabetic group
Jelink <i>et al.</i>	1994	Cutaneous manifestations of DM	Case-control study	1.6% of DM patients showed incidence of LP lesions
Quirine <i>et al.</i>	1995	Oral manifestations of DM in controlled and uncontrolled patients	Prospective study	No significant association between OLP and DM
Amenikanou <i>et al.</i>	1998	Prevalence of OLP in DM according to the type of diabetes	Case-control study	OLP prevalence was higher in type I DM, slightly higher in type II DM than the control population
Guggenheimer <i>et al.</i>	2000	Insulin dependent DM and oral soft tissue pathologies: I - Prevalence and characteristics of non-candidal lesions	Cross-sectional epidemiologic study	No significant association between OLP and DM
Ponte <i>et al.</i>	2001	DM and oral diseases	Review of literature	No significant association between OLP and DM
Romero <i>et al.</i>	2002	Prevalence of DM in OLP patients: Clinical and pathological characteristics	Prospective study	27.4% of OLP patients had type II DM and 17.7% had impaired fasting blood glucose levels; no significant differences observed in terms of clinical and pathological features between diabetic and nondiabetic OLP patients
Naheed <i>et al.</i>	2002	Skin manifestations among diabetic patients admitted in general medical wards for various medical problems	Prospective case study	LP was seen in 4.4% of patients with DM
Denli <i>et al.</i>	2004	Diabetes and hepatitis frequency in 140 LP cases in Cukurove region	Retrospective case-control study	Coassociations between OLP/LP and HBV, DM
Aldelai <i>et al.</i>	2005	Occurrence of LP in DM	Case-control study	OLP lesions were seen in both diabetic (9.8%) and nondiabetic or control group (5.3%)
Seyham <i>et al.</i>	2007	High prevalence of glucose metabolism disturbances in LP patients	Case-control study	Approximately one-half LP patients had glucose metabolism disturbances and one-fourth had DM
Castelle <i>et al.</i>	2010	Clinical features of OLP: A retrospective study of 5 cases	Retrospective study	DM patients are more prone to develop erosive/atrophic OLP lesions

Contd...

Table 3: Contd...

Authors(s)	Year	Title of study	Type of study	Outcome
Bagewadi <i>et al.</i>	2011	OLP and its association with DM and hypertension	Case-control study	DM and hypertension do not appear to play a direct role in the etiology of OLP
Arshiya <i>et al.</i>	2011	Incidence of DM in LP patients	Case-control study	Weak association between OLP and DM
Ateffi <i>et al.</i>	2012	Prevalence of DM and impaired blood glucose in patients with LP	Cross-sectional study	Higher prevalence of DM in LP patients; 20% of the patients had DM and 17.5% had impaired fasting blood glucose levels; Also, duration of LP in DM patients was longer than the nondiabetics
Ahmed <i>et al.</i>	2012	Frequency of OLP in patients with non-insulin dependent DM	Case-control study	6.9% of non-insulin dependent DM patients had histopathologically confirmed OLP; 1.2% of DM patients in control
Mozaffari <i>et al.</i>	2016	Prevalence of OLP in DM: A meta-analysis study	Meta-analysis study	Statistically significant difference in the prevalence of OLP in DM patients when compared with control. (1.37% in DM and 0.75% in control)
Otoro Rey <i>et al.</i>	2018	LP and DM: Systematic review and meta analysis	Systematic review and meta-analysis	Two-fold objective: prevalence of DM in OLP (1.67%-37.7%); prevalence of OLP in DM patients (0.5%—6.1%)

OLP: Oral lichen planus; DM: Diabetes mellitus; LP: Lichen planus

common in trauma-prone sites (buccal mucosa and lateral aspect of the tongue).^[33]

Plaque and calculus

Erosive/atrophic LP patients, especially with desquamative gingivitis, face difficulty in tooth brushing because of gingival pain and bleeding. Gingival lesions of LP may be worsened by dental plaque and calculus.^[44]

Clinical Manifestations

OLP is a mucocutaneous disorder of unknown etiology. In a majority of cases, LP may affect only the oral cavity. The condition may also affect other mucosal sites such as skin, genitals, scalp, and nails.^[45] OLP primarily affects perimenopausal females with a prevalence of 0.1%–4%. Most OLP patients are in the age range of 30–60 years; however, no age group is spared.^[46]

Skin lesions: Cutaneous LP lesions are usually self-limiting, cause itching, and are delineated by the characteristic six P’s – planar, polygonal, pruritic, purplish, papules, and plaques. The disease has an acute onset, and the commonly affected sites are flexor surfaces of the wrists, forearms, and legs. Interlacing, fine, reticular-white lines (Wickham striae) often surround the skin lesions^[47] [Figure 1].

