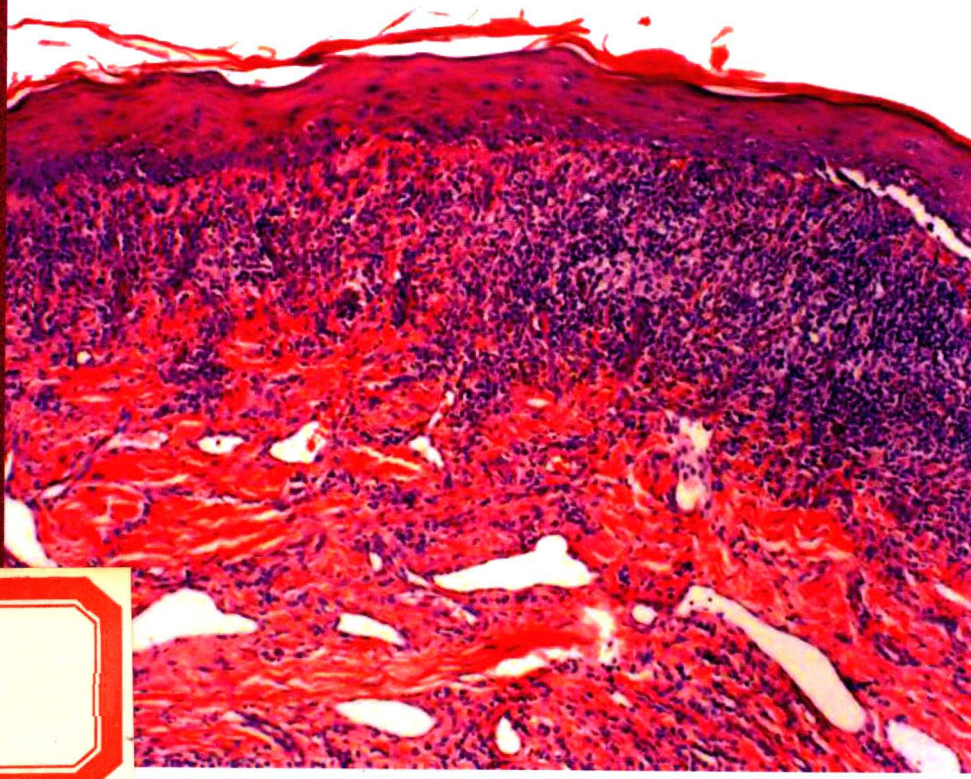
Dermatology - Laboratory and Clinical Research

Lichen Planus

Epidemiology, Symptoms and Treatment



Yvonne L. Summers
Editor

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DERMATOLOGY - LABORATORY AND CLINICAL RESEARCH

LICHEN PLANUS

EPIDEMIOLOGY, SYMPTOMS AND TREATMENT

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New York

NOTICE TO THE READER

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PREFACE

This book examines the potential pathogenesis of oral lichen planus, the clinical and histopathological criteria that need to be taken into consideration of the diagnosis of OLP and the association of oral lichen planus with systemic diseases and amalgam restorations.

Chapter 1 - Lichen planus is a chronic inflammatory mucocutaneous disease of unknown cause, rarely observed in young individuals primarily affecting women between the fifth and sixth decades of life. Although its pathogenesis is unclear, several studies suggest this is a persistent immune disorder where the basal keratinocytes are probably attacked by T lymphocytes. In the skin free from hair, the lichen planus lesion is characterized by small flat-topped papules that may coalesce into plaques that may be localized or extensive. The papules often show a network of white lines known as Wickham's striae. Pruritus is usually pronounced and has a predilection for the inside of the wrists, legs, torso, or genitals. The lichen planus oral has distinct features and is easy to identify, appearing in two main forms: reticular and erosive. Other forms of the disease are not rare and four other shapes were described: papular, plake-like, bullous and atrophic. The reticular form is usually asymptomatic and involves the posterior buccal mucosa bilaterally. The erosive, although in a lesser proportion, is the most significant for the patient since they are often symptomatic lesions ranging from mild discomfort to severe pain episodes. The treatment of patients with lichen planus must be individualized. Most of recent reviews suggest that the best treatment remains high-potency topical corticosteroids, whereas systemic corticosteroids may be occasionally indicated.

