# ORAL LICHEN PLANUS

## A clinical study

A.B.E. Voûte

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VRIJE UNIVERSITEIT

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Aan Yolanthe, mijn vader
en ter nagedachtenis aan
mijn moeder

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# CHAPTER 1

# INTRODUCTION

# AND

# AIM OF THE STUDY

## 1. INTRODUCTION

Oral lichen planus (OLP) is a rather common disease. Yet, many aspects remain puzzling.[1] For instance, the etiology and pathogenesis are still poorly understood.[2] The clinical appearence is characterized by a wide range of manifestations and includes such expressions as white, reticular striae, and red atrophic changes of the oral mucosa.[3,4] Clinically, there may be an overlap with oral leukoplakia and erythroplakia.[5,6,7] Also histopathologic aspects of OLP may vary and are, in themselves, not always pathognomonic. Then, too, an overlap may exist with the histopathologic features of oral leukoplakia and erythroplakia, and also with discoid lupus erythematosus.[6,8,9]

The possible malignant transformation of OLP is the subject of debate for some decades already.[10,11,12] Unfortunately, limited possibilities are available for treatment.[4,13] Actually, no measures of prevention are available.

## 2. AIM OF THE STUDY

In this thesis the following questions have been addressed:

1. Does the 21-years experience in the Department of Oral and Maxillofacial Surgery / Oral Pathology, Free University Hospital, Amsterdam, with patients having OLP give support to the hypothesis of OLP being a premalignant condition.
2. Is topical fluocinonide a useful treatment modality in patients with symptomatic OLP?
3. Is topical cyclosporin-A a useful treatment modality in recalcitrant, corticosteroid-resistant OLP?
4. What are the results of longterm follow-up of untreated and treated patients with OLP.

In **chapter 2** a review of the literature on both oral and cutaneous lichen planus is given.

In **chapter 3** the 21-years experience of the Department of Oral and Maxillofacial Surgery/ Oral Pathology, and the Department of Otorhinolaryngology of the Free University Hospital, Amsterdam, is reported with regard to the possible premalignant character of OLP. The study consisted of two parts. In the first part, patients with OLP seen for follow-up, were screened for the presence of malignant lesions. In the second part, a search for OLP in patients who had been admitted for oral cancer, was carried out.

In **chapter 4** the results of a randomized, double-blind, placebo-controlled study, with regard to the efficacy of topical application of 0.025% fluocinonide, are described.
In **chapter 5** the efficacy of another immunosuppressive drug, cyclosporin-A (CsA) is evaluated, also being applied as a topical drug, in patients, who have been unsuccessfully treated previously with topical or systemic corticosteroids.
In **chapter 6** the clinical follow-up data of 153 patients with OLP in a selected Dutch population are described with regard to age, gender, signs and symptoms, duration of disease, presence of skin lesions, medical history and medication.
In **chapter 7** a summary and conclusions of the results reported in this thesis are given.

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# CHAPTER 2

## LICHEN PLANUS

### A review of the literature

## 1. INTRODUCTION

Erasmus Wilson initially coined the term lichen planus (LP) in 1869.[1] He considered this to be the same disease as "leichen ruber", previously described by Hebra. The first variant of LP was reported by Kaposi in 1892 and was termed lichen ruber pemphigoides.[2] Wickham noted the punctations and striae atop the lesions that currently bear his name.[3]

Today LP, including oral lichen planus (OLP) and cutaneous lichen planus (CLP), is considered as a relatively common chronic inflammatory disease of unknown cause, affecting mucosa and/or skin of squamous cell origin.

In the following paragraphs, epidemiology, pathogenesis, etiology, clinical features, histopathological features, differential diagnosis, malignant transformation, treatment, and prognosis of both oral and cutaneous LP will be discussed.

## 2. EPIDEMIOLOGY

The prevalence of LP is unknown. Current estimates place the figure of CLP at less than 1% of the population.[4-7] A Scandinavian study has shown a prevalence of 0.8%.[5] The estimate of CLP among Americans as a whole is 0.4%.[7] The reported prevalence of OLP varies between 0.7% and 1.89%.[8] Although individual lichenoid skin eruptions are generally cleared in one year, OLP is usually chronic in nature.[9] No racial predilection is believed to exist in LP.[7]

LP appears to affect women preferentially. Among patients with OLP, 63% to 67% are women, and between 55% and 65% of patients with CLP are women.[10-13] LP usually appears initially during the fifth or sixth decade. In patients with OLP the peak age is between 52 and 53.3 years.[12,14] Men may have cutaneous involvement early in their thirties, whereas most women develop LP in their fifties.[6] LP in childhood is unusual, and pediatric patients comprise only 2% to 3% of all patients.[15,16] Familial LP refers to the occurrence of this disease among members of the same family.[17] In this variant skin involvement tends to occur at a younger age, with most patients in the 20 to 29-year-old age group.[17]

Outbreaks of LP occur throughout the year, although in one study it was suggested that an unexplained seasonal influence existed, showing an increase between January and July.[18]

## 3. PATHOGENESIS

The cause of LP is unknown. Many etiologic mechanisms and associations have been suggested. Basal cells, with diminished metabolic and regenerative capacity, behave more like keratinocytes, resulting in granular cell production.[19] Metabolic abnormalities, impaired tonofilament production, and defective desmosomal construction have also been implicated.[20]
In the following paragraphs a number of aspects regarding the etiology and pathogenesis of LP is discussed.

### 3.1.Immunology

**3.1.1.Humoral aspects.** In various studies of patients with LP an array of seemingly contradictory observations of immunoglobulins has been reported: decreased serum IgM, decreased serum IgA, increased serum IgA, and increased serum IgG have been documented.[21-25] Normal serum values have been described for IgA, IgG, IgM, IgE, and IgD.[22,24,26,27] Complement levels have also been found to be normal.[24] Mahood evaluated 45 patients with LP and found that if the disease was active or recently resolved (<2 years) serum IgM levels were slightly low.[28] Patients with "previous" disease (>2 years) had normal serum immunoglobulin levels. LP has also been reported in patients with hypogammaglobulinemia.[29,30,31] In one study serum cryoglobulins were found in 31% of patients with oral and cutaneous LP.[25] Circulating immune complexes and complement components, as $C_3$, have been described in patients with OLP and drug-induced LP.[32,33]
The role of these immunoglobulins in the pathogenesis of LP is speculative. LP seems to be less strongly associated with the humoral arm of the immune system than with the cellular arm.[34,35]

**3.1.2.Cellular aspects.** T-lymphocytes found in the subepithelial area, have been postulated to initiate or stimulate the pathogenic mechanisms responsible for LP. Grafting of lesional skin onto nude (immuno-incompetent) mice results in the disappearance of histopathologic abnormalities.[36] De Panfilis et al. suggested that activated T-cells may view keratinocytes as "target" cells and interact with them.[37] Some investigators believe that tumor antigens, to which patients with LP have become sensitized, may cross-react with epidermal antigens and may lead to clinical lesions.[38] Recent evidence has shown that gamma-interferon, produced by T-cells, may induce monocyte expression of lymphocyte function-associated antigen-1 that helps these cells attaching to keratinocytes.[39] The apposition of activated immune cells and keratinocytes could then lead to destruction of the latter.

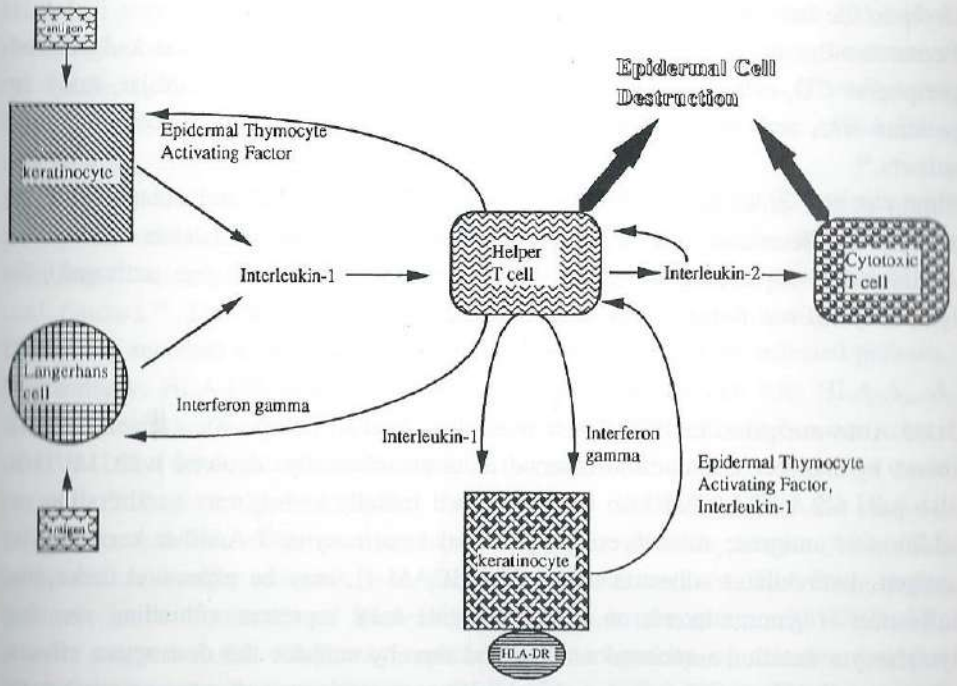


Fig. 2.1. Diagrammatic representation of a proposed immunologic lichenoid tissue reaction.[40]

Cytokines are soluble messenger proteins elaborated by cells, usually involved in inflammatory processes, and may influence the expression of LP (Fig. 2.1). In this model some type of antigen or stimulus (viral, pharmacologic, cellular) interacts with a keratinocyte or Langerhans' cell in a normal or abnormal manner. Interleukin-1, a monokine, is produced and promotes interleukin-2 elaboration by

lymphocytes.[40] Additionally, epidermal cell-derived thymocyte activating factor, an interleukin-1-like protein, is produced by HLA-DR positive keratinocytes.[39] The activated lymphocytes (T-cells) increase their production of gamma-interferon, which in turn causes keratinocytes to express HLA-DR antigens, and progress into lesional cells.[40] T-helper/inducer ($CD_4$) cells and T-cytotoxic/suppressor ($CD_8$) cells destroy epidermal cells via interaction with HLA-DR and class-I-antigens, respectively. Lymphokines may cause direct cellular damage themselves, most likely to the basal cells, or local down-regulation of $CD_8$ cells.[41]
Fernandez-Bussey et al. evaluated nine patients with CLP and noted a decreased peripheral $CD_8$-cell count and an increased $CD_4/CD_8$-ratio.[42] A similar study in patients with oral involvement of LP revealed no significant alterations in T-cell subsets.[43]
Simon et al.[44] studied natural killer cells in patients with LP and noted that their activity was decreased. This impairment seemed to be related to disease severity.
Additionally, $ß_2$-microglobulin, a serum protein produced by activated T-lymphocytes, was found in normal amounts in patients with LP.[45]

**3.1.3.Auto-antigens.** In 1983 Olsen et al. described an LP-specific antigen (LPSA) found by indirect immunofluorescence in tissue clinically involved with LP (see also par. 6.2.1).[46] LP has also been proposed initially to begin as an alteration or addition of antigenic substances on epidermal keratinocytes.[10] Another keratinocyte antigen, intercellular adhesion molecule-1 (ICAM-1), may be expressed under the influence of gamma-interferon. This molecule may represent a binding site for lymphocyte function-associated antigen and thereby enhance the destructive efforts of these cells. The processes that alter keratinocyte antigens and subsequently result in immune reactions to them, may also be responsible for damaging the cells of other organ systems such as hepatocytes.[47]
Basal membrane zone (BMZ) changes in LP may produce antigenic proteins to which the host forms antibodies.[48] The clinical and histopathologic features of LP pemphigoides may be produced by such a process.[49,50]

# 4. ETIOLOGY

## 4.1.Genetic aspects

**4.1.1.HLA-antigens.** HLA-antigens are cellular proteins on the surfaces of all nucleated cells. Lowe et al. evaluated 57 patients and 300 control subjects.[51] A significantly higher prevalence of $HLA\text{-}A_3$ was found (54% vs 29.7%), and more than twice as many patients affected (19.3% vs 9%) carried $HLA\text{-}A_5$. Additional HLA-loci were not evaluated. Halevy et al. found that patients with LP and a normal glucose metabolism showed a significantly greater likelihood to be positive for $HLA\text{-}A_{28}$.[52] Simon et al. reported elevated rates of $HLA\text{-}B_{16}$, $HLA\text{-}B_8$, and $HLA\text{-}Bw_{35}$.[53] In those patients with cutaneous and oral lesions alone, $HLA\text{-}Bw_{35}$ and $HLA\text{-}B_8$, respectively, were more prevalent.
HLA-class-II-antigens have also been studied. Powell et al. studied 72 patients with LP and found $HLA\text{-}DR_1$ in 80% of those with generalized disease, 56% with LP resulting from drugs, 54% with localized lesions, and 31% with involvement of the oral mucosa.[54] This antigen was detected in only 25% of the control subjects. $DQw_1$ was reported in 62% of the control sera and in 83% of the affected patients. Interestingly, $HLA\text{-}DR_1$ is known to be in linkage disequilibrium with $HLA\text{-}A_3$. A subsequent evaluation of 40 patients also showed a significantly higher occurrence of $HLA\text{-}DR_1$, although no correlation with the various clinical disease states could be made.[55] Porter et al. investigated the prevalence of HLA-A, HLA-B, HLA-C, HLA-DR, and $HLA\text{-}DQ_1$ in a group of 40 white British patients with OLP compared to healthy controls.[56] In particular, an increase of $HLA\text{-}Bw_{57}$ and a decrease in the frequency of $HLA\text{-}DQ_1$ were seen in the group with OLP. The authors suggested that OLP may represent a heterogeneity of diseases and that $HLA\text{-}Bw_{57}$ may predispose a person to OLP, whereas $HLA\text{-}DQ_1$ may be associated with resistance to it. Other investigators have not found a significant association between HLA allelic products and LP, suggesting that further studies will be required in this area before the associations between HLA and LP are clearly understood.[57]

**4.1.2.Familial lichen planus.** In one evaluation of 140 patients with LP (with or without oral lesions), 15 patients were found having a positive family history for LP.[58] Gibstine and Esterly[59] described monozygotic twin girls who developed lesions within a few weeks after each other. Conversely, Silverman et al. in their analysis of 570 patients with OLP, were unable to correlate the onset of disease

with a positive family history.[12]
A possible explanation for the findings of LP grouped in families would be similar HLA-allels. Copeman et al. described 10 patients with familial LP (5 different families).[60] They analyzed the HLA-antigens and found $B_7$ to be statistically more frequent than in the normal population or in patients with more conventional forms of LP. Mahood, however, refuted these findings in his analysis of nine similar cases.[17] Grunnet and Schmidt described a family in which the father, his son, and his daughter were affected.[61] All three patients shared HLA-$Aw_{19}$, HLA-$B_{18}$, and HLA-$Cw_8$. An unaffected son had none of these allels.

### 4.2.Emotional stress

Patients with OLP frequently report worsening of the disease during periods of stress, while others have noticed onset and exacerbation with fatigue.[62,63] The disease has been observed to erupt usually 1 to 2 weeks after severe emotional stress, or have been seen in "nervous, highly tensed" persons.[13] Altman and Perry, in a large questionnaire survey, found that although only 10% of affected patients could recall a stressful situation at the onset of their disease, 60% believed that chronic tension aggravated it.[64]
Most studies investigating the link between mental health and LP focus on oral disease. Lowental and Pisanti evaluated 49 patients with OLP.[65] They concluded that an association existed between emotional stress and erosive OLP, but not with the reticular type of OLP. A similar study involving 48 patients with OLP and a control group did not reveal a significant link between stressful life events and the presence of oral lesions.[14]
Other authors have also mentioned a possible relation between LP and emotional stress.[66,67]

### 4.3.Infection

An infectious agent for the development of LP is an attractive hypothesis, particularly considering its occasional response to various antimicrobial agents. Brody first described the presence of rod-shaped structures seen on electron microscopic examination of CLP tissue.[68] These structures were believed to be consistent with gram-negative bacteria. Wahba-Yahav noted a positive response to administration of oral metronidazole in a patient with CLP and amebiasis.[69]
Pathogenetically, the most attractive hypothesis would include viral involvement, much like the dermatomal pattern of herpes zoster.[70] Immunocompromised patients are mostly susceptible to viral infections, perhaps with an unknown type capable of provoking LP.[23] This may account for the LP-like eruption seen in bone marrow transplant patients.[71] Fry and Whiters, however, were unsuccessful in their attempts to culture either viruses or Mycoplasma from 11 patients with CLP.[72]

**4.3.1.Candida.** Several of the conditions that provoke oral candidiasis (endocrinopathies, medications, immunodeficiency) may also be associated with LP. Consequently, a role for Candida albicans in the propagation of oral disease has been considered.[73] This yeast can enzymatically catalyze the formation of N-nitrosobenzyl-methylamine, a substance with potential carcinogenicity.[74]
Most evidence, however, does not favor a role for Candida albicans. Silverman et al. in their analysis of 570 patients with OLP, were unable to correlate the presence of Candida albicans and the development of oral lesions.[12] There is not a statistically higher rate of Candida albicans colonization among patients with OLP.[73,75]

### 4.4.Tobacco

The incidence of tobacco use among patients with OLP varies from 15% to 93%.[10,76]
Murti et al. examined 722 Indian patients with OLP and found a strong association between the disease and tobacco use.[76] However, an analysis of 570 similar patients from San Francisco did not show any correlation.[12]

### 4.5.Dental restoration materials

Laine et al. investigated the effect of replacement of amalgam restorations in patients allergic to mercury compounds.[77] This study group consisted of 91 patients; 18 patients had oral "lichenoid lesions". Out of this group of 18 patients, 15 patients had all or almost all their fillings replaced by another dental restoration material. After a mean follow-up period of 3.2 years a complete resolution of lesions was seen in seven patients. A marked improvement occurred in six patients, and there was no change in the two remaining patients. Ibbotson et al. found similar results in patients with a mercury allergy with a positive patch test for ammoniated mercury (see also par. 7.7).[78] Laeijendecker et al. suggested that

sensitization to gold should be considered as a possible cause of allergic contact dermatitis and allergic stomatitis, as well as a triggering factor in OLP.[79]

### 4.6.Miscellaneous

Additional pathogenetic hypotheses exist. Including hydroxy-ethyl starch used in granulocyte harvestings, hormonal factors in women affected with actinic LP, thermal injury associated with erythema ab igne, and electrogalvanic effects from dental amalgam restorations.[80-83]

Conklin and Blasberg have suggested that the reticular pattern of OLP resembles the underlying vasculature and that these vessels may in some way be responsible for the overlying lesions.[83] Finally, LP has been considered a possible genodermatosis.[17]

## 5. CLINICAL FEATURES AND ASPECTS

### 5.1.Cutaneous lichen planus

The cutaneous lesions of LP consist of faintly erythematous to violaceous papules (Fig. 2.2). They are flat topped and occasionally take on a polygonal form. A thin, somewhat transparent scale may be present in many papules; these are known as Wickham's striae.