Oral manifestations: Oral lesions have a chronic course with infrequent spontaneous remission and are potentially premalignant. In addition, oral lesions are difficult to treat, and hence, a source of morbidity.

Andreason classified OLP into six clinical types: reticular [Figure 2a and b], papular, plaque-like [Figure 3], atrophic [Figure 4], ulcerative [Figure 5], and bullous [Figure 6].^[48] OLP was further classified into reticular (reticular, plaque-like, and papular), erythematous (atrophic), and erosive type (ulcerative, bullous).^[49] However, according to a few authors, OLP is of two types:



Figure 1: Solitary papular lesion on the dorsum of the leg

reticular (reticular, plaque-like) and erosive (atrophic, ulcerative, and bullous).^[50]

The reticular type is the most frequently encountered form and manifests as bilateral asymptomatic Wickham striae on the buccal mucosa, labial mucosa, tongue, palate, and gingiva. Atrophic and erythematous oral mucosa is seen in the atrophic LP. The vesicles filled with fluid are characteristically seen in bullous LP. Erosive LP presents as an ulcerated, erythematous, and painful lesion. These erosive lesions are frequently accompanied by secondary opportunistic candidal infections.^[51]

Most of the OLP cases are seen on the buccal mucosa, followed by dorsum of tongue, gingiva, labial mucosa, and vermilion border of the lower lip.^[33,52] Exclusive gingival lesions are seen in about 10% of patients with OLP. Erythematous gingival lesions result in desquamative gingivitis, the most frequently seen form of gingival LP [Figure 7].^[53] These lesions also manifest as a minute, raised, fine white interlacing papules or plaques and may mimic keratotic lesions (frictional keratosis or leukoplakia).

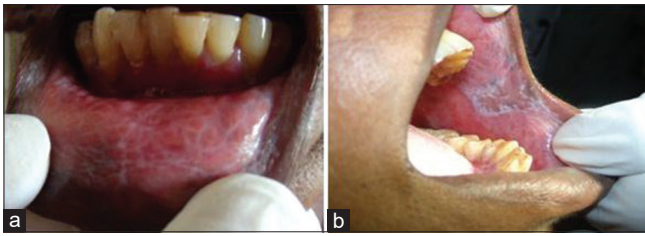


Figure 2: (a and b) Reticular lichen planus. Wickham's striae on the (a) lower labial mucosa and (b) buccal mucosa



Figure 3: Plaque-like lichen planus on the dorsum of the tongue



Figure 4: Atrophic lichen planus on the buccal mucosa



Figure 5: Ulcerated lichen planus on the lower lip



Figure 6: Bullous lichen planus



Figure 7: Desquamative gingivitis in lichen planus

Isolated OLP cases at sites other than the gingiva are rarely seen, although few isolated lip^[54] or tongue^[48] lesions have been reported.

Genital mucosa: Genital mucosa is the most commonly involved extraoral site in female patients, and about 20% of females with OLP develop genital lesions.^[55] Vulvovaginal–gingival syndrome denotes the relationship of LP with the vulva, vagina, and gingiva.^[56] Usually, genital lesions are primarily erosive. However, few patients may present with asymptomatic reticular genital lesions.^[57]

The penogingival syndrome denotes the male analog of the vulvovaginal–gingival syndrome of LP.^[58]

Skin appendages: Scaly, violaceous, pruritic papular lesions affecting the scalp are known as Lichen planopilaris. Untreated cases may result in scarring alopecia.^[59]

Nails: Irregular, longitudinal grooving, ridging, and thinning of the nail plate are seen. This causes shedding of the nail plate with