Chapter 2 - Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease mediated through T- lymphocytes albeit still of unknown

etiology. OLP is characterized by periods of acute disease and remission period. Oral lichen planus is more frequent than skin lichen planus, it lasts longer and is more reluctant to treatment. Rarely, the dissapearance of OLP is seen. Numerous studies point out malignant potential of OLP. Prevalence of OLP is 0.5-2.2% within general population. Most frequently OLP affects persons aged 30-60 years, and more often women. OLP female to male ratio is 2:1. Oral lichen planus rarely affects children. Approximately 16% patients with OLP have concomitant skin lesions, while genital lesions are seen in 25% of females with OLP and in 2-4% of males with OLP. Other extraoral lichen planus lesions such as esophageal, nail ones are rarely seen together with OLP.

Chapter 3 - Oral lichen planus (OLP) is a chronic autoimmune disease characterized by type IV hypersensitivity, which manifests as a cell response to antigen changes that occur in the lining oral mucosa. Among patients affected by this systemic disease, 25% only have lesions in the mouth and 50% simultaneously exhibit lesions in the oral mucosa and on the skin. Oral lichen planus is more common in adult middle-aged women in their 5^{th} and 6^{th} decades of life. The lesions are usually bilateral, symmetrical and multifocal, and the buccal mucosa is the most commonly affected site. Six clinical forms of OLP have been described, which usually coexist: reticular, papular, plaque-like, atrophic, erosive, and bullous. In 2005, the World Health Organization classified OLP as a potentially malignant disorder. However, there is still much controversy about this classification. Several epidemiological, retrospective and prospective studies conducted over the last 20 years in different parts of the world suggest the probability of a lesion initially diagnosed as OLP to progress to squamous cell carcinoma to be 0.65 to 1.9%. Nevertheless, some authors highlight the difficulty in diagnosing OLP. Others report the lack of a universal and specific standard method for the diagnosis of this disease, which can often be confused with lesions of epithelial cell atypias exhibiting a lichenoid appearance. Hence, clinical and histopathological criteria need to be taken into consideration for the diagnosis of OLP. There is no specific treatment. Oral lichen planus should be treated when the patient manifests symptoms, since no standardized management exists that is completely satisfactory and definitive. Since most patients do not complain of symptoms, periodical follow-up for reassessment of the lesions should be performed. Moreover, the erosive and atrophic forms are almost always symptomatic and professional follow-up at shorter intervals is necessary in these cases. Corticosteroids are the most widely used drugs for the management of symptomatic lesions.

Chapter 4 - Oral lichen planus (OLP) is a still poorly understood and relatively common chronic inflammatory disease of oral mucosa. A connection between OLP and certain diseases have been reported in the past, such as diabetes, hypertension, hepatitis C infection (HCV), thyroid disease, and malignant diseases. The most previous studies reporting an association between amalgam restorations and OLP /oral lichenoid lesions (OLL) suffer from absence of the control group. There is still insufficient evidence to support routine removal of all amalgam fillings in patients with OLP/OLL. This study has two objectives, first was to investigate associated systemic diseases in OLP patients, and second to estimate association between amalgam restoration and the prevalence of OLP. A total of 99 patients (74 females and 25 males, mean age 59.4 ± 13.9) with clinical and histopathological proven OLP, along with 99 matched controls without oral mucosa lesions were included in the study. This was a retrospective case-control study conducted in patients who had visited the Dental Clinic, Faculty of Medicine, University of Novi Sad, between January 2007 and December 2014. Clinical characteristics of OLP lesions, other oral mucosal diseases, presence of cutaneous LP, history of allergies, medical history with special regard to their systemic diseases and medication intake, number, class (Black's classification) of amalgam restoration and its contact with lesion were recorded. The electric potential difference was measured using digital milivoltmeter, while the measurement of salivary pH was determined using pH paper indicator strips. Significant association regarding systemic diseases was found in prevalence of thyroid, autoimmune and cardiovascular diseases. The authors did not find any significance regarding the presence of OLP and other coexisting diseases. The mean number of amalgam restoration per patient and electric potential difference in OLP group was 4.7 ± 3.0 and 88.7 ± 76.8, and in control group was 3.6 ± 2.9 and 97.5 ± 84.7 respectively. Analysis showed that there were no significant differences in the number, class, electrical potential and salivary pH between the tested groups. This study indicates connection between thyroid gland disorders (especially hypothyroidism) and OLP. There is a need for further investigations as a screening for asymptomatic OLP in woman over the 40 years old with thyroid gland disorders, particularly hypothyroidism. There is no association between amalgam restoration and OLP, as well. Thus, result of this study does not support routine removal of all amalgam restorations in patients with OLP.