The papules of LP tend to involve the flexural areas preferentially; the flexural side of the wrist is the classically characteristic site (Fig. 2.3). The arms and legs are the most common sites of involvement, although the thighs, lower back, trunk, and neck may also bear lesions. Lesions of the male genitalia consist of violaceous papules, principally on the glans penis, but involvement of the penile shaft, scrotum, and perineum also occurs. The face and scalp are usually spared in classic LP. "Inverse" involvement (other than the predilection sites) has been reported.[63,64,70,84]

LP may be intensely pruritic. Oddly, physical evidence of scratching, such as excoriations, secondary infections, and blood crusts, is infrequently seen. Twenty percent of persons affected are asymptomatic.[85]

**5.1.1.Nail involvement**. Nail changes have been reported in 1% to 16% of the patients with CLP.[64,86] Usually only a few fingernails or toenails are involved, but occasionally all are affected. Typical cutaneous and oral lesions are usually present as well.

The nails involved show longitudinal ridging and grooving (Fig. 2.4), splitting (onychoschizia), shedding (onychomadesis), longitudinal striation (onychorrhexis), nail absence (anonychia), subungual hyperkeratosis, and thinning of the nail plate.

Nail findings, however, are neither specific nor pathognomic. Similar changes can occur in fungal infections, drug reactions, trauma, systemic illness, or other skin diseases.[86]

**5.1.2.The Koebner phenomenon**. The Koebner phenomenon or isomorphic response is a common feature in LP, and develops in areas previously subjected to some type of trauma in the absence of clinically visible lesions.[87] Almost any type of irritant, for example, burns, lacerations, friction, or UV-light, may provoke the isomorphic response. Koebnerization is most frequently seen, if the patient's disease is unstable or in an acute stage of flaring.

### 5.2.Lichen planus of the mucous membranes

In addition to the cutaneous lesions, the oral mucosa is the most commonly reported site of LP. As a sole manifestation of the disease, OLP makes up 15% to 35% of the patient population with LP.[64,88] Furthermore, mucosal lesions in the upper part of the esophagus, conjunctivae, bladder, nose, larynx, stomach, vulva, and anus have been described.[89] In one study esophageal involvement was found in 5 of 19 patients (26%) with idiopathic LP, which may result in stenosis and dysphagia.[90] Multifocal LP of the mucous membranes occurs and is described as plurimucosal LP or vulvo-vagino-gingival syndrome.[91]

**5.2.1.Oral lichen planus**. A Scandinavian study suggest that oral involvement is eight times more common than cutaneous involvement.[83] Of patients with OLP 20 to 34% have been reported to have concomitant cutaneous involvement.[12,92] Conversely, up to 65% of the patients with classical CLP have oral involvement.[92]

Six different clinical subtypes of OLP have been described in the literature: reticular (Fig. 2.5), plaque-type (Fig. 2.6), papular (Fig. 2.7), erosive (Fig. 2.8),

atrophic (Fig. 2.9) and ulcerative/bullous (Fig. 2.10).[93,94] From a practical point of view two groups seem to be more important, namely the reticular and erosive forms of OLP. The reticular form is usually considered to be the most prevalent form, although in one large study of 570 patients with OLP the erosive form of OLP was found to be most common.[12] Erosive OLP may produce symptoms of pain or "burning" sensation.[13] A metallic taste in the mouth has also been described.[95] Older patients tend more often to have erosive lesions at initial presentation.[95]

The buccal mucosa and the lateral borders of the tongue are the most commonly involved sites in the oral cavity,[12,76,89,96] whereas the palate and the floor of mouth are uncommon sites.[89] The lips are considered to be part of the oral cavity. The lower lip is more frequently involved than the upper lip. Gingival involvement may potentially lead to a picture of "desquamative gingivitis". Symmetric involvement of the oral mucosa is more or less a rule. In 95% of the cases, patients have bilateral lesions of OLP.[12,89] OLP may be precipitated by trauma, because lesions have been observed to develop after periodontal surgery and after previous irradiation for oral malignant lymphoma.[97,98]

**5.2.2.Genital lichen planus**. Genital involvement of LP has been reported in 25% of men with typical skin lesions and in an unknown percentage of women.[7] The female genitalia may exhibit less specific involvement consisting of leukoplakic or erythroplakic lesions with a variable atrophy. Desquamative vaginitis is most commonly due to LP and may be the presenting feature of the disease.[99] Symptoms, such as fluor vaginalis, burning, and dyspareunia are common.[100,101] The labia minora agglutinate and vaginal adhesions may make sexual intercourse impossible.[99]

### 5.3.Associated diseases

LP has been reported to be associated with a variety of other disorders. It is difficult to determine, whether there is a causal or a purely fortuitous association. It is possible that LP seen in association with other diseases may be just a lichenoid drug reaction. In those patients with an immunodeficiency, it seems more likely that an underlying cause may trigger both conditions.



**5.3.1.Malignancies.** LP, usually the vesiculobullous variants, has been reported in association with underlying malignancies. LP pemphigoides has been described in association with stomach cancer, lymphosarcoma, reticulum cell sarcoma, neuroblastoma, craniopharyngioma, and a "pararenal malignancy".[98,102-105] A pituitary adenoma was found in a 50-year-old man with bullous LP.[104] Concurrence of LP with a malignant fibrohistiocytoma has been also reported.[38] The association of LP with thymoma and with IgA-kappa-monoclonal-paraproteinemia has also been described.[25,29,30,106]

**5.3.2.Gastrointestinal and liver diseases.** A potential but unproven link between LP and gastrointestinal disease has been suggested. Abnormal hepatic enzyme elevations have been observed in 7% to 52% of patients with LP.[47,107] In 12% of the biopsy specimens liver disease was revealed,[47] and in one study 52% of patients with erosive OLP developed cirrhosis.[108] Patrone et al. reported a higher incidence of hepatic disease among patients with nonerosive OLP of more than one year duration compared to those patients whose disease was present less than one year.[109] Once again, these data suggest that a lichenoid dermatitis may be a nonspecific cutaneous marker of an underlying disease.

**5.3.2.1.Primary biliary cirrhosis (PBC).** Graham-Brown et al. were among the first to describe the association of LP and PBC.[110] A larger study reported that 7 out of 268 patients with PBC (2.6%) had LP.[111] D-penicillamine, used to treat PBC can also provoke an LP-like drug eruption.[112] Powell et al. described 17 patients with PBC, who developed LP during treatment with d-penicillamine, thus raising the question of a lichenoid drug eruption.[111] In nine of these 17 patients exacerbation of LP by d-penicillamine re-administration was observed. The authors concluded that there did seem to be an association between LP and PBC seperate from d-penicillamine administration.

**5.3.2.2.Chronic active hepatitis (CAH).** An association between LP and CAH has also been suggested. The incidence of this disease in patients with LP varies between 9.5% and 13.5%.[25,108,113] Rebora and Rongioletti evaluated 44 patients with LP and noted CAH in 5 (11.3%).[114] The prevalence of CAH in the local population (Genoa, Italy) was 0.25% to 0.5%, which prompted these authors to suggest that

LP may be a significant risk for hepatic cirrhosis. It may be that the association between CAH and LP is more prevalent in Southern Europe.[114] LP has also been described in a patient who received hepatitis B vaccine.[115]

**5.3.2.3.Ulcerative colitis (UC).** Several reports have described patients with UC and LP.[25,116-118] Cusano and Errico reported a patient whose cutaneous and gastrointestinal symptoms paralleled one another, and Wyatt noted two patients whose onset of LP coincided with that of their bowel disease.[118,119]

**5.3.3.Diabetes mellitus (DM).** Investigations have shown a wide range of plasma glucose values in patients with LP.[10,12,21,120-126] In those studies that utilized oral glucose tolerance testing, the prevalence of overt DM ranged from 12.8%[124] to 85%.[120] Christensen et al. and Lozada-Nur et al. utilized fasting blood and plasma glucose levels, respectively, to categorize their patients.[123,126] They found no evidence of an increased prevalence of glucose intolerance in 222 patients with LP. Differences in the interpretation of oral glucose tolerance tests may account for some of the wide discrepancies reported. The two American investigations revealed a low prevalence of DM, whereas a high and low prevalence was found in two Australian studies.[10,12120,126] English and Scandinavian investigators have found the prevalence of abnormal glucose tolerance in patients with LP to fall between the two extremes.[121-125]

In the Bedford diabetic survey it was found that 12% to 14% of the general population, if studied, will show a glucose intolerance.[127] Various studies have shown a substantially higher percentage of such patients in the LP population.[21,120-122,125] The reason for such an increase remains obscure. Jolly has suggested that defective carbohydrate handling may cause LP.[120] Others have observed that LP, like necrobiosis lipoidica diabeticorum, may antedate diabetes.[121]

Halevy et al. found a significant elevation of HLA-$A_{28}$ in nondiabetic patients with LP.[52] They postulated that two populations of LP patients may exist, one of which may be genetically prone to DM. Other investigators, however, have found no differences between the diabetic and nondiabetic LP population. Those LP patients with erosive OLP showed no major differences in fasting plasma glucose values compared to patients with nonerosive lesions.[126] Additionally, among LP patients as a whole, there is no association between age, sex, distribution, duration, or



mucosal involvement and with glucose intolerance.[21,122] Within the diabetic population the incidence of LP has been reported as 1.6%.[126]

**5.3.4. Autoimmune diseases.** As shown in Table 2.1, LP has been associated with a number of autoimmune disorders. It is not known, whether patients with LP are more inclined to develop these diseases or the diseases are somehow etiologically related. Shuttleworth et al. studied 54 patients with LP and an equal number of matched control subjects.[31] They noted no association with autoimmune disease.

**Table 2.1.** Autoimmune diseases observed in patients with lichen planus

| |
|---|
| Alopecia areata[29,31,117,128,129] |
| Dermatomyositis[29] |
| Dermatitis herpetiformis[26] |
| Hashimoto's thyreoiditis[99,102] |
| Keratoconjunctivitis sicca and xerostomia[130] |
| Morphea[128] |
| Myasthenia gravis[106,116,117] |
| Pemphigus vulgaris[131,132] |
| Pemphigus foliaceus[31] |
| Pernicious anemia[31] |
| Systemic sclerosis[110] |
| Thymoma[25,29,30,106] |
| Vitiligo[25,117,128,129] |

**5.3.5.Miscellaneous.** An early investigation by Lynch included 67 patients with LP (with or without oral lesions) and showed a positive correlation between LP and increased blood pressure.[133] The triad of hypertension, diabetes mellitus, and LP was reported as Grinspan's disease.[92] Subsequent studies of oral and cutaneous disease, however, have demonstrated no such association, and currently none is believed to exist.[134,135]

In 1983 Halevy and Feurerman reported 130 patients with LP (with or without oral lesions), 19 (14.6%) of whom had concomitant urolithiasis.[136] This prevalence of renal stones was 6 to 12 times higher than in the general population. They postulated that perhaps a similar metabolic derangement led to both disorders.

Additional studies in patients with OLP have noted iron or folate deficiencies, normal bone marrow, decreased erythrocyte glucose-6-phosphate dehydrogenase,

compensatory hyperhidrosis of the head and neck, and an increased prevalence of blood type O.[137-141]

There is disagreement among investigators, whether LP is associated with other systemic diseases in more than a fortuitous manner. Altman and Perry, in an analysis of 307 patients with CLP, did not find a consistent link with other disorders.[64]

## 6. HISTOPATHOLOGY AND IMMUNOFLUORESCENCE

### 6.1. Light microscopic and ultrastructural features

In general, the light microscopic and ultrastructural features of OLP and CLP are the same. The stratum corneum in CLP usually shows thickening with orthokeratosis, parakeratosis may be seen more frequently in OLP.[89,142,143] The granular cell layer is increased, with prominent granules that result in a "beaded" appearence (Fig. 2.11).

The reticulated Wickham's striae appear to be correlated with an increased granular cell layer.[144,145] Irregular acanthosis is usually present, with rete ridges that form a "sawtooth" pattern, although this feature is not allways present in OLP (Fig. 2.12). Langerhans' cells and melanocytes appear normal, although there is often an increase in their number.[34,42,83,146,147] Histiocytes and lymphocytes are occasionally seen within the epidermis.

In LP the basal membrane zone (BMZ) plays a prominent role in the pathogenesis and expression of the disease, and most specimens show on elecronmicroscopy a duplication of the basal lamina.[20,146,148] Basilar gaps between the keratinocytes are formed and perhaps account for the pigmentary incontinence.

As the BMZ becomes vacuolated, fluid accumulates and leads to the formation of clefts, known as Max Joseph spaces. These may be seen in up to 17% of the specimens.[149] This separation is believed to precede the forming of bullae, seen in bullous LP.

Civatte bodies (hyaline bodies, colloid bodies, cytoid bodies) represent dyskeratotic basal keratinocytes that have undergone premature keratinization and have been extruded into the papillary dermis.[150,151] They are found in 37% to 100% of biopsy specimens from CLP, and were noted in 27% of patients with OLP.[34,149,152] They are considered to be among the earliest histopathologic changes.

As the disease process continues, electronmicroscopic examination shows a steady loss of tonofilaments, desmosomes, and hemidesmosomes.[20,146]



One of the principal features of LP is the bandlike subepithelial inflammatory infiltrate that mainly consists of T-lymphocytes and histiocytes, that hug the basal cell layer. Plasma cells and dermal melanophages are also present.[148,149]

Electronmicroscopic studies have shown normal mitochondria in the early stages of the disease, but as time progresses a decrease in the number of cristae and changes of vacuolization appear.[146] Clausen et al. believed that the mitochondria of the basal cells were swollen, but that this was indicative of nonspecific cellular injury.[20] The endoplasmic reticulum and Golgi-apparatus do not seem to be affected.[146,153]

In OLP no strictly defined histopathologic features are described for the different clinical subtypes. Different LP variants may show characteristic histopathologic features, however. For example, in lichen planopilaris a perifollicular inflammatory cell infiltrate is seen early, with subsequent destruction of the follicles.[154] The follicle involved contains a mass of hyperkeratotic debris and liquefactive degeneration of the basement membrane.[64,154] Eventually, the hair follicle is destroyed and the pilosebaceous structures vanish.

Lesions of drug-induced LP tend to have more parakeratosis than idiopathic disease.[85] Lesional and plasma eosinophilia frequently occurs.[85] In LP pigmentosus there is a melanin deposition in the basal and malpighian layers.[155] Hypertrophic LP usually shows extensive acanthosis.[95]

### 6.2. Immunohistochemical features

**6.2.1. Lichen planus-specific antigen.** In 1983 Olsen et al.[46] described an LP-specific antigen (LPSA) found by indirect immunofluorescence in tissue clinically involved with LP. Subsequent investigation revealed this antigen to be present in 20 patients (80%) with CLP.[156] However, not all lesions of cutaneous LP in the same patient exhibit the LPSA. The circulating antibodies to LPSA are more likely to be markers of the disease than to be causative.[157]

The LPSA does not seem to be as prevalent in oral disease, but patients with OLP may have antibodies directed to this antigen.[157] The LPSA is found in the granular or spinous cell layer and seems to be specific for LP, because it has not been found in the skin of patients with other dermatoses.[158] LPSA has been reported in childhood bullous LP.[158]

**6.2.2.Basal membrane zone (BMZ).** The fibrillar, rarely linear deposition of fibrin/fibrinogen is the most important marker of both OLP and CLP.[159] One study of 40 patients with CLP showed IgM in the BMZ of each patient.[148] IgA could not be demonstrated. A similar study of OLP showed IgM in 4% and IgA and IgG in none of the cases.[160] Fibrin and fibrinogen may be found in a linear pattern at the BMZ in a high percentage of both oral and cutaneous lesions.[148,151,160,161] It is not clear whether these immunohistochemical findings are the cause or the effect of the disease. Complement components, principally $C_3$, $C_4$, and $C_5$, have been reported in the BMZ in oral and cutaneous LP (Fig. 2.13).[148,160] Specimens from glabrous skin lesions may exhibit complement deposition more frequently than those taken from the oral mucosa.[148,160]

**6.2.3.Civatte bodies.** IgM, $C_3$, and $C_4$, are routinely found in colloid bodies (i.e. civatte bodies).[148] IgA, IgG, $C_1$, and $C_5$ may also be detected, but in smaller quantities.[148,151,161] IgM is believed to be deposited during the early stages of colloid body formation. Fibrin and albumin have also been found to occur.[148,151]

**6.2.4.Round cell infiltrate.** The round cell infiltrate characteristic of LP predominantly consists of lymphocytes. Early studies found the lymphocytes to be principally T-cells with primarily helper/inducer markers ($CD_4$, Leu-3a).[34,37] Few or no B-cells were identified. Other investigators have found a predominance of T-cytotoxic/suppressor cells ($CD_8$, Leu-2a).[41,162,163] The duration of the lesions seems to influence the composition of the inflammatory infiltrate; early lesions show an infiltrate of T-helper/inducer cells and macrophages, and advanced lesions contain primarily T-suppressor/cytotoxic cells. These T-cells are also known to express HLA-DR antigens.[37,89]

**6.2.5.Keratinocyte markers.** Keratinocytes in skin lesions express the HLA-DR or Ia-antigens.[164] Keratinocytes from oral lesions exhibit the HLA-DR, but not the HLA-DP or HLA-DQ antigens.[165] Simon suggested that gamma-interferon causes the dermal lymphocytes to induce these changes.[164] In this context also ICAM-1 is mentioned (see also par. 3.1.3.)