Table 4: Studies showing association of LP with thyroid diseases

Authors(s)	Year	Title of study	Type of study	Outcome
Soy <i>et al.</i>	2007	Frequency of rheumatic diseases in patients with autoimmune thyroid diseases	Cross-sectional study	OLP was seen in 2 of 65 patients (3.1) with autoimmune thyroid diseases
Siponon <i>et al.</i>	2010	Association of OLP with thyroid disease in a Finish population: A retrospective case-control study	Retrospective case-control study	Higher prevalence of thyroid diseases (esp. hypothyroidism) in OLP and OLL groups
Compilato <i>et al.</i>	2011	Association of OLP with thyroid disease in a Finish population: A retrospective case-control study - A different finding from Mediterranean area	A retrospective case-control study	No significant association of thyroid disease with OLP
Lo Muzio <i>et al.</i>	2013	Possible link between Hoshimoto thyroiditis and OLP: A novel association found	Cross-sectional study	Higher prevalence of Hoshimoto thyroiditis in OLP (13%)
Robledo-Sierra <i>et al.</i>	2013	Use of systemic medications in OLP patients - A possible association of hypothyroidism	Case-control study	Use of thyroid medications (levothyroxine) is associated with OLP, suggesting a possible connection with hypothyroidism
Branisteanu <i>et al.</i>	2014	Cutaneous manifestations associated with thyroid diseases	Retrospective prevalence study	LP was seen in 18% of patients and was the second most common dermatological disease after alopecia aerata
Vanja <i>et al.</i>	2014	The significance of oral % systemic factors in Australian and Croatian patients with OLP	Cross-sectional study	No significant association of OLP with thyroid disease/malignancy
Robledo-Sierra <i>et al.</i>	2015	Clinical characteristics of patients with concomitant OLP and thyroid diseases	Case-control study	Significantly higher prevalence of thyroid diseases among OLP group
Lavee <i>et al.</i>	2016	Evaluation of the association between OLP and hypothyroidism: A retrospective comparative study	Retrospective comparative study	A majority of OLP patients (6.7) presented with history of hypothyroidism than controls (4%)
Garcia-Polo <i>et al.</i>	2016	Thyroid diseases and OLP: A prospective case control	A prospective case control study	Higher prevalence of thyroid diseases (esp. hypothyroidism) in OLP (15.3%) in contrast to control (5.2%) groups
Guarneri <i>et al.</i>	2017	Thyroid autoimmunity and lichen	Cross-sectional study	Common pathogenic mechanisms may be responsible for co-occurrence of LP and autoimmune thyroid diseases and molecular mimicry could trigger both diseases
Ardino <i>et al.</i>	2017	Evidence of earlier thyroid dysfunction in newly diagnosed OLP patients: A hint for endocrinologists	Case-control study	Patients with thyroid diseases have 3-fold increased odds of having OLP
Li <i>et al.</i>	2017	Association of OLP with thyroid disease: A literature review and meta analysis	Literature review and meta-analysis	Significantly higher prevalence of thyroid diseases among OLP group.
Alikhani <i>et al.</i>	2017	Association between clinical severity of OLP and anti-TPO levels in thyroid patients	Case-control study	Erosive OLP is associated with TPO antibodies in thyroid patients; hence, TPO antibodies in such patients may be useful to diagnose a possible undetected thyroid disorder
Zhou <i>et al.</i>	2018	Correlation between oral lichen planus and thyroid diseases in China: A case-control study	Case-control study	Higher prevalence of thyroid diseases (esp. Hoshimoto thyroiditis and thyroid nodule) in OLP (72.4%) and OLL (68.3%) groups
Robledo-Sierra <i>et al.</i>	2018	A mechanistic linkage OLP and auto-immune thyroid disease	Case-control study	Expression of thyroid stimulating hormone receptor in OLP lesion suggest that mechanism associated with autoimmune thyroid diseases is involved in OLP etiology
Kats <i>et al.</i>	2019	OLP and thyroid gland diseases: possible association	Case-control study	No significant association of OLP with thyroid gland disease or related medications
Kumar <i>et al.</i>	2019	Association of OLP with thyroid disease: Case report and review of literature	Case report and review of literature	Possible presentation of OLP in a hypothyroid patient as a marker of thyroid disease status and the possible pathogenic link between both the conditions

OLP: Oral lichen planus; OLL: Oral lichenoid lesion; LP: Lichen planus

atrophy of the nail bed. Pterygium (i.e. cuticular overgrowth) is a characteristic finding.^[60]

Esophageal LP may manifest as dysphagia, chronic pain, and strictures.^[61]

Diagnosis

Bilaterally, symmetrical, white interlacing striae, and/or popular lesion is the most peculiar clinical manifestation of OLP.^[62] The presence of bilateral, often