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Chapter 1

LICHEN PLANUS: GENERAL CHARACTERISTICS

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ABSTRACT

Lichen planus is a chronic inflammatory mucocutaneous disease of unknown cause, rarely observed in young individuals primarily affecting women between the fifth and sixth decades of life. Although its pathogenesis is unclear, several studies suggest this is a persistent immune disorder where the basal keratinocytes are probably attacked by T lymphocytes. In the skin free from hair, the lichen planus lesion is characterized by small flat-topped papules that may coalesce into plaques that may be localized or extensive. The papules often show a network of white lines known as Wickham's striae. Pruritus is usually pronounced

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and has a predilection for the inside of the wrists, legs, torso, or genitals. The lichen planus oral has distinct features and is easy to identify, appearing in two main forms: reticular and erosive. Other forms of the disease are not rare and four other shapes were described: papular, plake-like, bullous and atrophic. The reticular form is usually asymptomatic and involves the posterior buccal mucosa bilaterally. The erosive, although in a lesser proportion, is the most significant for the patient since they are often symptomatic lesions ranging from mild discomfort to severe pain episodes. The treatment of patients with lichen planus must be individualized. Most of recent reviews suggest that the best treatment remains high-potency topical corticosteroids, whereas systemic corticosteroids may be occasionally indicated.

INTRODUCTION

Lichen Planus (Greek "Leichen" = tree moss, Latin "Planus" = flat) was described by the British physician Erasmus Wilson in 1869 as a chronic inflammatory disease of the epithelium with an unknown etiology. Although the term "lichen planus" suggests a flat fungal condition, current evidence indicates that this is a mucocutaneous disease immunologically mediated. Initially, this disorder was named "lichen ruber planus" and "lichen psoriasis." In 1885, the surface aspect of the lesion was described as "lichen planus papules" and in 1895 Wickham explained it further and called it "Wickham's striae." Posteriorly, the Wickham's striae were correlated with an increase in thickness of the granular cell layer. Guogertot and Burnier, in 1937, described the coexistence of oral, cervical, and stomach lichen planus lesions with no cutaneous involvement as "plurimucosal lichen planus." In 1982, Pelisse et al. reintroduced a similar variant of mucosal lichen planus the vulvovaginal-gingival syndrome with erosive lesions involving the oral and vulvovaginal mucosa.

EPIDEMIOLOGY

The exact prevalence of lichen planus varies according to different studies, however the estimated prevalence ranges of 0.9% to 1.2% worldwide and no more than 2% of the adult population are affected. Approximately 1% of the population may have skin lichen planus and the prevalence of oral lichen planus is between 0.1% and 2.2%. The epidemiological studies lack clear

diagnostic criteria or a uniform methodology. Furthermore, the diverse clinical presentation and the asymptomatic nature of the most common subtype of oral lichen planus make the disease an underdiagnosed health issue.

Lichen planus is primarily a disease of the middle-aged, although it can affect people of all ages, ranging from young adults to the elderly and rarely affect children. Interestingly enough, a high number of pediatric patients have either a personal or family history of autoimmune disease as well as atopy.

No sexual predilection is clearly evident but some reports indicate a slight predominance in women, usually in a ratio of 3:2 in comparison to men in most series cases. Women account for 60 to 75% of patients with oral lichen planus and 50% of those with cutaneous lichen planus. The mean age at diagnosis is between 50 and 60 years for oral disease and between 40 and 45 years for the cutaneous form. Nevertheless, there is a tendency for all types of oral lichen planus affect the male patients in earlier age than in females.

European studies suggest that up to 2.4% of Caucasians may have lichen planus, while the rates of 0.02-1.5% have been reported in studies of Indian patients. Still, it is generally agreed that the lichen planus affects all racial groups. There are little reports on the socio-economic status of patients with lichen planus, although it has been described that most patients are manual workers or retired.

Numerous medications can induce lesions that resemble clinically idiopathic form of lichen planus, however, the term lichenoid dermatitis (or lichenoid mucositis, depending on the involved site) is probably a more appropriate name for the changes related to the use of drugs. Likewise in oral mucosa, foreign bodies, which are incorporated into the gum, may inadvertently trigger a host response that is called gingivitis foreign body lichenoid.