**6.2.6.Immunofluorescence of vesiculobullous lesions.** LP pemphigoides, believed to represent a combination of LP and bullous pemphigoid, tends to show features of both diseases. IgG and $C_3$ are present at the BMZ, and IgM and IgA may also be deposited.[161,166] Circulating antibodies to the BMZ may or may not be found.[166,167] Lesions of bullous LP have not demonstrated immunoreactant staining.[166]

### 6.3.Enzymes and surface proteins

Epidermal glucose-6-phosphate dehydrogenase in LP has been reported as normal, increased, and decreased.[168-171] A diminished enzyme content may predispose patients to develop LP after certain drug ingestion such as that of antimalarial drugs.[170] Diminished levels of respiratory enzymes such as cytochrome oxidase, succinic-dehydrogenase, reduced form of nicotinamide-adenine-dinucleotide (-phosphate), and ß-hydroxyacyl-coenzyme-A-dehydrogenase have also been reported.[19,147,171]

Holmstrup and Dabelsteen reported that two plant agglutinins, concanavalin-A and Ricinus communis agglutinin fraction-I, did not bind to the cell membranes of basal cells in OLP.[172] They postulated that an antigenic change had taken place in the cells involved and that this change might play a role in the pathogenesis of OLP.

## 7. DIFFERENTIAL DIAGNOSIS

### 7.1.Cutaneous lichen planus

Clinically, CLP must be differentiated from other papulosquamous disorders such as psoriasis and secondary syphilis,[173] as well from lichen nitidus (LN) and lupus erythematosus (LE). Annular LP may be confused with granuloma annulare, and linear lesions may resemble lichen striatus or linear epidermal nevi. Desquamative vaginitis secondary to LP must be differentiated from lichen sclerosus et atrophicus, atrophic vaginitis, and bullous disorders.[99] The actinic variant of LP may resemble melasma.[81]

### 7.2.Oral lichen planus

The diagnosis of the reticular type of OLP can readily be established on clinical features by the characteristic striae of Wickham. The plaque-type, is sometimes difficult to differentiate clinically from oral leukoplakia and/or LE. Only biopsy and consecutive histopathological examination can be an aid in the final diagnosis.[153,174] Papular OLP, is not very commonly seen, but has a typical appearence. Clinically, the most difficult forms of OLP to differentiate from other oral entities are the erosive and ulcerative lesions. Erythematous candidiasis, erythroplakia, discoid LE, secondary syphilis, erythema exudativum multiforme, cicatricial pemphigoid, pemphigus and even squamous cell carcinoma may all clinically mimic OLP.[175-178] Drug-induced or allergy-induced lesions must be ruled out as well.

One of the disorders difficult to differentiate histopathologically from OLP is LE of the mucous membranes. A lupus band test may be helpful in distinguishing between the two entities.[179] Oliver et al. believe that there is no microscopic feature to differentiate LE from LP conclusively.[180]

### 7.3.Vesiculobullous lichen planus

LP with blister formation is uncommon and was noted in only 3.5% of patients in one study.[64] Two types are distinguished, bullous LP and LP pemphigoides.

Bullous LP refers to the development of vesicles and bullae on pre-existing lesions of LP.[167,181] Bullae typically are tense, with minimal surrounding inflammatory reaction. Nikolsky's and Asboe-Hansen signs have been described.[182] Chemical agents, such as tolazamide, chlorpropamide, and mercaptopropionyl glycine, may precipitate such an outbreak.[183,184] Histopathologic examinations reveals findings compatible with typical LP and a subepidermal bulla.[182]

LP pemphigoides consists of bullae on lesional and nonlesional skin.[102,161,181] This clinical variant is believed to represent an association between LP and bullous pemphigoid (BP).[166,167,185] Recent investigations, however, have shown that the antigen of LP pemphigoides may be different from that associated with BP.[102] Circulating antibodies to the BMZ have been described.[48,49,181] Histopathologic characteristics of LP may be noted, and direct immunofluorescence demonstrates deposition of IgG and $C_3$ in a manner consistent with that of BP.[161,166] Joshi et al. suggested that LP pemphigoides is a separate entity in its own right, distinct from both bullous LP and BP.[186] Captopril and cinnarizine have been reported to



provoke this disorder.[181,187] The extremities are frequently involved with tense bullae.[161] Oral vesicles have also been described.[50]

### 7.4.Lichen sclerosus et atrophicus

Lichen sclerosus et atrophicus (LSA) was first described by Hallopeau in 1887.[188] In 1892, Darier reported on the histopathological features.[189] Although both authors initially considered LSA to be a form of LP, it is now regarded as a separate entity with distinct clinical and histopathological features.[190,191] LSA is a relatively rare dermatosis of unknown etiology, occurring both extra-genitally and genitally.

The extra-genital cutaneous lesions of LSA are clinically characterized by small, ivory or porcelain-white, shiny, round macules or papules, that may coalesce to form plaques.[190,192] Small intralesional haemorrhages are frequently present. They usually occur on the trunk, particularly on the upper part and around the umbilicus, around the neck, in the axillae, and on the flexor surfaces of the wrist. The lesions are slightly raised or level with the surface of the skin, and are usually asymptomatic. Ano-genital lesions in women usually involve the vulva and peri-anal skin, sometimes extending to the skin of the thighs. The ivory-coloured, atrophic papules with follicular hyperkeratosis and plugging can be often identified on the peri-anal region and/or the vulva, but due to friction and moisture the lesions frequently break down to form a red, raw, macerated surface. Complaints of soreness and pruritis are frequently present.[190,192] Involvement of the oral mucosa with or without concurrent genital or skin lesions has been reported only occasionally in the literature.[193-199] Schulten et al. reviewed the literature and additionally described two patients with oral LSA as the only manifestation of this dermatosis.[200]

The most striking histopathological feature in LSA of the skin is a band of hyalinization of the dermal collagen below the epidermis.[190-192] The hyalinized tissue appears structureless, oedematous and contains sparse cells, but may show dilated capillaries. The epidermis shows variable thickness, hyperkeratosis and follicular plugging. Later, the epidermis becomes atrophic. Beneath the hyalinized area a band of lymphocytic infiltration may be seen. The subepidermal elastic fibers tend to be decreased and separated from the epidermis by oedema. In vulval lesions secondary infection and superficial erosion are common and may mask the primary changes.[190]

### 7.5.Lupus erythematosus-overlap syndrome

Copeman et al. described four patients with features characteristic of LE and LP in what is now known as the LE-overlap syndrome.[201] They reported violaceous round to oval plaques that were centrally ulcerated and slowly heal. One patient had bullae and later developed a fatal systemic LE. Similar lesions have subsequently been reported, including oral manifestations.[202-204]

Clinically, these lesions are acrally located, with an appearance that combines features of both LE and LP. These patients frequently have systemic complaints consistent with those found in LE.[179,201,204] However, van der Horst et al. studied six cases with clinical manifestations of both diseases, including five patients with features of OLP. They concluded that some patients had a coexistence of both diseases while others suffered from an unusual variant of chronic discoid LE. They did not support the suggestion that "LP-LE disease" should be considered as a distinct entity.[205]

The presence of systemic immunologic markers is controversial. A report by Ahmed et al. documented three patients with significant anti-nuclear antigen (ANA) titers.[179] Romero et al, however, found that of their 11 patients with the LE-overlap syndrome only 3 were positive for ANA, and then only in low titers.[203] A report by Jamison et al. described a patient with cryoglobulinemia, positive rheumatoid factor, and $C_4$ deficiency.[202]

Differentiating between the disorders usually requires histopathologic analysis. Again, these two disorders may display similar features microscopically. Points of differentiation include colloid (Civatte) bodies, basement membrane changes, and immunologic findings. Civatte bodies may be found in both conditions, but in LP they tend to be more numerous and situated deeper, even into the upper area of reticular dermis.[203] Binkley et al. analysed the disulfide bonds found in colloid bodies and noted differences between those of the two diseases.[206] A different pathophysiologic mechanism may account for such discrepancies. In LP basement membrane clefts may be due to lysis of keratinocytes, whereas in LE vacuolization forms on either side of this membrane.[203] Additionally, areas of thickened BMZs are more common in LE. Lastly, direct immunoglobulin and complement deposition occur in a granular, linear band along the dermo-epidermal junction in LE, whereas in LP these immunoreactants tend to be limited to colloid bodies.[203] It should be noted, however, that a patient has been described in whom biopsies from separate sites showed LP and LE consistently.[204] Ahmed et al. postulated overlapping etiologic factors.[179]



### 7.6.Lichen planus erythematosus (LPE)

LPE is a rare form of the disease. Asymptomatic papules appear on the trunk and extremities. They are deep red, soft, and blanch with pressure.[95] Oral lesions can be identical to OLP.[178] Histopathologic findings are consistent with LP.[7] An overlap between LP and LE has been proposed.[201] Violaceous to erythematous plaques and patches are typically seen on the extremities. The lesions are of long duration, and the clinical differentiation between the two diseases may be impossible.

### 7.7.Lichenoid eruptions or reactions

LP-like lesions has been associated with contact, inhalation, or ingestion of various chemical agents (Table 2.2). Clinically, these lesions may display findings typical or atypical of classic LP. Eczemation, hypertrophy, unusual pigmentation, scaling, and intense postinflammatory hyperpigmentation commonly occur.[209,233] Alopecia may be profound and unrelenting.[209] Atrophy of dermal sweat glands has been reported.[209,210,233]

Lesions of the mucous membranes are unusual.[209,249] However, oral lichenoid lesions have been reported in relation to aforementioned substances (Table 2.2). In this context, the association with dental restoration materials like amalgam is subject of much discussion.[254-257] However, the mechanism remains obscure, and is, therefore, commonly accepted as a hypothesis. For this reason, some investigators advise to remove dental restoration material (see also par. 4.5).[77] Hypersensitivity is also believed to play a role, but on the other hand the oral mucosa is far more hypo-allergic than the skin.[258] Watanabe et al. evaluated drug-induced LP with lesional immunofluorescence and noted no significant differences with idiopathic LP.[33] The histopathologic features of LP may also be found to some degree in other oral and cutaneous disorders.[259] These lichenoid aspects are characterized by acanthosis, damage to the BMZ and the epidermal basal cells, pigmentary incontinence, orthokeratosis, and a dermal bandlike inflammatory infiltrate invading the basalcell layer.[260,261] Colloid bodies, parakeratosis, and periadnexal infiltrates may also be present.[210]

A unifying theme among these diseases is the bandlike dermal infiltrate of mononuclear cells. Initially, most of these cells were characterized as T-helper/inducer cells, but some may have suppressor/cytotoxic function.[39] Basal cell destruction ultimately results in detachment of the basal cell plasma membrane from the lamina densa and causes vacuolar changes.[260]

Most substances that provoke LP-like lesions are ingested or given parenterally.

Many allied servicemen developed LP after receiving quinacrine for malaria prophylaxis while serving in the South Pacific during World War II.[262] Follicular involvement frequently ensued and led to alopecia. Fellner has suggested that gold most commonly leads to lichenoid eruptions.[85]

**Table 2.2.** Drugs associated with a lichen planus-like reaction

- Antihypertensives
  - Captopril[187,207,208]
  - Chlorothiazide[209]
  - Enalapril[208]
  - Hydrochlorothiazide[209]
  - Labetalol[211]
  - Methyldopa[212-214]
  - Practolol[215]
  - Propanolol[216,217]
  - Spironolactone[218]
- Antibiotics
  - Demeclocycline[219,220]
  - Ethambutol[221]
  - Griseofulvin[222]
  - Ketoconazole[223]
  - Levamisole[224]
  - Para-amino-salicylic-acid[225]
  - Streptomycin[226]
  - Tetracycline[227]
- Nonsteroidal antiinflammatory drugs
  - Naproxen[228]
  - Indomethacin[229]
  - Feclofenac[229]
  - Diflunisal[229]
  - Flurbiprofen[229]
  - Ibuprofen[229]
  - Benoxaprofen[229]
  - Acetylsalicylic acid[230]
- Antimalarials
  - Chloroquine[231]
  - Mepacrine[232,233]
  - Quinine[234]
- Anti-arrhythmics
  - Quinidine[235-237]
- Psychotropics/neurological agent
  - Carbamazepine[238]
  - Levomepromazine[239]
  - Lorazepam[240]
  - Metopromazine[239]
- Film developing/fixing agents
  - 4-Amino-N-diethyl-analine
  - Sodium Thiosulfate (TTS)[241]
  - CD-2[241,242] and CD-3[242]
  - p-Isopropylamino-diphenyl amine (IPPD)[243]
- Oral antidiabetics
  - Chlorpropamide[183,244]
  - Tolazamide[183]
  - Tolbutamide[245]
- Miscellaneous
  - Allopurinol[246]
  - Amiphenazole[247]
  - Arsenicals[248]
  - Cinnarizine[181,33]
  - Gold compounds[249]
  - Tiopronin[184,250]
  - Methycran[33]
  - Musk ambrette[251]
- Penicillamine[112,252]
  - Probenecide[33]
  - Pyrimethamine[253]
  - Pyritinol[33]
- Trihexyphenidyl[33]



A lichenoid contact dermatitis has been described after exposure to nickel, aminoglycoside antibiotics, color film developers, and dental amalgams.[83,242,263,264] A photocontact lichenoid eruption occurred after musk ambrette application.[251] De Graciansky and Boulle investigated patients with lichenoid dermatitis resulting from color film developer contact and divided them into two general categories.[265] The first group were those who experience a slight but continuous exposure to the offending agent and who developed classic LP. The second category included patients who had a single but much larger acute exposure. They displayed the typical findings of contact dermatitis that ultimately resulted in lichenoid lesions. Patch testing has shown some correlation with color film developers,[242] but not with dental amalgams.[83,242] Inhalation of substances may be partially responsible.[265]

The cause of lichenoid drug eruptions remains unclear. The adulteration of cellular molecules by the offending agents may be operative. Penicillamine changes cell surface antigens, and the sulfhydryl groups of captopril are known to alter enzyme systems.[111,207] These aberrations may precipitate an immune response to epidermal neo-antigens resulting in production LP-like lesions.[111] Stereochemical similarities between drugs may also represent a potential etiologic link.[239]

It is also possible that the compounds in question merely unmask latent LP.[92,110,223,266] HLA- phenotypes may determine which patients are susceptible.[223]

### 7.8.Graft-versus-host disease (GVHD)

In 1975 two French investigative groups reported a lichenoid eruption that occurred in two men who had received allogenic bone marrow transplants from their sisters.[267,268] Similar cases have been subsequently reported.[71]

GVHD occurs most commonly in patients undergoing bone marrow transplantation (30% to 60%), but is also seen in fetuses obtaining maternal leukocytes via maternal-fetal transfusion and in blood transfusions transplanting immunocompetent cells into immunodeficient recipients.[269-271] Surprisingly, GVHD has also been seen in healthy patients who had received blood transfusions after heart surgery.[272]

There are two main forms of GVHD, the acute and chronic form. In acute disease a morbilliform, blanchable, erythematous eruption occurs on the upper trunk, neck, hands, feet, and erosive lesions of the oral mucosa, 10 to 40 days after transplantation.[273,274] Pruritis may be present, as may bullae in severe cases. The disorder is a systemic one, as evidenced by concomitant involvement of the gastrointestinal tract, and bronchial mucous membranes.

Chronic disease appears weeks to months after transfusion or transplantation and is

not always preceded by the acute phase. In chronic disease lichenoid lesions appear acrally and may be seen on the palms, soles, and the oral mucosa.[274] Pruritis and postinflammatory hyperpigmentation are present. The papules themselves are violaceous, with less distinct margins and diminished angulations. Oral findings are indistinguishable from OLP. A sclerodermoid variant of GVHD may be seen in long-standing disease.[273] The severity of the skin eruption frequently parallels that of the reaction overall.

Acute disease shows vacuolization of the basement membrane, diminished Langerhans' cell number, Ia+ keratinocytes, and a mononuclear cell inflammatory infiltrate in both papillary and reticular dermis.[273,274] Immunofluorescent studies for complement and immunoglobulins have been shown both positive and negative results.[275,276] The histopathologic changes of chronic GVHD are essentially the same as those in LP.[276] Lesions show hypergranulosis, hyperkeratosis, basal cell layer vacuolization, colloid bodies, and inflammatory cell infiltrate in the epithelium. Immunofluorescent findings are similar to those in LP.[276]

The acute form seems to result from an attack by immunocompetent donor T-cells and null cells against incompatible host histocompatibility antigens.[273] Chronic disease is believed to be due to an attack on the host by immune cells that have already begun to differentiate within the host.[274] The unusual situation in which healthy recipients develop GVHD after routine transfusion (cardiac surgery patients) may result from the infusion of leucocytes homozygous for identical HLA-antigens into patients with heterozygous HLA- antigens.[277] T-cells that have become sensitized by host cell interaction may release various lymphokines (e.g. interferon, interleukin-2) and activate donor and recipient mononuclear cells.[274] A viral cause has also been considered.[71] Chronic disease may be seen despite marrow donation from an identical twin, and raises the possibility that minor histocompatibility antigens may be important in this eruption.[274]

The best means of treating GVHD is to prevent it from occurring by irradiating blood products prior to transfusion. If the disease has already occurred, corticosteroids in high doses and adjunctive drugs, such as azathioprine or methotrexate, may be effective.[273] Early therapy results in improved outcomes.[273] Cyclosporin-A (CsA) is being used with some benefit in established disease.[278] Prevention or modification of GVHD has been attempted with chemotherapeutic agents such as CsA or methotrexate.[279] Pretreatment of marrow to be infused has also been attempted.[273]

Acute GVHD is the primary or associated cause of death in 17% to 73% of patients who succumb after allogenic bone marrow transplantation.[273] Interstitial



pneumonitis, viral infections, and disseminated fungal infections are also commonly seen.[273] In chronic GVHD cutaneous ulcerations and bacterial infections, especially with Staphylococcus aureus are frequently seen.[273] The disease also may resolve spontaneously after months to years.