Table 5: Studies showing association of LP and dyslipidemia

Authors(s)	Year	Title of study	Type of study	Outcome
Dreihner <i>et al.</i>	2009	LP and dyslipidemia: A case control study	Case-control study	Higher prevalence of dyslipidemia in LP group (42.5%) in contrast to 37.8% of control group
Santiago <i>et al.</i>	2011	CVS risk factors in patients with LP	Case-control study	Higher prevalence of dyslipidemia in both cutaneous oral LP
Santiago <i>et al.</i>	2011	Lipid levels in patients with LP: A Case control study	Case-control study	Strong association between LP and dyslipidemia: Lipid level screening in LP patients for early treatment and prevention of CVS diseases
Jornet <i>et al.</i>	2012	Alterations of serum lipid profile patterns in OLP patients: A cross-sectional study	Cross-sectional study	Dyslipidemia in 58% of OLP patients and 50% of controls. Statistically significant difference in HDL between OLP and controls
Saleh <i>et al.</i>	2014	Homocystine and other CV risk factors in LP patients	Case-control study	LP patients were found to have higher markers of both metabolic and CV risk factors.
Krishnamoorthy <i>et al.</i>	2014	Lipid profile and metabolic syndrome status in patients with OLP, OLL and healthy individuals attending a dental college in North India: A descriptive study	Case-control descriptive study	Significant levels of dyslipidemia in OLP patients when compared with control group, posing an increased risk for CVS disorders
Yusuf <i>et al.</i>	2015	Dislipidemia: Prevalence and associated risk factors among patients with LP in Kano, north west Nigeria	Case-control study	Higher prevalence of dyslipidemia among LP patients
Panchal <i>et al.</i>	2015	Alterations in lipid metabolism and anti oxidant status in LP	Case-control study	Chronic inflammation in LP may explain the association of dyslipidemia and CVS risk
Mehdipour <i>et al.</i>	2015	Evaluation of relationship between serum lipid profile and OLP	Cross-sectional study	Triglycerides and cholesterol can be considered to have a critical role in the incidence of LP
Kar <i>et al.</i>	2016	Metabolic derangements in LP: A case control study	Case-control study	Higher mean values of all the lipid and glucose parameters, posing increased risk for CVS disorders
Kuntoji <i>et al.</i>	2016	Dyslipidemia and metabolic syndrome in patients with lichen planus: A case control study	Case-control study	Significant association of dyslipidemia in LP group; screening of dyslipidemia to reduce the risk and complications of cardiovascular disorders (CVS) disorders
Lai <i>et al.</i>	2016	LP and dyslipidemia: A systematic review and meta analysis of observational studies	Systematic review and meta-analysis	LP was significantly associated with increased risk for dyslipidemia
Anyaniyan <i>et al.</i>	2018	Alterations of serum lipid profile patterns in OLP patients: A case-control study	Case-control study	Evident association between dyslipidemia and OLP

LP: Lichen planus; CVS: Cyclic vomiting syndrome; OLP: Oral lichen planus

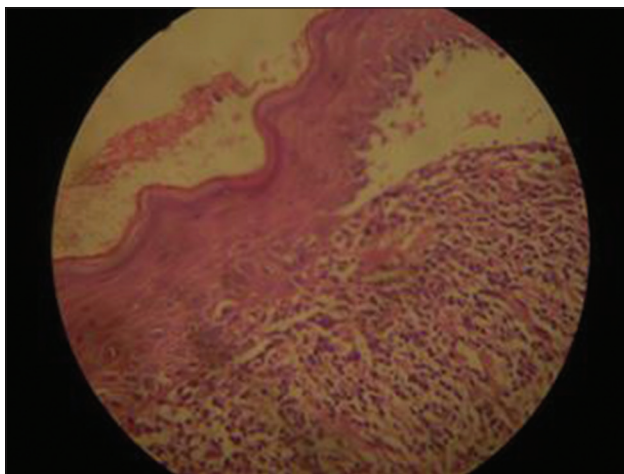


Figure 8: Histopathology of lichen planus

symmetrical reticular lesions was also considered as an essential clinical criterion.