Lichen planus was also related to systemic diseases mainly hepatitis C. In the last 20 years, there have been many publications on the association between hepatitis C and lichen planus. Patients with lichen planus have almost 6 times the odds of having concurrent HCV infection than the regular population.

Associated factors and disease conditions seen in lichen planus include but are not limited to hepatitis C virus (HCV), autoimmune diseases, internal malignancies, dyslipidemia, and viral infections. There are still reports of patients with lichen planus with history of arterial hypertension, cardiovascular and rheumatological diseases, and that consumed antidepressants. The relationship of stress or anxiety with the development of lichen planus is

controversial, and most reported cases seems to be speculation or do not have adequate controls.

Symptoms

Lichen planus has different clinical presentations based on the morphology of the lesions and the site of involvement. In some variants the etiology is also taken into consideration. Combinations of morphological peculiarities are possible in the individual case.

Cutaneous lichen planus includes several subtypes like papular (classic), annular, hypertrophic, atrophic, ulcerative, vesiculobullous, lichen planus pemphigoides, lichen planus pigmentosus, erythrodermic lichen planus, inverse lichen planus, linear, actinic, and follicular lichen planus.

The classic cutaneous lichen planus is characterized by flat-topped, violaceous papules. Wickham's striae, which are defined as fine whitish points or lacy lines, may be seen on the surface of well-developed papules. Particularly in dark-skinned patients, the lesions may result in long-standing residual hyperpigmentation. The appearance of the lesions may cause embarrassment and which in some cases can be intensely itchy (Figure 1).

Annular lichen planus is a lichen planus variant not only on the skin but also on the mucous membrane. Classically, annular lichen planus involves the male genitalia (glans penis and penile shaft) and also axilla, groin, and extremities. Although classic cutaneous lichen planus usually presents with pruritus, the annular form is often asymptomatic especially when arising in the genital area.

Hypertrophic lichen planus, also known as lichen planus verrucosus or lichen planus hyperkeratosis, is characterized by hyperkeratotic thick pruritic red-brown to purple-gray plaques with follicular accentuation that commonly involves the extremities, especially the anterior legs and the interphalangeal joints in a symmetrical distribution. Polygonal papules may be seen surrounding the main lesion that can coalesce and possess a popular, verrucous or hyperkeratotic surface. Upon palpation the lesions are firm or hard. Most are intensely pruritic.

Atrophic lichen planus is a rare variant usually observed on the legs. As clinical morphology round to oval, centrally atrophic depressed, brown or also violet papules and plaques are seen. Atrophic lichen planus is the clinical endpoint of chronic annular or hypertrophic lichen planus with atrophic lesions. Diagnosis may be difficult unless classic lichen planus is present

elsewhere on the body. Long-term use of topical corticosteroids may predispose the patient to developing atrophic lesions.

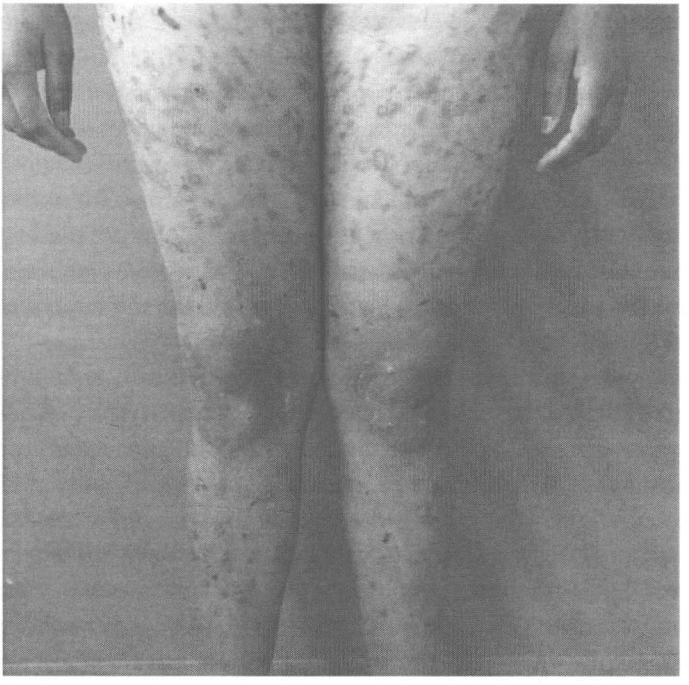

Figure 1. Classic cutaneous lichen planus: The skin lesions appear as violaceous flat-topped papules. Careful examination shows reticulated white lines (Wickham's striae) on the surface of papules. Residual hyperpigmentation may be seen. (Courtesy of Dr. Cléverson Teixeira Soares).