## 8. MALIGNANT TRANSFORMATION

Although very rare and controversial, the malignant transformation of CLP has been reported.[280-282] Malignant transformation is usually associated with OLP, but in a review of the literature, it was noted that 10% of LP-associated cancers arose outside the oral cavity.[282-284] In contrast, some clinicians have been unable to detect a significant malignant potential for OLP.[76] However, the most likely range of malignant transformation of OLP described in the literature varies between 0.1% and 3%.[283,285]

It remains a controversial issue, whether OLP should be regarded as a premalignant condition or lesion at all. In this context the erosive and atrophic forms of OLP are mentioned most frequently. These forms also account for the largest number of erroneously made clinical or histopathological diagnoses. Many investigators suggest that in OLP, the mucosa is more susceptible to carcinogenic agents.[286] The consequence of this theory is that the lesion itself is not considered as premalignant, but as a premalignant condition.

Holmstrup and Pindborg commented on the risk of erythroplakic oral lesions.[175] In a follow-up study of 740 patients with OLP (median observation period of 3.6 years), seven out of eight erythroplakic lesions associated with OLP showed dysplasia on microscopic examination. Two showed squamous cell carcinoma at the time of initial diagnosis, and one changed into oral squamous cell carcinoma (0.14%) after 6 years.[175] The authors state some nine years later, that OLP fullfils the WHO criterion of a premalignant condition.[74] Many investigators studied the premalignant nature of LP. Although they reached a high degree of certainty, no final conclusions could be made.[76]

There is still a wide variety in the interpretation of the diagnostic criteria for OLP. For example, De Jong et al. stated that in approximately 25% of all biopsies from OLP showed some features of epithelial dysplasia.[287] Krutchkoff and Eisenberg proposed the term "lichenoid dysplasia" for this form of slight epithelial dysplasia.[288] It is well recognized that both the clinical and histopathological criteria

of OLP leave room for some subjectivity in the interpretation. Especially the plaque-type and also the erosive type of OLP may sometimes be difficult to distinguish clinically from the various manifestations of homogeneous and non-homogeneous leukoplakia. The possibility of the synchronous presence of OLP and oral erythroplakia or an erythroplakic lesion has been discribed by Holmstrup and Pindborg.[175]

In a review of the literature of 223 cases of reported malignant transformation occurring in OLP, Krutchkoff et al. only found 15 cases that fullfilled their criteria.[289] In a follow-up study of 225 cases of OLP one carcinoma (0.5%) developed after an observation period of five years.[11] In another follow-up study of 611 patients, probably including the latter group of 225 patients, nine patients (1.5%) developed oral squamous cell carcinoma during follow-up, ranging from 4.9 to 24 years.[74] In yet another follow-up study of OLP reported from India, 3 carcinomas (0.4%) developed in 722 patients after a mean observation period of 5.1 years.[76] In a prospective study in San Francisco, consisting of 570 patients, malignant transformation occurred in 1.2 per cent in a mean time of 3.4 years after the onset of OLP.[12]

There is a discrepancy with regard to the finding of high percentages of epithelial dysplasia in OLP, varying from 25-57 % and the apparently low malignant transformation rate.[287,288] The influences responsible for precipitating malignant transformation of OLP are not known, but may be associated with chronicity of the oral lesions, tobacco use, and oral yeast colonization.[75,76]

At the molecular level a neoplastic cellular clone may develop in an epithelium that is undergoing constant renewal.[74] Long-standing inflammation, or a reaction to the original underlying provocation may also be operative.[76,92,140]

## 9. TREATMENT

### 9.1.General considerations

Apart from the extremely rare instances of possible malignant transformation, LP is essentially benign and usually self-limiting, although recurrences and exacerbations occur for many years. Consequently, any treatment strategy must be safe and unlikely to aggravate the disease. Activities that traumatize susceptible tissues, such as alcohol or tobacco consumption, bruxism, sharp or roughened teeth (or dentures), ill-fitting oral appliances, or tongue thrusting should be eliminated.



Patients with actinic LP must be protected by sunscreens. Potentially provocative medications, unless absolutely required, should be discontinued. Patients who come into contact with color photographic developers should rinse well with water after exposure and should be given an acidic skin cleanser to use.[210]

### 9.2.Corticosteroids

Systemic administration of corticosteroids is useful in relieving pruritis in CLP and reducing symptoms in OLP, and in inducing remission of lesions. Bursts of orally administered prednisone are effective in case of vaginal involvement.[99] Nail atrophy and pterygia formation may be prevented by steroid administration.[86] Snyder et al. reported good results with the use of megadose pulsing of prednisone in patients with resistant disease.[290]

The minimal effective dose of daily prednisone used to treat patients with LP is usually 15 to 20 mg. Treatment is continued for 6 weeks and then gradually tapered down for another 6 weeks.[15] In some patients maintenance therapy is required.

For limited lesions or for elimination of adverse side effects, topical application of corticosteroid preparations may suffice. In CLP, occlusion overnight with corticosteroids incorporated in polyethylene film is useful. Vulvar involvement often responds to topical applications of corticosteroids. Vaginal or rectal cortisone suppositories are helpful.[99,101] One percent hydrocortisone cream as lubricant, with regular vaginal dilatation, may prevent vaginal synechiae.[99]

With regard to oral lesions, ointments tend to be the most helpful vehiculum, because gels may irritate and creams are often bitter.[83] The use of topical steroids is reported with various outcome. Steroid ointments-covered pledgets inserted intraorally for several minutes have been recommended.[83] Betamethasone valerate inhalers are effective in OLP, and the lozenge form is used to treat esophageal involvement.[88,291]

Triamcinolone acetonide has been injected into the affected matrices of patients with nail involvement.[86] Cutaneous and oral lesions sometimes respond well to intralesional steroids.[292]

### 9.3.Retinoids

Günther successfully treated five patients with oral and topical tretinoin.[293] Sloberg et al. used 0.1% tretinoin gel in a double-blind study among patients with OLP.[294] Significant improvement was seen in patients receiving the drug. Slight irritation and burning may be noted and can usually be controlled by decreasing the frequency of application. Long-term maintenance therapy may be necessary.

Isotretinoin has been successfully used in patients with LP, but recurrence was noted after discontinuation of the drug.[90] Topical 0.1% isotretinoin gel was tested in a double-blind study among 20 patients with OLP, with significant improvement of the lesions.[295] The erosive type of OLP responded more slowly. Again, relapse occurred after discontinuation of the drug.

OLP has been treated with a newer retinoid, etretinate. Hersle et al. used 75 mg/day in 28 patients with oral disease and noted a prompt beneficial response.[296] Ferguson et al, however, found little benefit in 10 patients with the erosive type of OLP using similar doses.[297] Dramatic improvement after etretinate administration has been described in a human immunodeficiency virus-positive patient with hypertrophic LP.[298]

The arotenoids, a class of experimental vitamin-A-derivates, have also been shown to be of benefit in treating LP. Temarotene (Ro-15-0778) was administered to 13 patients with CLP in doses of 800 to 4800 mg/day for up to 441 days.[299] Twelve patients reported significant improvement or clearing of their disease.

The retinoids are known to possess anti-inflammatory properties, perhaps through their interaction with the arachidonic acid cascade, and may alter cell surface antigens of the keratinocytes.[295] An interaction with lesional T-lymphocytes may also be operative.[297]

### 9.4.Griseofulvin

Griseofulvin was first reported to be effective in the therapy of patients with CLP by Shegal et al. Improvement was noted within 2 weeks in 10 patients given 500 mg/day orally.[300] One double-blind, placebo-controlled study showed similar results.[301] In another study, long-term (3 to 6 months) administration of griseofulvin resulted in an 86% rate of clearing of lesions among 22 patients with CLP.[302] Oral erosive lesions have responded favorably to this drug.[303]

Massa and Rogers, however, failed to demonstrate significant improvement in patients with CLP.[304] Bagan et al. noted no improvement and, in fact some worsening in seven patients with OLP who were given griseofulvin.[222] CLP has also been noted to develop while a patient was taken the drug for a mycotic infection.[222]

Griseofulvin is known to exhibit an increased affinity for abnormal epithelium.[303] Its interaction in LP may be by interference with nucleic acid metabolism that is important to normal cell keratinization.[301,302] Amphotericin-B, a broad-spectrum antimycotic drug, if administered to patients with OLP and positive Candida albicans cultures, resulted in a 94% clinical improvement.[73]

### 9.5.Psoralen-ultraviolet-A (PUVA)

An early study by Ortonne et al.[305] on PUVA-therapy in seven patients with LP resulted in remission in six, including two 8-year-old boys. No recurrences were reported in the ensuing 2 to 8 months, and histopathologic evaluation disclosed a loss of inflammatory cells in the affected skin. In an additional study of 10 patients with LP, two exacerbations cleared completely and needed no maintenance therapy during 4 years of follow-up.[306] Once remission is achieved, maintenance doses may be unnecessary.

Chen used UVA alone in once-weekly doses to treat 35 patients with OLP.[307] In 30 patients (86%) the oral lesions improved or were cured after 8 weeks.

### 9.6.Surgery

Surgical excision of LP has been undertaken. Emslie and Hardman described four patients with symptomatic OLP lesions who were treated with primary excision and closure, in all four with good results.[308]

Erosive and hypertrophic disease of the palms and soles is frequently disabling and uncomfortable. Use of split-thickness skin grafts to cover these lesions has been proven an effective way to manage such patients.[309-311] Follow-up revealed no recurrences, but prolonged postoperative care was required.[310,311]

Cryosurgery has also been used to treat oral lesions.[312-314] Treated areas healed within 3 weeks and were histopathologically normal by 4 weeks.

Frame et al. treated three patients with erosive OLP with use of carbon dioxide laser.[315] They noted reepithelialization by 4 to 6 weeks, minimal wound contraction, and a normalization of oral function. Two patients experienced a recurrence.

### 9.7.Cyclosporin-A (CsA)

The primary target of the drug seems to be the T-helper/inducer cell.[316] The production or release (or both) of interleukin-1 from monocytes and of interleukin-2 from T-cells is also inhibited by this drug. Higgins et al. were among the first to use this drug for treatment of CLP in six patients.[317] They were given 5 mg/kg day orally; the disease cleared in all six, but recurrence occurred after discontinuation of the medication. In a similar study in two patients with chronic CLP, a prompt response was also noted.[316] "Swish and spit" CsA in patients with OLP has been helpful.[318] Shiohara et al. have proposed that CsA's capacity to inhibit interferon-gamma production by lymphocytes may make it of possible benefit in treating lichenoid drug eruptions.[39]

Long term systemic CsA administration may have many side effects, including hypertension, paresthesias, hirsutism, and, most importantly, renal dysfunction.[319] As such it should be considered a drug of last resort.

### 9.8.Antibiotics

In 1954 Hard and Homberg treated 79 patients with CLP with 600.000 IU of penicillin intramuscularly daily, for an average of 6.8 million units total dosage.[5] The disease improved in 59 (75%). Hard and Homberg believed that penicillin helped easing pruritis and that it also treated the underlying cause.

Shaps et al. used levamisole, an antinematodal drug, to treat recalcitrant CLP in six patients.[320] The CLP improved significantly in four within 4 to 6 weeks.

An 80% response rate among patients with early disease was noted in a study from Egypt with use of a dosage of trimethoprim 80 mg/sulfamethoxazole 400 mg four times daily for 5 days.[321] No effect was noted in patients with chronic CLP. Aureomycin and tetracycline mouthwash have also been used with success in patients with OLP.[95,322] Case reports describe improvement of the disease in patients undergoing treatment with metronidazole and isoniazid.[59,98]

### 9.9.Dapsone

Success with dapsone has been described both in children and in adults in the treatment of bullous CLP.[158,185] Erosive LP of the glabrous skin and oral mucosa has also been aided by administration of this drug.[323,324] Dapsone may inhibit the myeloperoxidase cytotoxicity within the cells that form the lichenoid infiltrate or



may inhibit the release from mast cells of proinflammatory or chemotactic molecules.[323,324]

### 9.10.Miscellaneous

Azathioprine has been successfully used to treat LP pemphigoides.[49] Another patient with LP and hypogammaglobulinemia responded positively to replacement of immunoglobulins.[31]

Paslin treated three patients with cyclophosphamide, and in all three sustained remission of CLP was achieved.[325] This medication appears, unlike corticosteroids, to induce a lasting remission. Methotrexate has been used with some success, although worsening of the disease in a patient while on the drug has been reported.[290]

Radiation therapy temporarily healed erosive lesions of the soles in one patient.[309] Superficial irradiation of cutaneous lesions have been described.[63]

Antimalarial drugs have been successfully used in treating actinic LP and nail involvement.[326,327] Phenytoin in doses of 100 to 200 mg/day was used in 25 patients with LP and resulted in complete clearing of the disease in 14 patients.[328]

Hampf et al. reported the use of psychotherapy and psychiatric medications to treat OLP successfully.[62] Pelisse described a patient with vulvovaginal gingivitis syndrome that was succesfully treated with sulpiride.[101] Older therapies include mercapto-ethane-sulphonic acid, systemic mercury, nicotide acid or nicotinamide, bismuth, vitamins, intravenous calcium gluconate, and arsenicals.[5,63,64,239,329,330]

## 10. PROGNOSIS

OLP is more chronic and recalcitrant to therapy than CLP and may persist for up to 20 years.[92] Andreasen found that 41% of reticular oral lesions, 12% of atrophic lesions, 7% of plaque-type lesions, and none of the erosive lesions underwent spontaneous resolution.[93] Fulling reported a clearance rate of only 15% with therapy in an average of 3.6 years.[11] Cutaneous involvement usually has a shorter course. Tompkins reported an average of 11 months duration in patients with only glabrous skin lesions versus 17 months in patients with combined oral and cutaneous LP.[63] The latter investigation showed a 6.5 months duration of the disorder for those patients in whom a sustained remission of the disease was

achieved. LP in patients with only glabrous skin lesions tended to be easier to clear, and mucous membrane involvement, with or without cutaneous lesions prolonged the course.[13] The eruption may be self-limiting regardless of therapy. In one study involving 23 patients with glabrous and oral disease, an average of 8 months between onset of the lesions and spontaneous involution was reported in untreated patients.[6] This result tends to cloud most studies employing different therapeutic agents.

Early investigators attempted to categorize patients with LP by anatomic involvement, duration, and recalcitrance of the disease.[63,64] Tompkins found that generalized disease had an average duration of 8 months, whereas average duration in localized lesions was 46 months.[63]

Relapse occasionally occurs after initial clearing of skin lesions, in 12% to 20% of patients.[6,7] Tompkins found that five of his 41 patients (12%) underwent a recrudescence of CLP lesions.[63] In a subsequent evaluation 17% of patients with CLP were reported to experience a recurrence lasting an average of 8 months.[64]

Certain clinical variants of this disease display different prognostic features. Thorn et al. described that papular OLP was mainly seen in the initial phase and had a transitory course, whereas plaque-type OLP was a more chronic form.[94] Ulcerative OLP, although more persistent, generally showed a short-term course.[94] Atrophic OLP showed fluctuation with many remissions and newly established affections.[94] Familial LP tends to show an increased likelihood of early relapse.[58]

Several authors believe that therapy of LP does not influence the natural course of the disorder and that treatment is only palliative in nature.[63,64]



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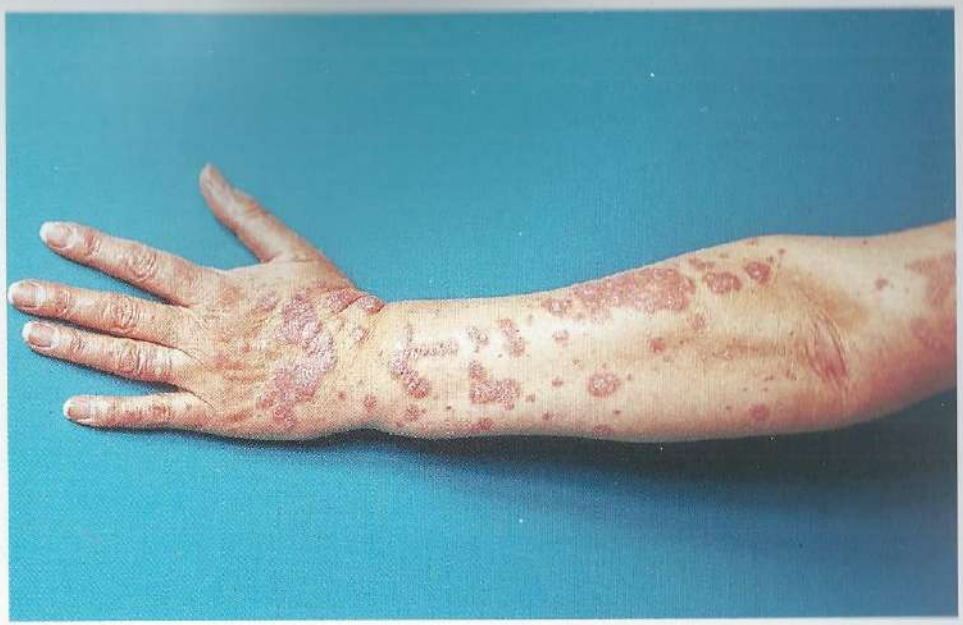

Figure 2.2. Flat topped and occasionally polygonal faintly erythematous to violaceous papules in cutaneous lichen planus.