The following histopathological features are fundamental for OLP diagnosis [Figure 8]:

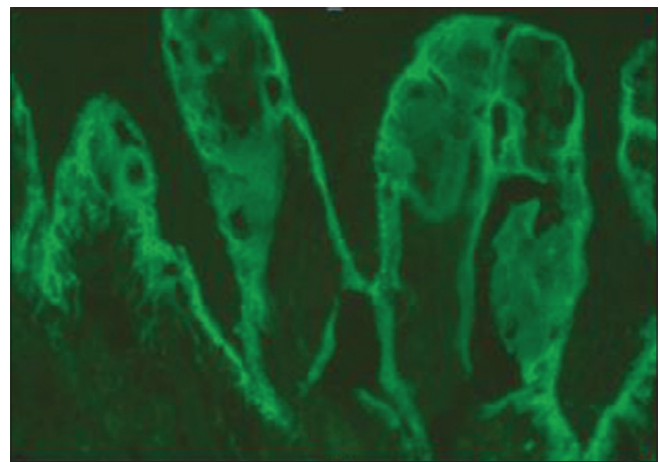


Figure 9: Direct immunofluorescence showing shaggy bands of fibrinogen

A distinct band-like lymphocytic infiltrate in the connective tissue zone.

Presence of epithelial basal layer liquefaction degeneration

No signs of atypia/epithelial dysplasia.^[63]

Table 6: Studies showing association of LP and psychosomatic disorders

Authors	Year	Title of study	Type of study	Outcome
Andreasen <i>et al.</i>	1968	OLP: A clinical evaluation of 115 cases	Prospective case study	49% of OLP patients reported strong episodes of stress
Kovesi <i>et al.</i>	1973	Follow up studies in OLP	Prospective case study	Psychological stress, anxiety and depressive are closely associated with OLP
Lowental <i>et al.</i>	1984	OLP association to the moderate medical model	Case-control study	Erosive OLP patients reported with stress related history in contrast to patients with reticular form
Allen <i>et al.</i>	1986	Relationship of stress and anxiety to OLP	Case-control study	No significant association of stress and anxiety with OLP
Hamef <i>et al.</i>	1987	Psychiatric disturbances in patients with OLP	Case-control study	OLP has a propensity to occur in psychologically stressful conditions
Humphris <i>et al.</i>	1992	Psychological factors in OLP	Descriptive case study	No statistically significant correlation between psychological factors and OLP
McLoed <i>et al.</i>	1992	Psychological factors in OLP	Descriptive case study	No statistically significant correlation between psychological factors and OLP
Colella <i>et al.</i>	1993	The Psychopathological aspect of OLP	Case-control study	Psychological stress, anxiety, and depressive are closely associated OLP
McCartan <i>et al.</i>	1995	Psychological factors associated with OLP	Prospective case study	No statistically significant correlation between erosive OLP and anxiety and depression
Burkhart <i>et al.</i>	1996	Assessing the characteristics of patients with OLP	Prospective case study	The study established a link between stress and OLP as 51.4% of OLP patients perceived stressful situations in their lives, workplace, and personal relationships
Chiappelli <i>et al.</i>	1997	Cellular immune correlated of clinical severity in OLP: Preliminary association with mood states	Case-control study	Erosive OLP has a more likely association with mood states
Rojo-Moreno <i>et al.</i>	1998	Psychiatric factors and OLP: A psychometric evaluation of 100 cases	Case-control study	OLP patients exhibited greater anxiety as reflected by statistically significant scores with anxiety tests: more vulnerable to psychiatric disorders
Koray <i>et al.</i>	2003	The evaluation of anxiety and salivary cortisol levels in OLP patients	Case-control study	Elevated levels of anxiety and salivary cortisol levels in OLP patients, thus emphasizes that OLP is closely associated with stress
Aroya <i>et al.</i>	2004	Association between psychiatric diseases and presence of OLP, RAS and burning mouth syndrome	Case-control study	Significant association of psychiatric ailments in oral mucosa lesions: higher stress levels in RAS patients and OLP
Choudhary <i>et al.</i>	2004	Psychological stressors in OLP	Double-controlled study	Significant higher stress levels in OLP
Ivanovski <i>et al.</i>	2005	Psychological profile in OLP	Case-control study	Significantly higher cortisol levels (more in erosive OLP); higher episodes of anxiety, depression, hysteria and hypochondriasis in OLP
Lindquist <i>et al.</i>	2006	Psychological health in patients with genital and oral erosive LP	Case-control study	Higher stress levels most common in erosive OLP
Perdigoon <i>et al.</i>	2007	Serotonin transporter gene polymorphism in OLP patients	Case-control study	No significant association between OLP and serotonin transporter gene polymorphism
Shah <i>et al.</i>	2009	Evaluation of salivary cortisol and psychological factors in OLP patients	Case-control study	Elevated stress levels in OLP patients
Pokupec <i>et al.</i>	2009	Lichen ruber planus as a psychiatric problem	Case report	Comorbidity of LP with occurrence of anxiety and depression suggest that oral diseases have an associated psychogenic component
Twail <i>et al.</i>	2009	Psychological aspects in patients with LP	Prospective case study	LP patients demonstrated higher prevalence of psychiatric comorbidities
Bajaj <i>et al.</i>	2010	OLP: A clinical study	Prospective clinicopathological study	OLP is a chronic disease with diverse comorbidities and stress was the most important aggravating factor
Girardi <i>et al.</i>	2011	Salivary cortisol and dehydroepiandrosterone (DHEA) levels: psychological factors in patients with OLP	Case-control study	No significant difference between stress and OLP OR morning and night salivary levels of cortisol and DHEA
Pourshahidi <i>et al.</i>	2011	Evaluation of the relationship between OLP and stress	Case-control study	Significant elevation of stress levels in patients with erosive OLP