The most common locations of ulcerative or erosive lichen planus are the feet, particularly the soles and interdigital spaces. The single or multiple lesions have sharp borders, bizarre configurations and are small to palm-size ulcers or erosions, sometimes with an elevated edge, or display rests of lattice-like leukoplakia. Typically marked pain is present that can severely impair walking or make it impossible.

In the vesiculobullous subtype, blisters develop within the plaques. Lower extremities are the main sites of involvement. Numerous small grouped or sometimes even larger tense blisters are seen; some are multilocular. The intact bullae contain clear or pale yellow fluid. This pattern of the disease has to be distinguished from lichen planus pemphigoides, a rare coexistence of lichen planus and bullous pemphigoid.

In lichen planus pemphigoides the blisters develop not only on pre-existing lichen planus lesions as is typical for bullous lichen planus, but also on unaltered skin. Tense or flat blisters appearing multilocular at the edge are characteristic. The lesions are found predominantly on the limbs, more rarely on the trunk in grouped or disseminated distribution.

Clinically, pigmented macular or papular lesions in variable distribution are seen in lichen planus pigmentosus. Lesions are characteristically bilateral and involve sun-exposed areas. Besides extensive, perifollicular, linear or zosteriform distribution, lichen planus pigmentosus may follow the lines of Blaschko or the course of the saphenous varicose veins on the legs. Sites of predilection include intertriginous regions or the flexures of the limbs. We have repeatedly observed lichen planus pigmentosus in the lumbar region. The pigmentation encompasses shades of gray-brown, violet and dark brown. Patients with pale skin appear to be preferentially affected.

Erythrodermic lichen planus is a rare lesion. Morphologically, red or violet papules and extensive infiltrated erythematous plaques with or without scaling are seen. Amidst the typical lichen planus lesions, blisters or erosions may appear in a localized fashion. Pruritus is severe and the general health is reduced.

Inverse lichen planus typically affects axillae, inguinal creases, limb flexures and submammary region. Clinically, extensive erythematous lesions with poorly defined borders are seen. Additionally, keratotic papules and erosions with a bizarre configuration can occur.

Linear lichen planus is a variant that possibly occurs more often in children and adolescents. Linearly oriented lesions of lichen planus can be caused by the Koebner phenomenon (isomorphic response), but this pattern is not considered as the true linear form. The true linear form is more extensive and follows the lines of normal cell development in the skin (lines of Blaschko). The individual lesions may be the typical flat-topped papules but purpuric papules, vesicular, hyperkeratotic and annular morphologies may be observed. In rare circumstances, if linear lichen planus presents in a dermatomal pattern, it is called zosteriform lichen planus. This rare variant is found either at the site of healed herpes zoster lesions (Wolf isotopic response) or de novo in normal skin.

Sites of predilection of follicular lichen planus, also called as lichen planopilaris, include the scalp, axilla, inguinal creases, sacrum and flexures of the limbs. Clinically, grouped or disseminated, follicular, flat, elevated or hemispherical erythematous papules with or without keratoses are observed. Follicular lichen planus on the scalp is likely to lead to scarring alopecia. The

Graham-Little-Piccardi-Lasseur syndrome, seen predominantly in women and also in a familial pattern, is characterized by the joint appearance of follicular lichen planus on the trunk with lichen planus follicularis decalvans on the scalp. Further features such as onychodystrophy can manifest as variable minor criteria. Frontal fibrosing alopecia was initially reported as a variant of lichen planopilaris. It is observed predominantly in postmenopausal women as progressive frontotemporal hair loss. The pattern of alopecia is analogous to male pattern androgenetic alopecia with frontal dominance and additional features such as scarring and a lichenoid pattern on histopathology. Due to lack of typical lichen planus criteria, some feel this is a separate form of scarring alopecia. Follicular lichen planus can also be induced by hair transplantation or face-lift surgery. The possible triggering factors include the Koebner phenomenon, perisurgery antigen release, or the postoperative immune-inflammatory response.