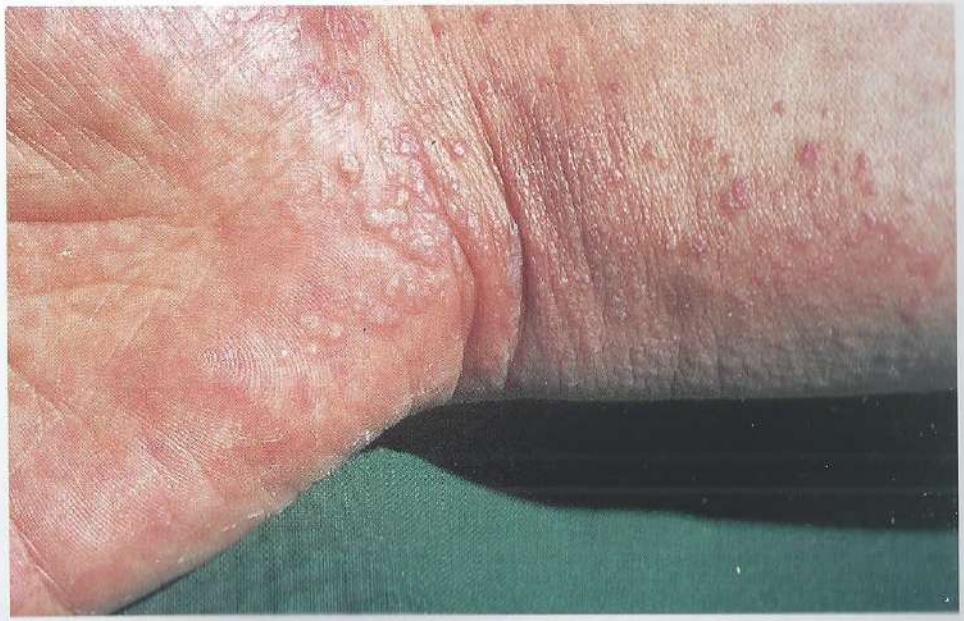

Figure 2.3. The flexural side of the wrist is the most classical and characteristic site involved in cutaneous lichen planus.

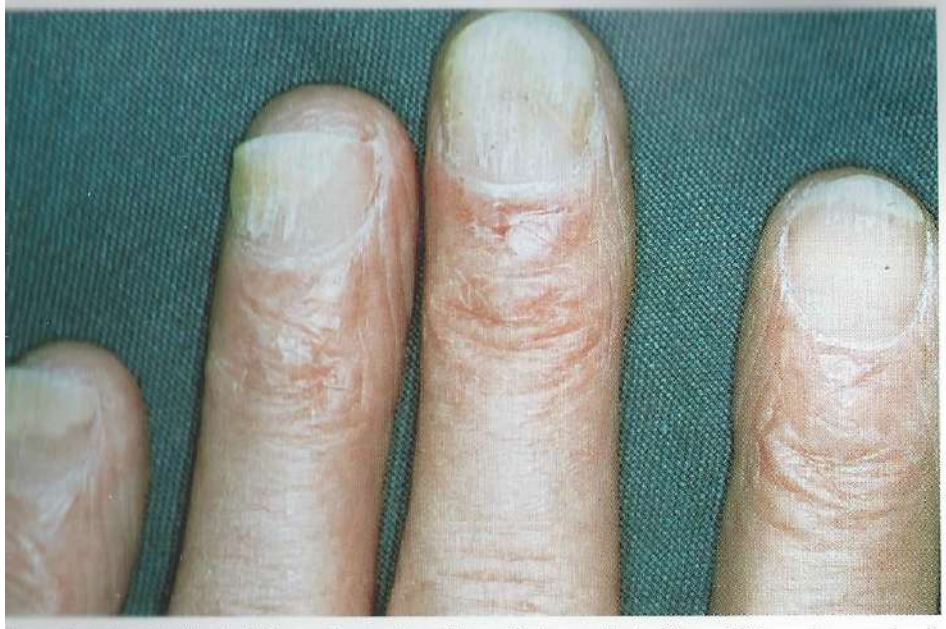

Figure 2.4. Longitudinal ridging and grooving of the nails in a patient with oral lichen planus and nail involvement.

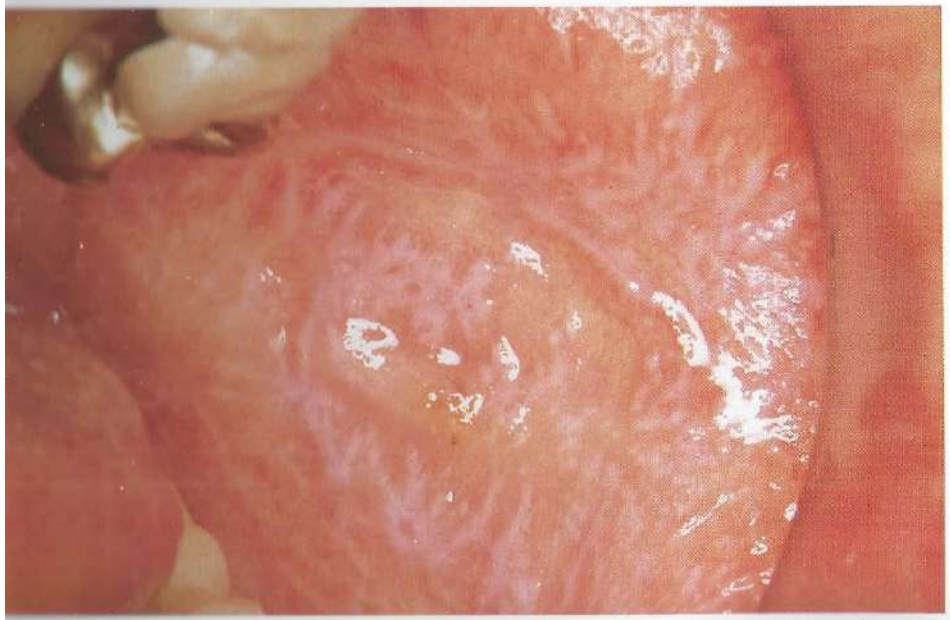

Figure 2.5. Striae of Wickham on the buccal mucosa in a patient with reticular oral lichen planus.



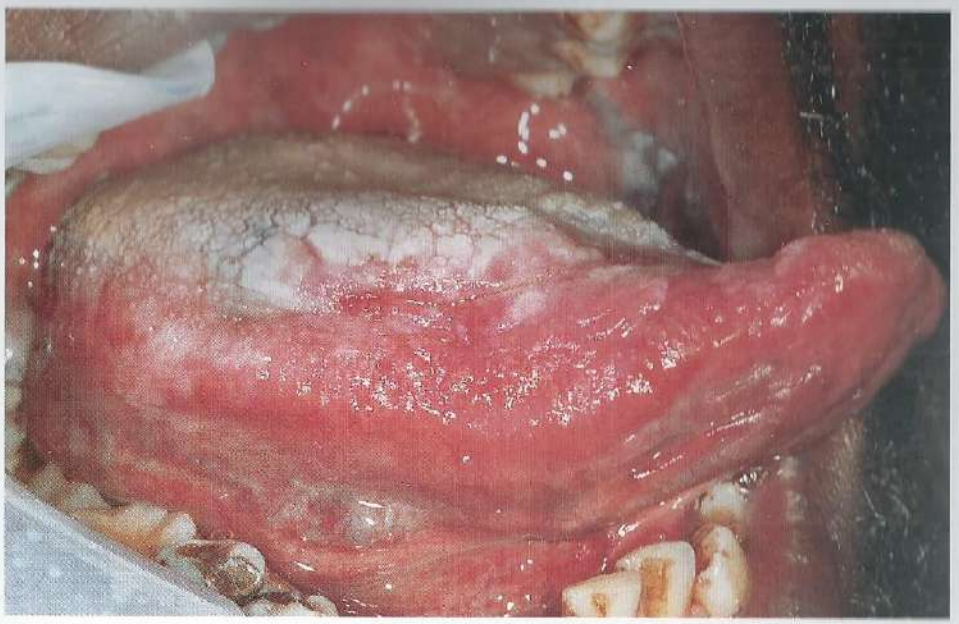

Figure 2.6. White plaques on the lateral border of the tongue in a patient with plaque-type oral lichen planus, slight ulceration is also seen.

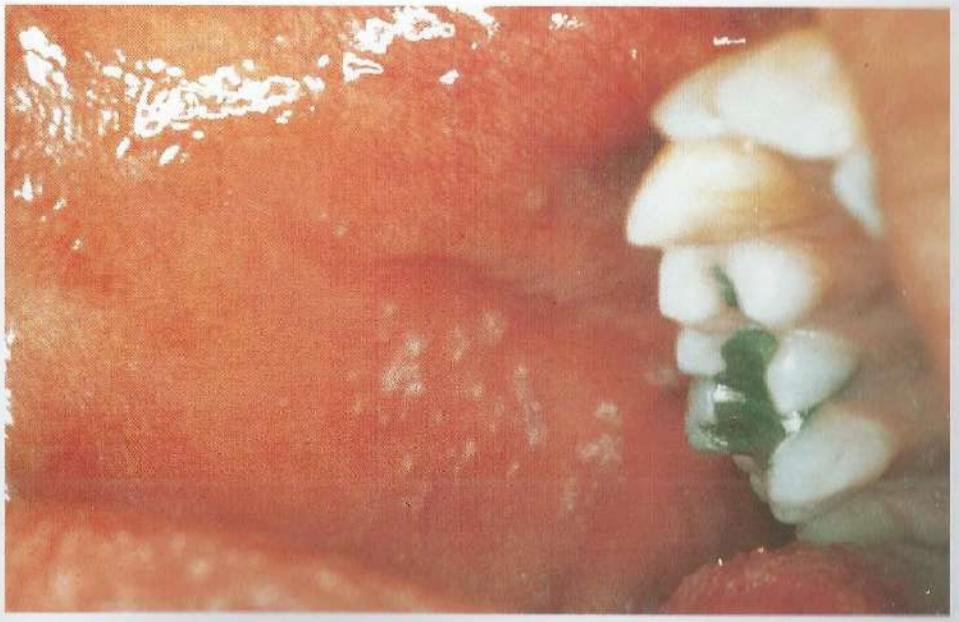

Figure 2.7. Little white papules, just rising above the mucosal surface in the cheek of a patient with papular oral lichen planus.

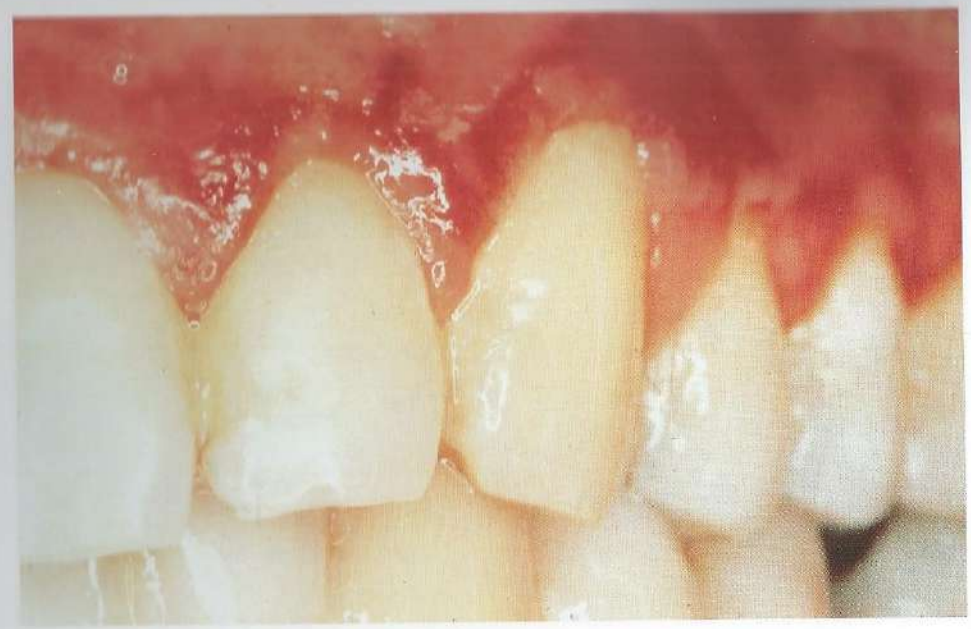

Figure 2.8. Erosive oral lichen planus on the gingiva.

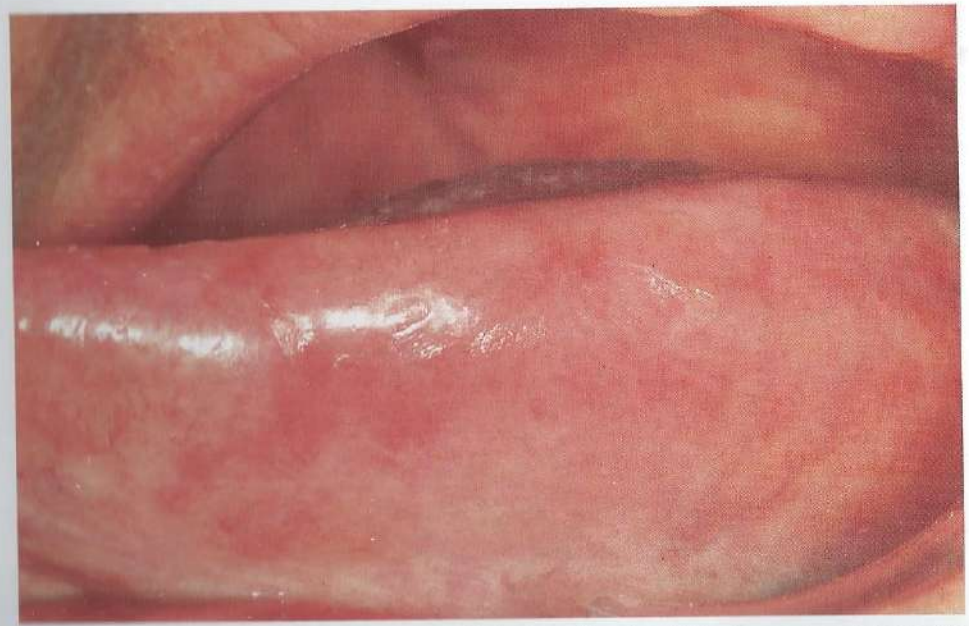

Figure 2.9. Atrophic changes in the mucosa of the lateral border of the tongue in a patient with atrophic oral lichen planus.



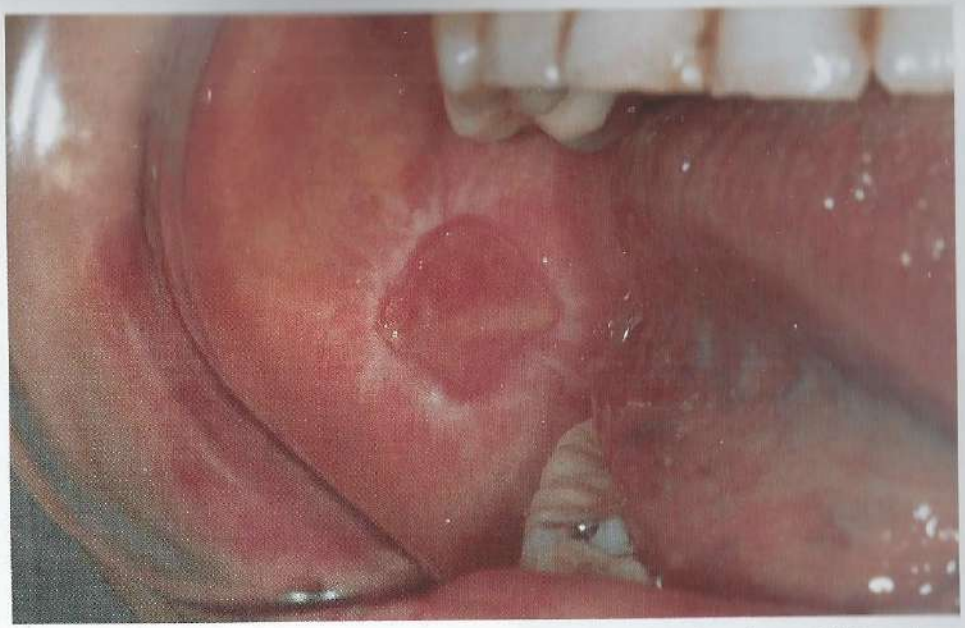

Figure 2.10. Ulcerations seen in the buccal mucosa of a patient with ulcerative oral lichen planus. Note the slight striation around the ulceration.

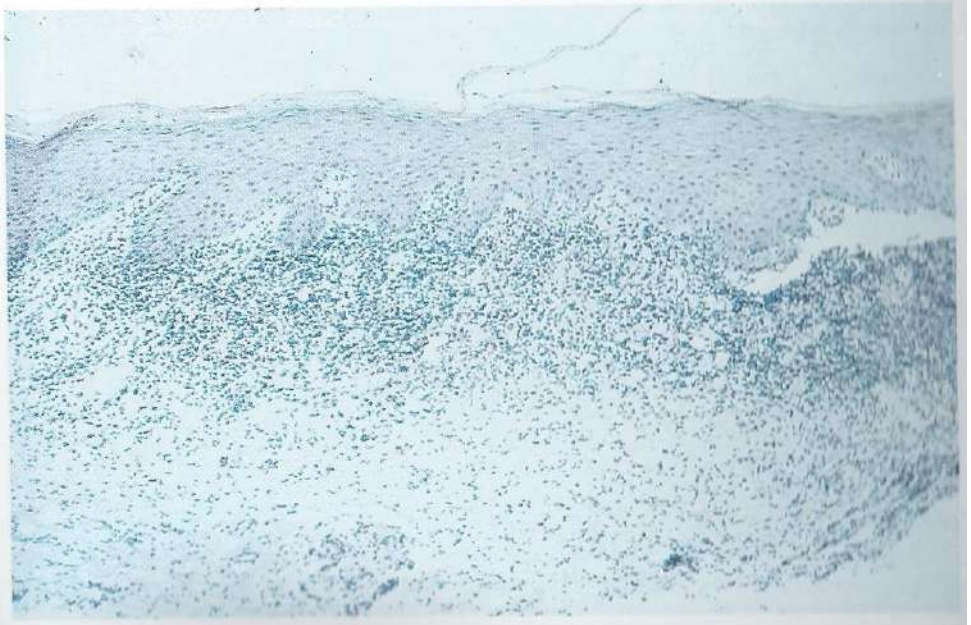

Figure 2.11. Photomicrograph of biopsy tissue from a patient with oral lichen planus. One of the principal features is the bandlike subepithelial inflammatory infiltrate that mainly consists of lymphocytes (HE-staining).