Contd...

Table 6: Contd...

Authors	Year	Title of study	Type of study	Outcome
Hasel <i>et al.</i>	2013	Relationship of personality factors to perceived stress, depression and OLP severity	Retrospective study	OLP patients are more prone to stress, anxiety, and depression
Hirota <i>et al.</i>	2013	Psychological profile (anxiety and depression) in patients with OLP: A controlled study	Cross-sectional study	No significant association of anxiety and depression in the development of OLP lesions
Pippi <i>et al.</i>	2014	Diurnal trajectories of salivary cortisol; salivary alpha-amylase and psychological profile in OLP patients	Case-control study	OLP patients had a decreased capability of coping with stress events and showed deregulation of HPA axis activity with hypocortisolism detected in morning hours
Hosseini <i>et al.</i>	2016	Assessment of relationship between stress and OLP: A review of literature	Review of literature	Confirmed higher stress levels in OLP patients
Mehdipour <i>et al.</i>	2016	The relationship between anger expression and its indices and OLP	Descriptive study	Significant association of anger control and suppression of LP development
Corqueira <i>et al.</i>	2018	Psychological disorders in OLP: A systematic review	Systematic review	Psychological disorders (stress, anxiety and depression) are associated with the development OLP

LP: Lichen planus; OLP: Oral lichen planus

Eisenberg^[64] suggested the optional histologic diagnostic features, including saw-toothed rete ridges, colloid/civatte bodies, and parakeratotic epithelium.

Immunofluorescence shows a linear pattern of fibrin and shaggy fibrinogen deposits at the epithelial basement membrane or cytoid bodies (Russell bodies), or both in the absence of deposition of fibrinogen [Figure 9].^[65]

Treatment

Currently, OLP treatment intends at minimizing the ulcerations and mucosal inflammation, diminish the flare-up of the lesions, and possibly enhance the disease-free period. However, no single therapeutic regimen has proven valuable in the management of OLP.^[66]

Usually, no treatment is warranted for the benign/asymptomatic form (reticular OLP), and periodic observation and evaluation is usually sufficient in such cases.^[67] Patient education and motivation for maintaining oral hygiene and corrective dentistry may play a pivotal role in OLP management.^[68] Topical high-potency corticosteroids comprise the cornerstone therapeutic regimen in patients presenting with severe pain and burning sensation.^[67]

A range of therapeutic regimen is used for the management of OLP, including corticosteroids (topical, intralesional, and systemic), immunosuppressive agents (tacrolimus, cyclosporin, mycophenolate mofetil, azathioprine), retinoids, and immunomodulatory agents (thalidomide and levamisole).^[69]

Mouth is a mirror of systemic diseases and oral manifestations of systemic disease may serve as an initial clue in the diagnosis and management of the primary systemic pathology. OLP is associated with numerous systemic manifestations (MS, chronic viral hepatitis, diabetes, hypertension, dyslipidemia, and psychosomatic disorders). The primary healthcare providers play an important role in the management of patients who have oral consequences of systemic disease, as they are often likely to

be the first clinicians to observe such abnormalities. They will ensure that any potential oral manifestation of systemic disease is managed quickly and appropriately to improve the patient's quality of life.^[70]

Conclusion

OLP has been associated with numerous systemic connotations and may necessitate a multidisciplinary treatment strategy. OLP should not be treated as an isolated entity, but utmost care should be taken to screen and treat the associated systemic manifestations. Hence, it is essential that the dental surgeon should be aware of the various systemic associations of LP and should work in close connect with physicians to rule out the predisposing factors for the associated comorbidities.

Financial support and sponsorship

Nil.

Conflict of interest

There is no conflict of interest.

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