Actinic lichen planus is a rare subtype presenting as nummular patches or plaques. Typically in the spring and summer actinic lichen planus develops on sun-exposed areas of the face, hands and forearms. Children and young adults with a dark skin type in the tropics and subtropics are preferentially affected, which explains the synonyms tropical and subtropical lichen planus. Clinical features are variable. Besides lichenoid or annular papules macular hyperpigmentation and infiltrated erythematous plaques with variable borders and scaling are observed. Even in severe cases pruritus is not obligatory.

Lichen planus of the nail organ, particularly in the matrix, can result in very diverse morphological alterations of the nail plate that are, nevertheless, not pathognomonic. Characteristic nail lesions of lichen planus include dorsal pterygium and trachyonychia. A pterygium develops through adhesion of eponychium and matrix leading first to a split nail and later to possible complete loss of the nail plate. Trachyonychia is characterized by marked roughness of the nail plate, loss of transparency and often by a gray discoloration. The nail alterations of lichen planus typically develop simultaneously on several nails. It is not uncommon for all 20 nails to be affected. Nail lesions can precede the appearance of lichen planus on the rest of the skin or on the mucous membranes or develop in a delayed fashion. With isolated nail involvement the diagnosis of should be confirmed histopathologically when in doubt.

The most common location of mucosal lichen planus is the oral mucosa (oral lichen planus). About half the patients have solitary lesions; an equal number have multiple clinical changes. Clinically, oral lichen planus has distinct features and easy to be identified, appearing in two main forms:

reticular and erosive. Other forms of the disease are not uncommon and originally four other forms of oral lichen planus have been described: the papular, plaque-type, bullous and atrophic.

The reticular subtype of oral lichen planus is more common and is characterized by interlaced lines, known as Wickham's striae, generally surrounded by discrete erythematous halo. However, such features may be less evident in some regions, such as the tongue, where lesions present as keratotic plaques. The reticular form is usually asymptomatic and involves the posterior buccal mucosa bilaterally (Figure 2). Nevertheless, other sites may be involved simultaneously as the dorsum and side of the tongue, gingiva and palate (Figure 3).

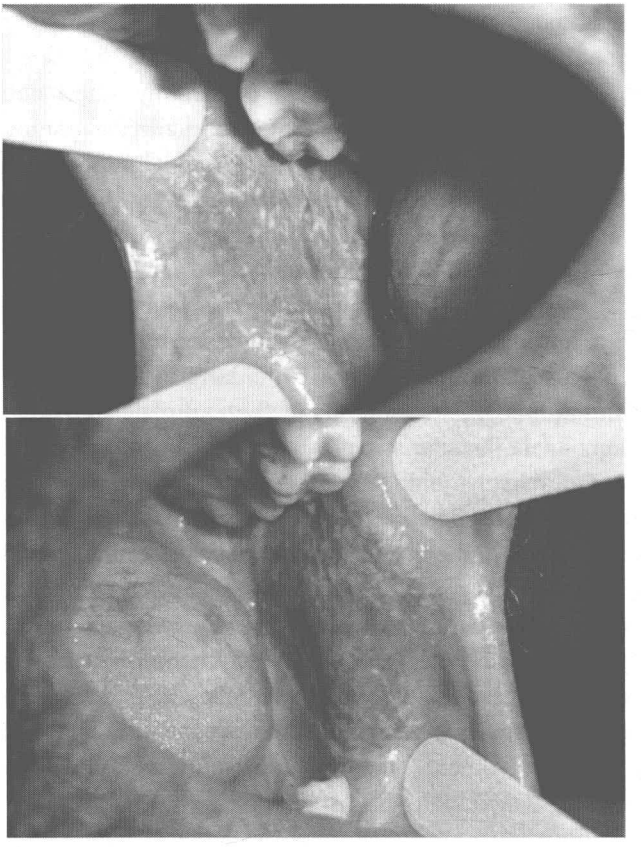

Figure 2. Reticular oral lichen planus: A) Presence of white lines intertwined diffuse the buccal mucosa on the right. B) The same patient showing the bilateral involvement of the buccal mucosa.