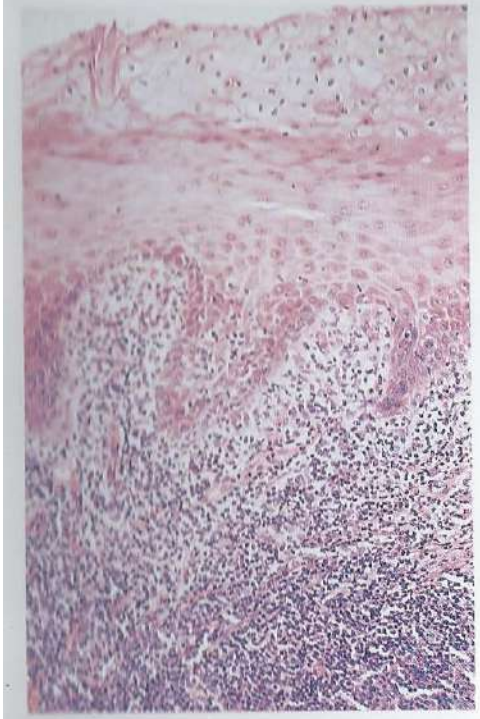

Figure 2.12. Rete ridges in lichen planus, "sawtooth" pattern (HE-staining).

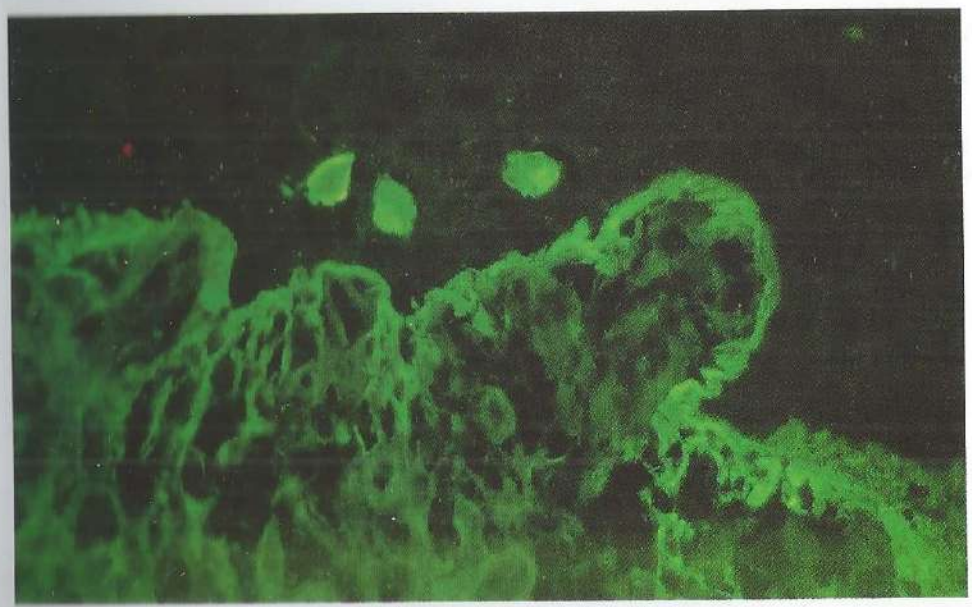

Figure 2.13. Immunofluorescence. Fibrillar deposition of fibrin/fibrinogen at the basal membrane zone.



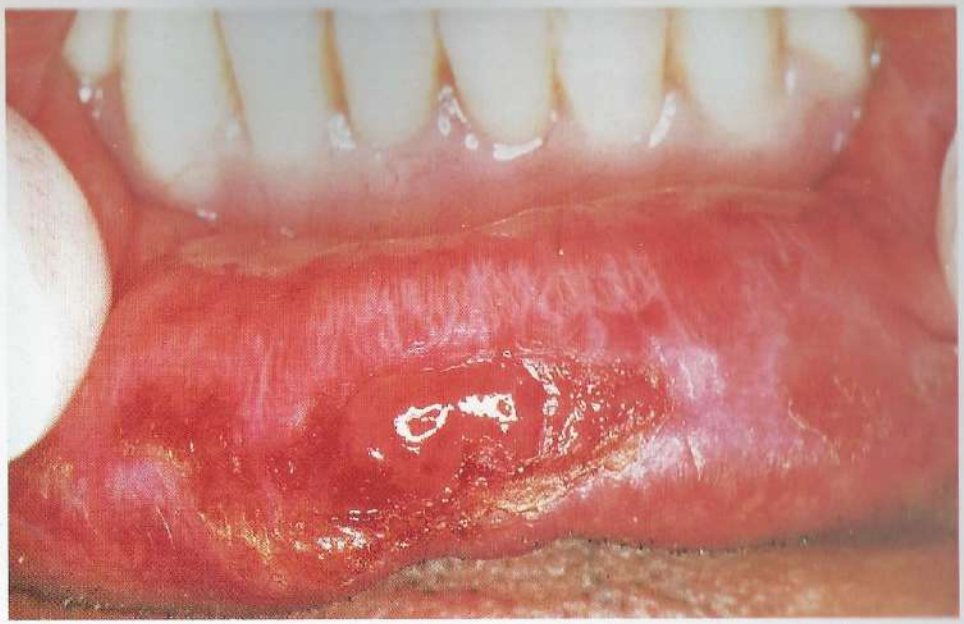

Figure 3.1a. Mucosal lesion of the lower lip, clinically and histopathologically diagnosed as "compatible with lichen planus".

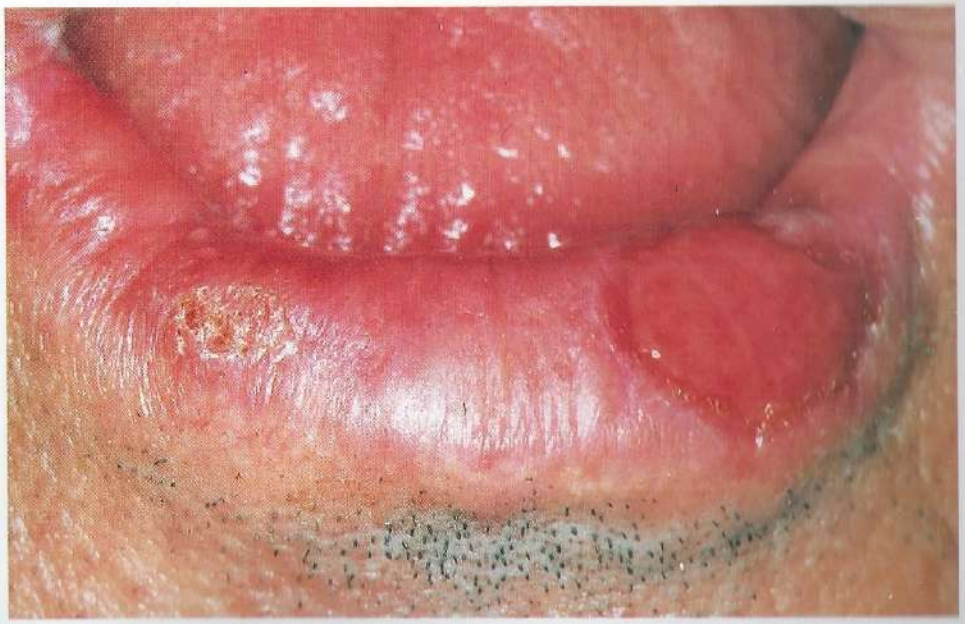

Figure 3.1b. Nine months later another erosive lesion developed. No biopsy has been taken, nor any treatment has been instituted.

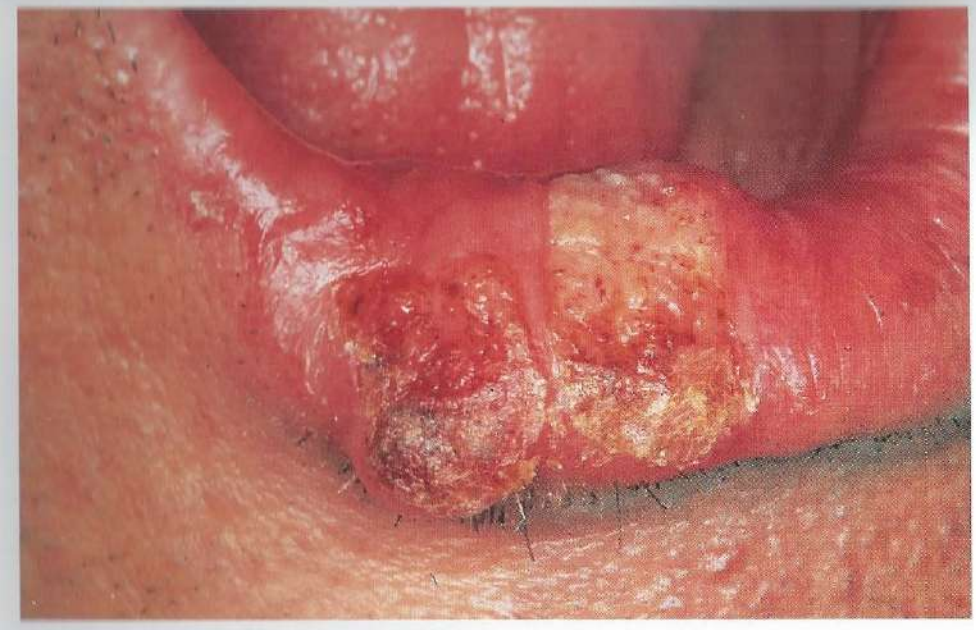

Figure 3.1c. Seven years after figure 3.1a was taken, a well differentiated squamous cell carcinoma developed.

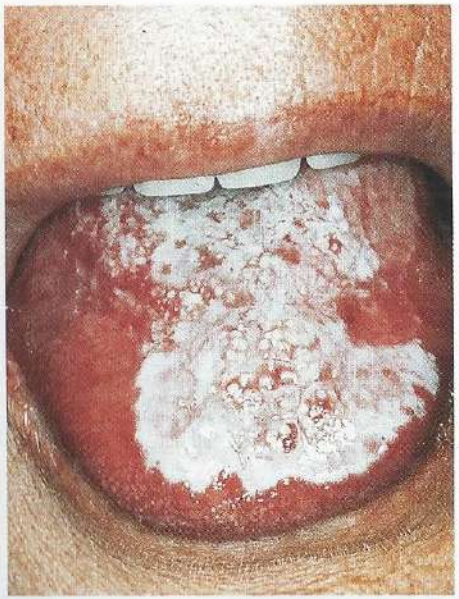

Figure 3.2a. Plaque-type lichen planus of the dorsal surface of the tongue.



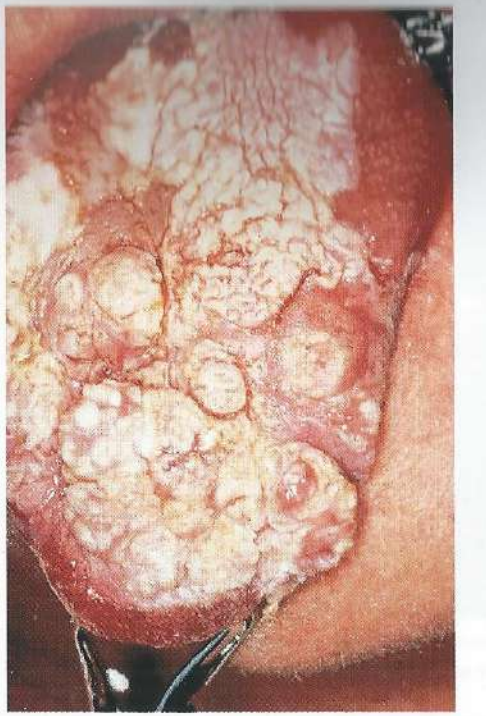

Figure 3.2b. Five years after the initial visit of the patient a verrucous carcinoma of the dorsal surface of the tongue developed.

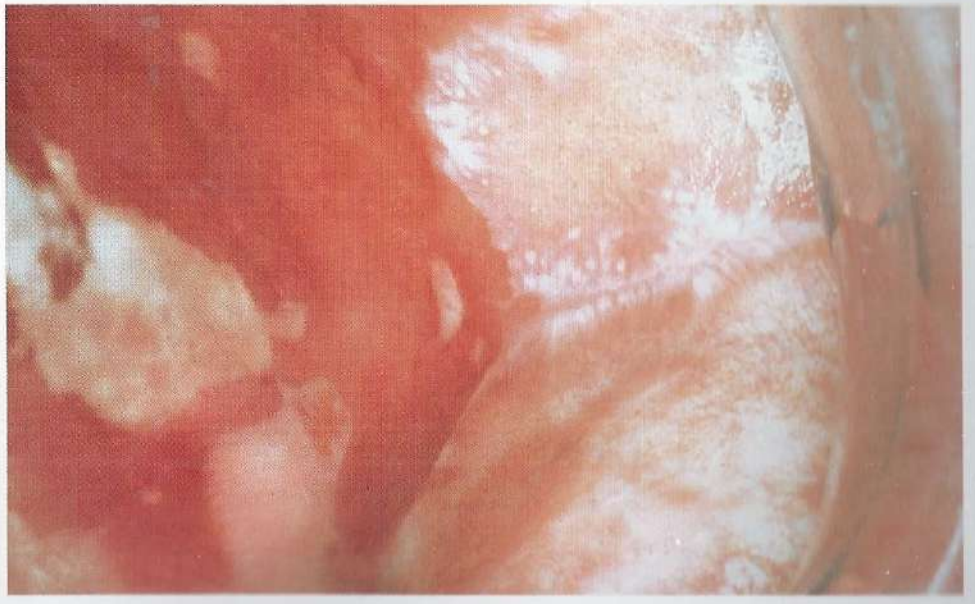

Figure 3.3. Erosive lichen planus of the buccal mucosa, clinically and histopathologically.

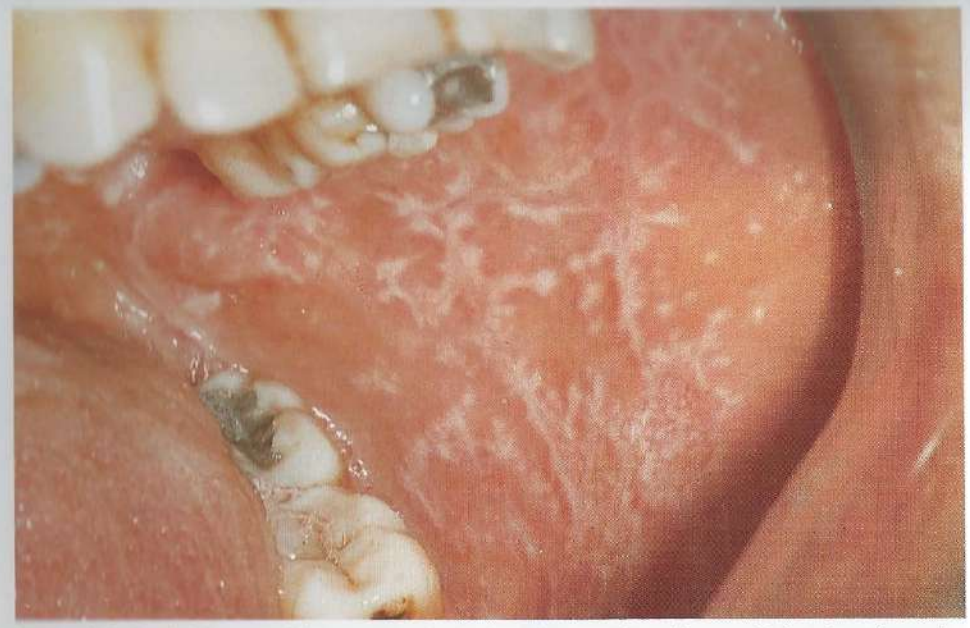

Figure 4.1a. Reticular type of lichen planus in the buccal mucosa in a 49-year-old female patient, who had symptoms of burning sensation and discomfort while eating for six months.

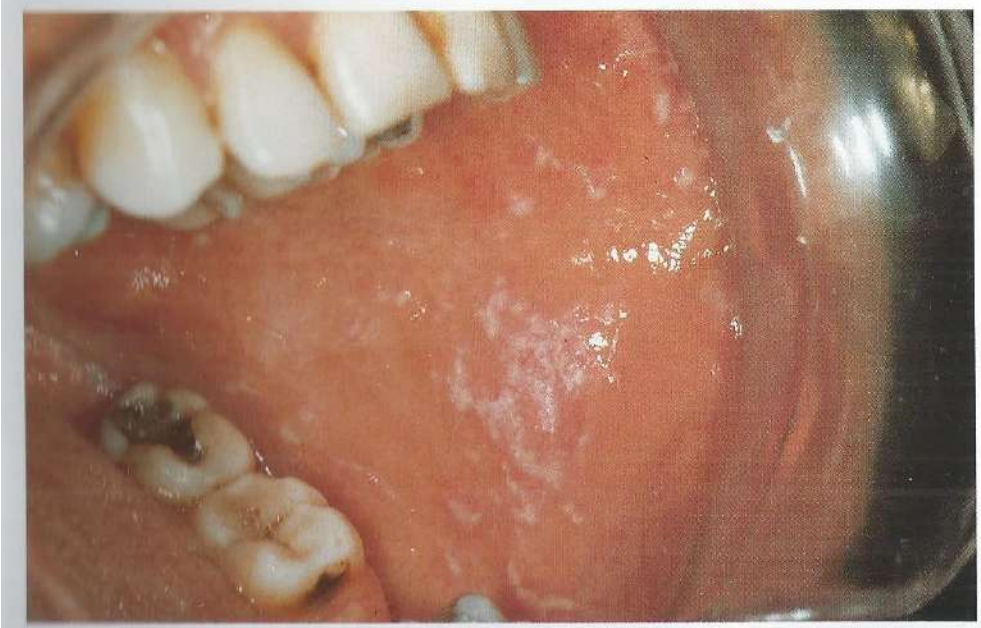

Figure 4.1b. Clinical aspect after three weeks of topical application of fluocinonide six times daily. A distinct regression of the buccal lesions was noted.



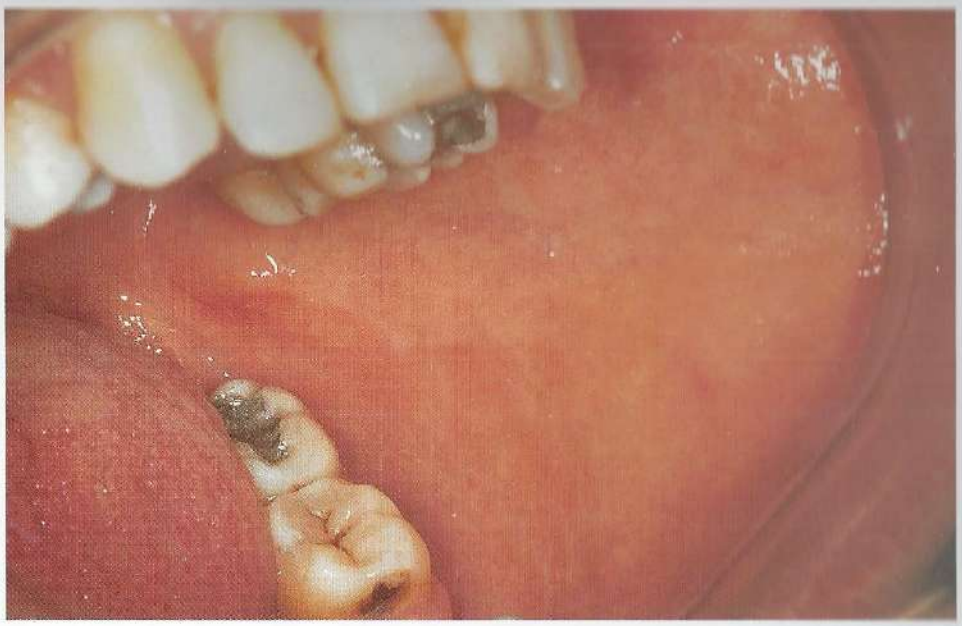

Figure 4.1c. Complete remission of reticular lichen planus of the buccal mucosa after nine weeks of treatment with fluocinonide ointment, applied two to six times daily.

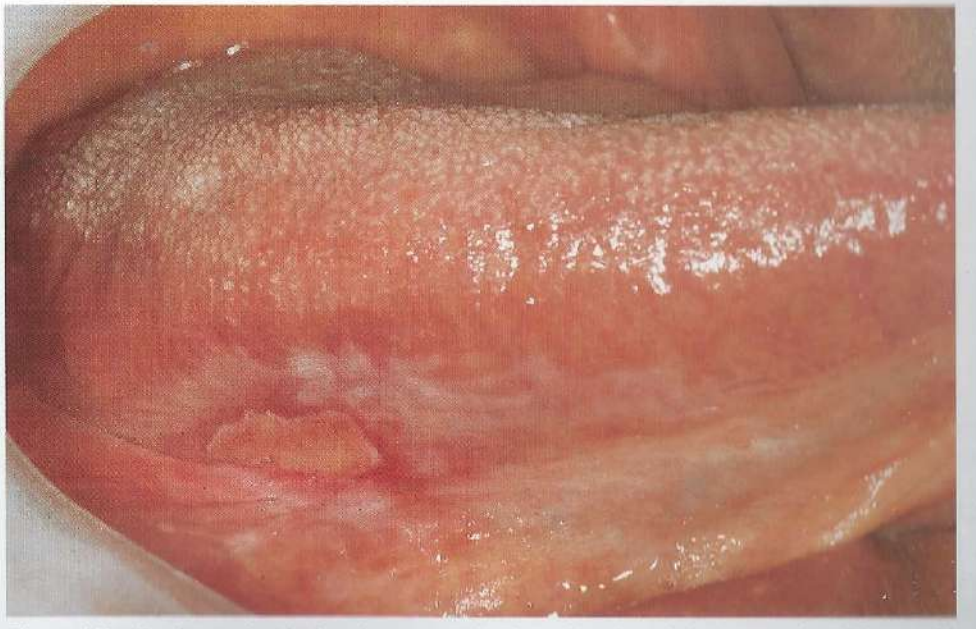

Figure 4.2a. Erosive and reticular changes on the lateral border of the tongue in a 83-year-old woman.

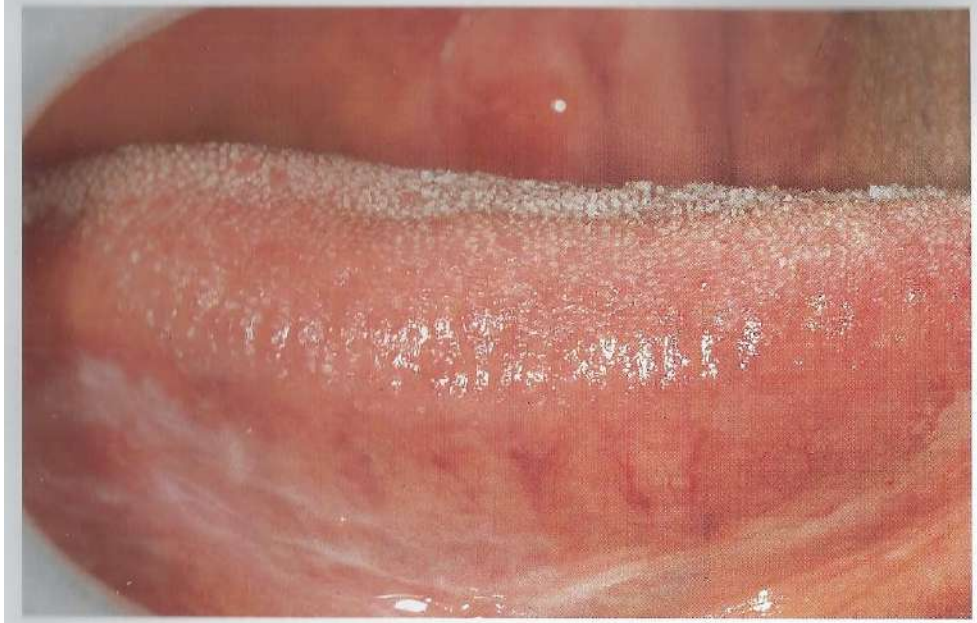

Figure 4.2b. Complete remission of the ulceration after nine weeks of treatment with fluocinonide ointment, applied two to six times daily.

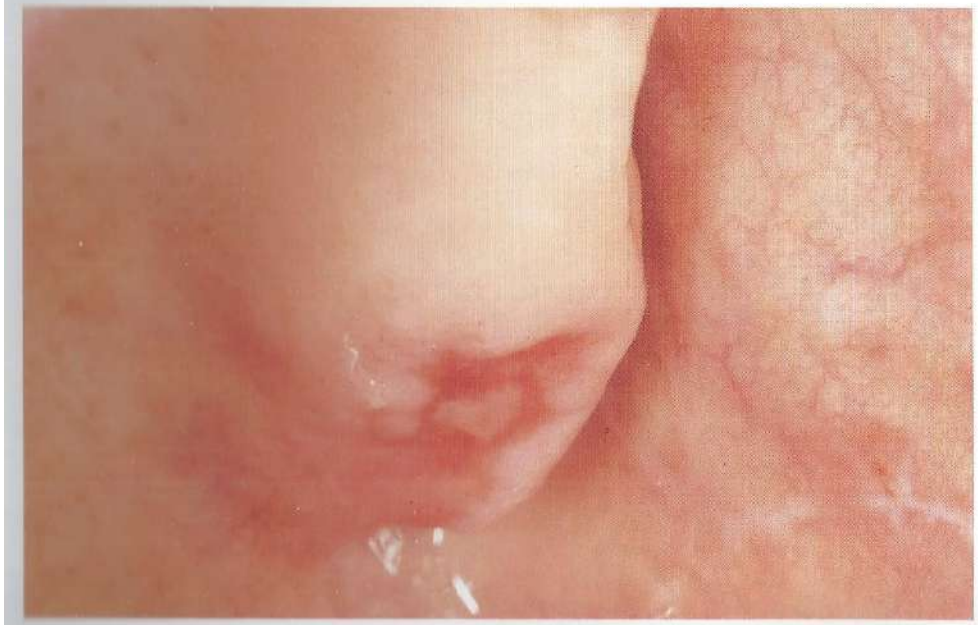

Figure 4.3a. Erosive type of lichen planus of 18 months duration on the maxillary tuberosity in a 66-year-old woman



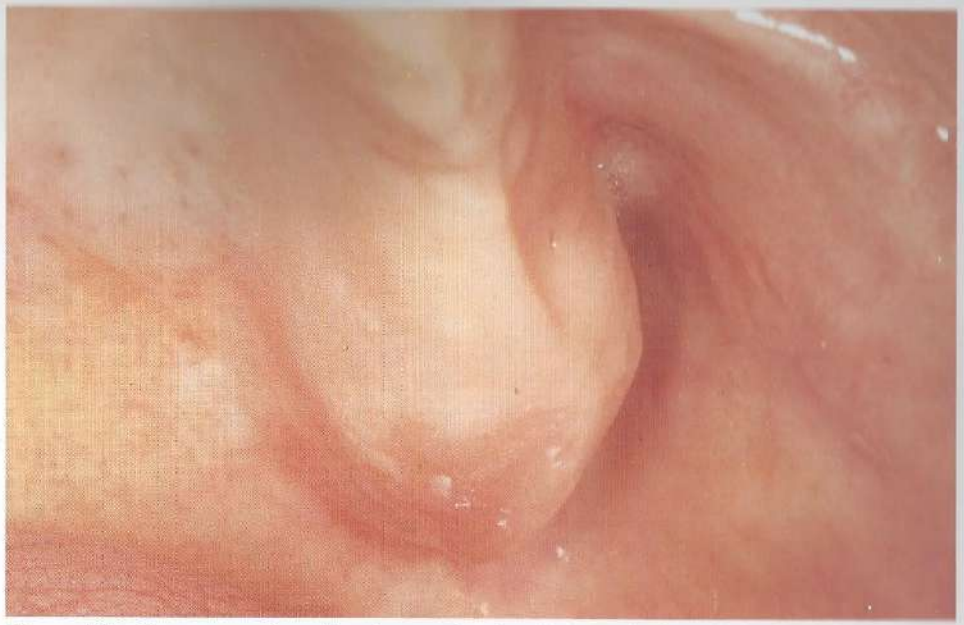

Figure 4.3b. The same patient after nine weeks of topical application of fluocinonide. Complete remission of the lesion was observed.

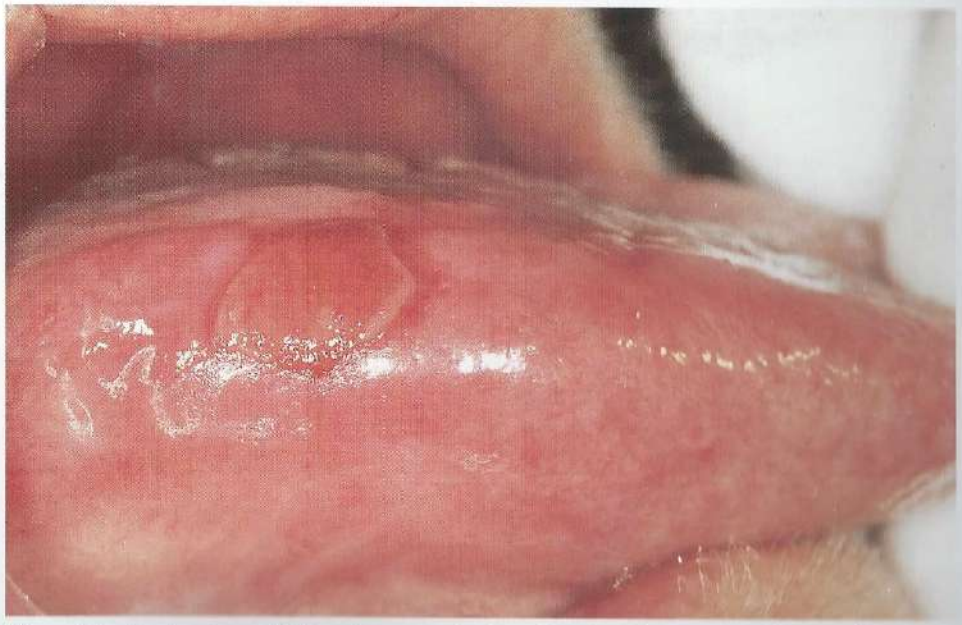

Figure 5.1a. Erosive type of lichen planus on the lateral border of tongue in a 69-year-old woman. Atrophy of the mucosa was noted throughout the oral cavity.

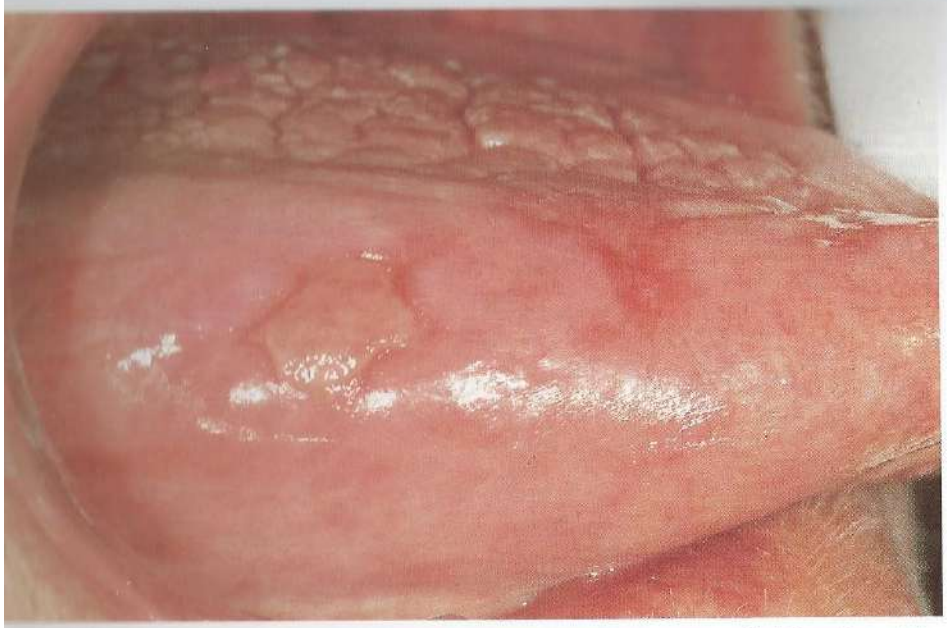

Figure 5.1b. Partial response after six weeks treatment with CsA ointment applied four times daily. Distinct regression of the ulceration was noted. No improvement of the atrophic mucosa was recorded.

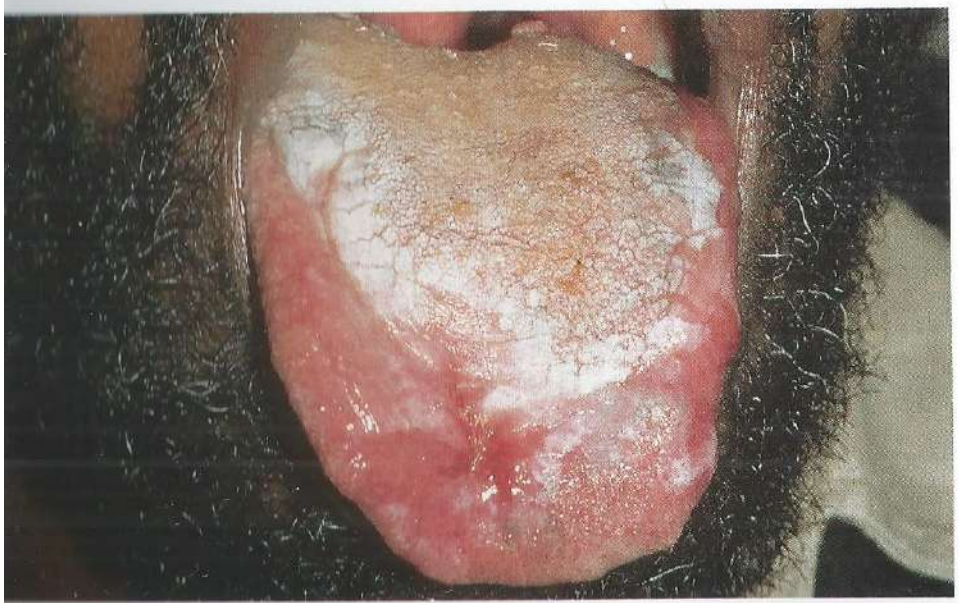

Figure 5.2a. Reticular and erosive type of lichen planus on the dorsum of tongue in a 40-year-old man, buccal mucosa and gingiva were also affected.



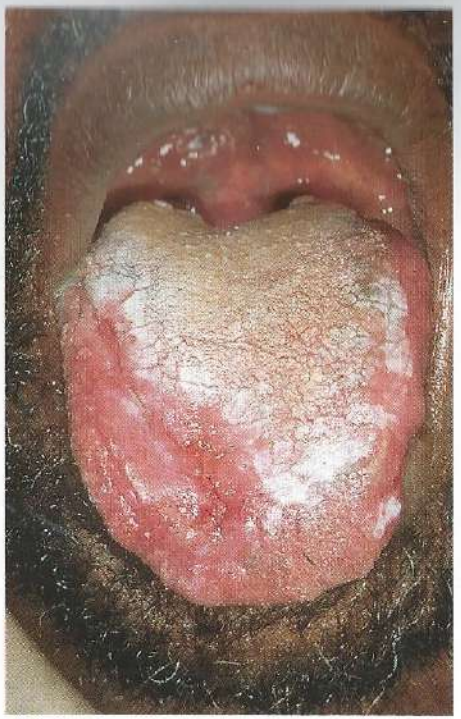

Figure 5.2b. Clinical aspect after ten weeks of topical application of CsA two to four times daily.
Increase of erosions was observed.