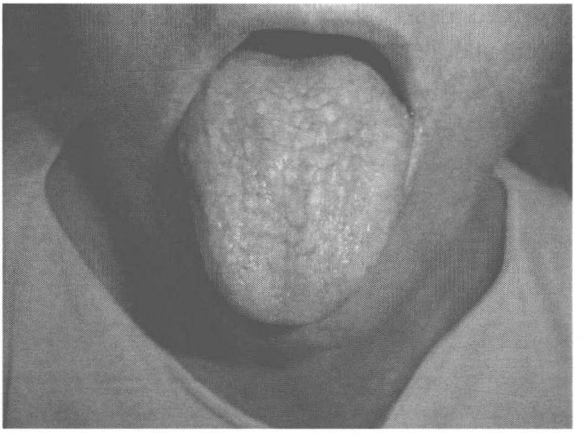

Figure 3. Reticular oral lichen planus: Involvement of the dorsal surface of the tongue by the reticular lichen planus. In these cases, the confluent white reticulated plaques are typically observed by replacing the normal surfaces of the tongue papillae.

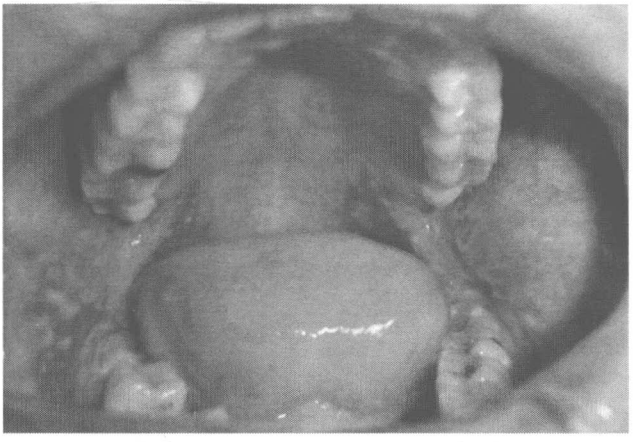

Figure 4. Erosive oral lichen planus: Ulceration of the buccal mucosa and soft palate displays peripheral areas surrounded by radiant white striae.

The erosive oral lichen planus though relates in a smaller proportion, is the most significant for the patient since they are often symptomatic lesions ranging from mild discomfort to severe pain episodes. Clinically, erosive oral lichen planus manifests as atrophic and erythematous areas surrounded by fine radiant striae, particularly on the gingiva that look raw and are painful (desquamative gingivitis) (Figures 4). The associated ulcers are sometimes

covered with a pseudomembrane. It is clinically important because the lesions can be quite painful and therefore it may negatively affect the patient's quality of life. Involvement of the dorsum of the tongue might cause dysgeusia.

Papular oral lichen planus is characterized by small white pinpoint papules that can be easily missed, as they are small and asymptomatic. It is referred to as the initial and transient phase of oral lichen planus. That is why it is a rare diagnosis.

In plaque-like oral lichen planus, large, homogeneous white patches are characteristic. Plaque-like oral lichen planus and leukoplakia have similar clinical presentations and therefore leukoplakia must always be ruled out and should always be biopsied. Solitary white plaques should not be considered plaque-type lichen planus but rather leukoplakia. This variant is more prevalent in tobacco smokers. The existence of plaque-like lesions is an indicator of a poor prognosis and a lesser likelihood of remission.

Oral bullous lichen planus lesions are commonly seen on the buccal mucosa, most frequently at the posterior areas adjacent to second and third molar teeth. Less common localizations are gingiva and inner aspect of the lips. Bullae are generally short lived and leave ulcerated lesions on rupturing. The clinical diagnosis of oral bullous lichen planus is extremely difficult and pathological examinations may be necessary to establish a definitive diagnosis.

The atrophic subtype is common presentation that has similarities to the erosive subtype with more prominent atrophic lesions on a background of erythema and radiating white striae at the margins. Thus, some experts combine the two entities and name it atrophic-erosive lichen planus. This subtype is more common in older oral lichen planus patients. Atrophic oral lichen planus primarily affects the attached gingiva. The buccal mucosa can also be involved.

Mucosal lichen planus of genital skin is preferentially located on the glans penis. Often lesions with an annular configuration are seen. In women the vulva and less commonly the vagina are involved. The simultaneous occurrence of mucosal lichen planus on the oral and female genital mucosa is termed vulvo-vaginal-gingival syndrome.

The typical clinical features of lichen planus are often sufficient for the diagnosis. However, the histopathological analysis is recommended to confirm the clinical diagnosis and mainly to exclude the presence of epithelial atypia.

Lichen planus is characterized by lichenoid interface dermatitis. The classic histopathological features include a dense, continuous, and band-like lymphohistiocytic infiltrate at the dermal-epidermal junction and in the upper dermis (Figure 5). Characteristically, the infiltrate disguises the dermal-