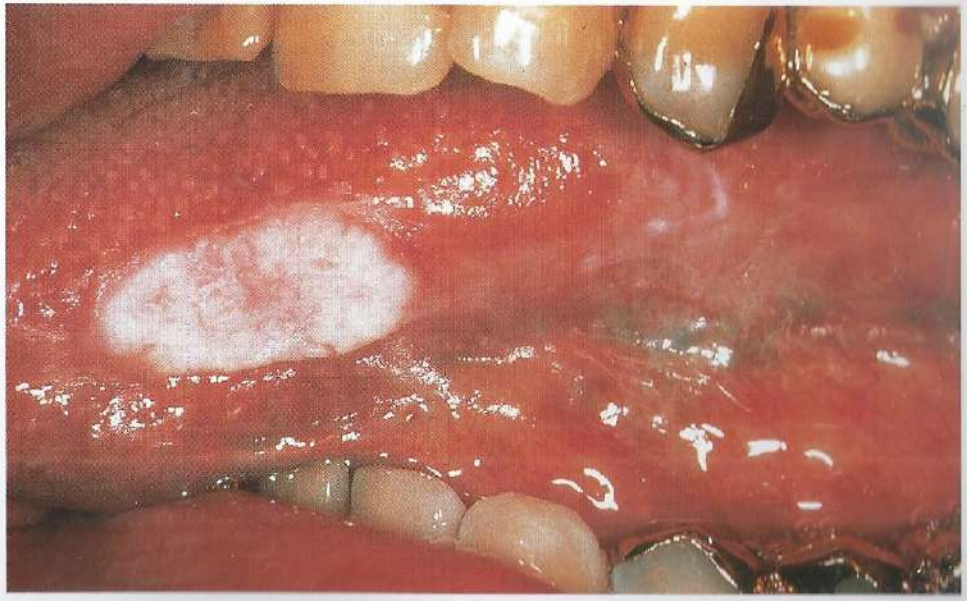

Figure 6.1. A "leukoplakic" plaque with slight induration, on the left margin of the tongue, had developed 4 years after the initial diagnosis of OLP was made. The biopsy showed "verrucous carcinoma".

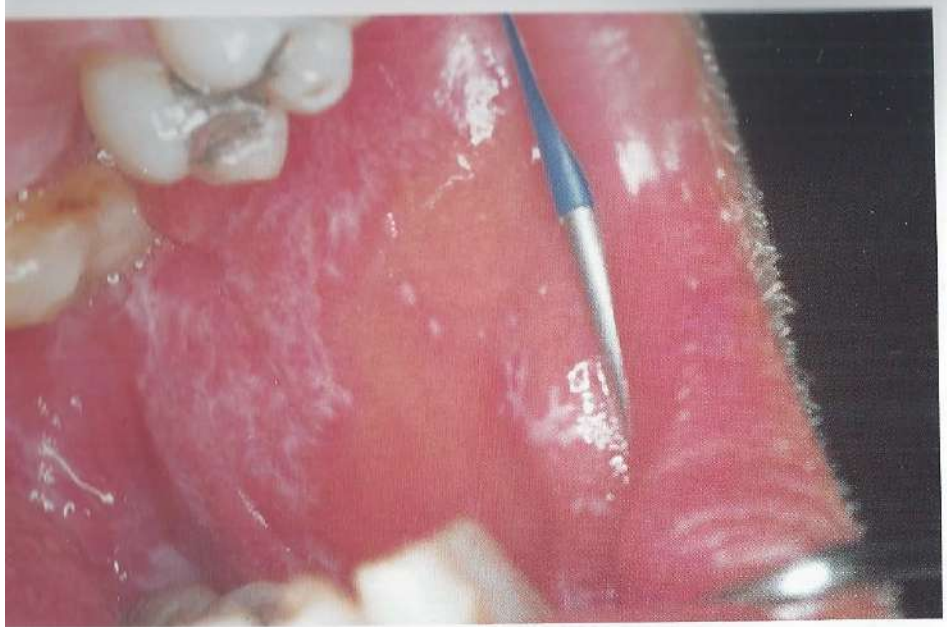

Figure 6.2a. Reticular type of OLP of the buccal mucosa in a 54-year-old male patient.

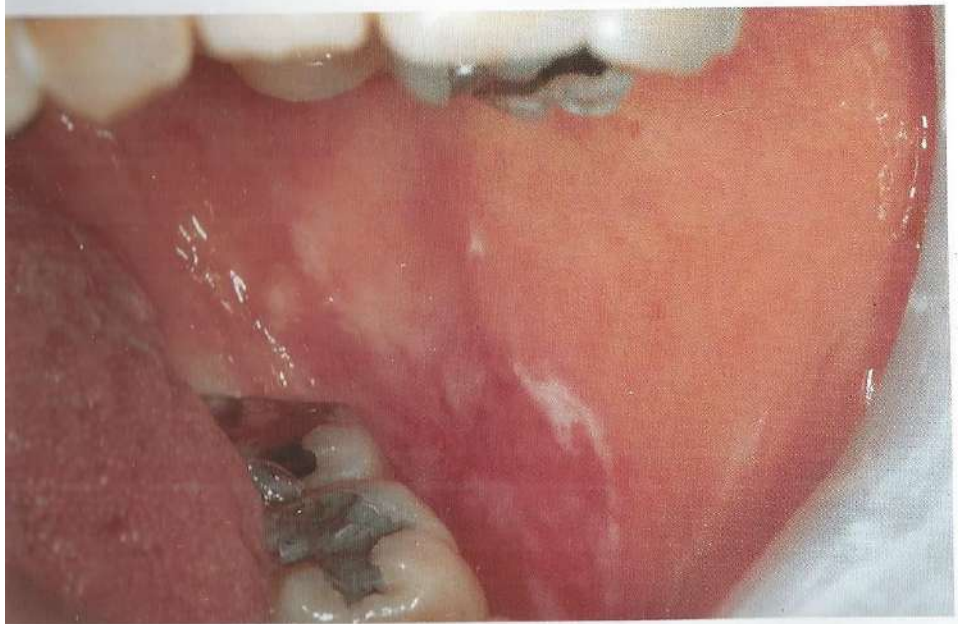

Figure 6.2b. Erosive/atrophic changes of the buccal mucosa of the same patient on the same localisation 20 years later.



CHAPTER 3

# THE POSSIBLE PREMALIGNANT CHARACTER OF ORAL LICHEN PLANUS

## The Amsterdam experience

This chapter is based on the following publication:
Voûte ABE, Jong de WFB, Schulten EAJM, Snow GB, Waal van der I. The possible premalignant character of oral lichen planus; The Amsterdam experience. J Oral Pathol Med 1992; 21: 326-9.

## INTRODUCTION

For a long time lichen planus of the oral mucosa has been considered a benign condition. In the seventies, however, the issue has been raised of a possible premalignant nature. In the 1978 report by the World Health Organisation it was stated: "While a number of reports have referred to cancer in the erosive or atrophic types of lichen planus, there remains considerable uncertainty about the frequency of this occurrence". Eversince, the literature contains a growing number of papers that suggest a premalignant character of oral lichen planus. The percentage of reported malignant transformation varies from 0.3 to three.[1]

In the present paper the 21-years experience of the Department of Oral and Maxillofacial Surgery and Oral Pathology, and the Department of Otorhinolaryngology of the Free University Hospital, Amsterdam, will be reported. The study consists of two parts: 1) the follow-up of patients with oral lichen planus, and 2) a search for lichen planus in patients who have been admitted for oral cancer.

## MATERIAL and METHODS

In a search of the files of the Department of Oral and Maxillofacial Surgery and Oral Pathology of the Free University Hospital, Amsterdam, in the period between January 1, 1970 and January 1, 1991, 176 patients could be retrieved in whom with a reasonable degree of certainty the diagnosis of oral lichen planus, being confirmed by histopathological examination, was made. For detailed information see chapter 2 paragraph 6. The clinical records of these patients have been studied with regard to the possible development of oral cancer. For those patients who had been lost for follow-up, recalls have been arranged, resulting in a total number of 113 patients that have been seen for follow-up. The mean follow-up of these patients was 7.8 years (range; 0.5-21) (Table 3.1).

In 727 patients with oral cancer, observed in the same period as mentioned before, the simultaneous or previous presence of oral lichen planus has been searched for in the records. This group consisted of 465 men and 262 women, the mean age being sixty-three, ranging from 23 to 99 years.

ble 3.1. Demographic data of 113 patients with histopathologically proven oral lichen planus

| nder | Number of patients | Mean age at onset (range)* | Mean duration of follow-up* |
|---|---|---|---|
| male | 79 | 49.2 (14.7-79.5) | 8.2 (0.5-21) |
| ale | 34 | 46.1 (10.6-70.0) | 6.9 (1.0-19) |
| tal | 113 | 48.3 (10.6-79.5) | 7.8 (0.5-22) |

in years

ESULTS

f the 113 patients who were available for follow-up, malignant changes of the oral ucosa had taken place in three of them (2.6%) in a mean follow-up period of seven ars. The data of these three patients are summarized in Table 3.2.

the group of 727 patients with oral squamous cell carcinoma the synchronous esence of lichen planus had been observed in five patients (0.7%) (Table 3.3),

ble 3.2. Malignant transformation in three patients with oral lichen planus

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| nder | Male | Female | Female |
| ge at onset* | 48 | 65 | 58 |
| iteria on which e diagnosis of hen planus as made | Clinical and histopathologic aspects | Clinical, histopathologic and immunofluo-rescence aspects | Clinical, histopathologic and immunofluo-rescence aspects |
| ype of OLP | Erosive type | Reticular type | Erosive type (or associated) |
| me interval in hich squamous cell rcinoma occurred* | 7 | 5 | 9 |
| obacco habits | none | none | none |
| ancer site | lower lip | Dorsum of the tongue and buccal mucosa | Buccal mucosa |

in years



including the three patients mentioned in Table 3.2. In two other patients the history was suggestive of the presence of previous oral lichen planus. In retrospect, however, that diagnosis was proven to be wrong (Table 3.4). In none of the patients with oral cancer, lichen planus of the oral mucosa developed during follow-up after treatment for their malignancy.

**Table 3.3.** Patients with oral squamous cell carcinoma and a past or present history of oral lichen planus (excluding the patients from Table 3.2)

| | Patient 1 | Patient 2 |
|---|---|---|
| Gender | Male | Female |
| Age at onset* | 76 | 71 |
| Criteria on which the diagnosis of lichen planus was made | Clinical aspects | Clinical aspects |
| Type of OLP | Reticular type | Plaque type |
| Tobacco habits | 25 cigarets per day | none |
| Cancer site | Tongue | Lower alveolar ridge |

*) in years

## DISCUSSION

No prevalence or incidence studies on oral lichen planus are available for The Netherlands. Of course, it is not possible to establish such figures on the basis of the number of patients who have been referred to a Department of Oral and Maxillofacial Surgery and Oral Pathology. Besides, there is another bias in the present study, since only those patients have been included in the follow-up study in whom the diagnosis oral lichen planus was supported by histopathological examination of the biopsy. In general, performance of a biopsy is not mandatory for the diagnosis of oral lichen planus in all cases, since in many instances the diagnosis can be reliably made on clinical features only. Just for the discussion we like to accept the prevalence found in Axéll's study among an adult Swedish population.[2] In that study the prevalence of oral lichen planus has been established at 1.89 per cent.

**Table 3.4.** Patients with oral cancer with an incorrect previous diagnosis of lichen planus

| | Patient 1 | Patient 2 |
|---|---|---|
| Gender | Female | Female |
| Age at onset* | 45 | 64 |
| Criteria on which the diagnosis of oral lichen planus was made | Clinical, histopathologic and immunofluorescence aspects | Clinical aspects only |
| Clinical aspect | Erosive type (erythroplakic lesion) | Erosive type (erythroplakia?) |
| Time interval between incorrect diagnosis of oral lichen planus and diagnosis of oral squamous cell carcinoma | 5 months | 13 months |
| Tobacco habits | none | gave up smoking 20 years ago |
| Cancer site | Lower lip | Buccal mucosa |

*) in years

It is well recognized that both the clinical and histopathological criteria of oral lichen planus leave room for some subjectivity in the interpretation. Especially the plaque type and also the erosive type of lichen planus may some times be difficult to distinguish clinically from the various manifestations of homogeneous and non-homogeneous leukoplakia. The specificity of the histopathologic diagnosis of oral lichen planus seems to be very much in accordance with that of the clinical diagnosis. The flaws in the clinical and histopathologic criteria of oral lichen planus may explain some of the discrepancies both in the prevalence of oral lichen planus and the reported rate of malignant transformation.

In all of our three patients in whom malignant transformation took place (Table 3.2), there is room for discussion about the correctness of the original diagnosis of lichen planus, both from a clinical and a histopathological point of view. In the first patient we may have actually been dealing with chronic discoid lupus erythematosus instead of lichen planus because of the site and clinical aspect (Fig 3.1). In the second patient a transformation seems to have taken place from lichen planus into leukoplakia and, finally, into verrucous carcinoma (Fig 3.2). In the third patient, there remains the



possibility of the synchronous presence of lichen planus and erythroplakia or an erythroplakic lesion (Fig 3.3), as has been described by Holmstrup and Pindborg.[3] If the initial diagnosis of oral lichen planus has been correctly made in all our three cases, then the statement could be made that 2.6 per cent of patients with histologically proven oral lichen planus showed malignant transformation in an average time of 7 years after establishment of the original diagnosis. Because of the referral bias this percentage cannot be accepted as being representative of the average malignant transformation rate of oral lichen planus. Furthermore, malignant transformation may have taken place in one or more of the patients who had been lost for follow-up. Because of the low migration rate of the Dutch population, such event is rather unlikely to have occurred without notification.

Assuming that the prevalence of oral lichen planus in adults found by Axéll[2] (1.89%) is valid for The Netherlands as well, one could expect that 13 of the 727 patients with oral squamous cell carcinoma would have had either a past or present history of lichen planus, while this actually has been the case in five patients (0.7%). In patient 2 of Table 3.3 also Candida-associated lesions were observed. In fact, a biopsy of the lesion of the dorsum of the tongue, taken four years later, was consistent with the diagnosis of chronic hyperplastic candidiasis. In retrospect, this patient may, therefore, erroneously have been included in Table 3.3.

In retrospect, it is difficult to understand from the clinical aspects, that in the two patients mentioned in Table 3.4 an initial diagnosis of oral lichen planus has been made. In one of these two patients a biopsy has been taken. In retrospect, this biopsy did show signs of at least slight epithelial dysplasia, possibly qualifying for the label of lichenoid dysplasia, as proposed by Krutchkoff and Eisenberg.[4] As a result, the correctness of the initial histopathologic diagnosis "compatible with oral lichen planus" is at least questionable. In the other patient of this group, it remains somewhat unexplainable why the clinical diagnosis of oral lichen planus was made initially instead of erythroplakia. Others have reported similar experiences.[5] In a review of the literature of 220 cases of reported malignant transformation occurring in oral lichen planus, Krutchkoff et al. only found 15 cases that satisfied their criteria.[6] In a follow-up study of 225 cases of oral lichen planus one carcinoma (0.5%) developed after an observation period of five years.[7] In another follow-up study of 611 patients, probably including the latter group of 225 patients, nine (1.5%) patients developed oral squamous cell carcinoma during follow-up, that ranged from 4.9 to 24 years.[8] In yet another follow-up study of oral lichen planus reported from India three carcinomas (0.4%) developed in 722 patients after a mean observation period of 5.1 years.[9] In a prospective study in San Francisco, consisting of 570 patients, malignant

transformation occurred in 1.2 per cent in a mean time of 3.4 years after the onset of lichen planus.[10]

There is a discrepancy with regard to the finding of high percentages of epithelial dysplasia in oral lichen planus, varying from 25-57 per cent and the extremely low malignant transformation rate.[11, 12]

In summary, our experience gives some but not convincing support to the hypothesis that oral lichen planus is a premalignant condition. From a practical point of view we feel somewhat reluctant to routinely inform each patient with oral lichen planus about the possible premalignant character of their lesions. In general, we advise bi-annual dental check-up, including thorough inspection of the oral mucosa.

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# CHAPTER 4

## FLUOCINONIDE IN AN ADHESIVE BASE FOR TREATMENT OF ORAL LICHEN PLANUS

### A double-blind, placebo-controlled clinical study

This chapter is based on the following publication:
Fluocinonide in an adhesive base for treatment of oral lichen planus: A double-blind, placebo-controlled clinical study. Voûte ABE, Schulten EAJM, Langendijk PNJ, Kostense PJ, van der Waal I. Oral Surg Oral Med Oral Pathol 1993; 75: 181-5.

## INTRODUCTION

Lichen planus is a common chronic inflammatory disease of unknown cause, affecting skin and mucosa of squamous cell origin. In general, the histopathological appearance in combination with immunohistochemical features is often characteristic. The disease seems to be predominantly present in women in their later decades. The prevalence of oral lichen planus varies in different studies from 0.7% to 2.2%.[1]

Since the etiology of lichen planus is still to be unraveled, the treatment of this disease can only be symptomatic. One of the main characteristics of lichen planus is a lymphocytic infiltrate, located in the subepithelial connective tissue along the basal membrane. Due to this infiltrate the overlying skin or mucosa can be damaged. Corticosteroids are known to reduce the forming of such a submucosal infiltrate and also reduce edema. Therefore, treatment with systemically or topically applied corticosteroids can be effective in decreasing signs and symptoms in lichen planus.

The purpose of the present study was to evaluate the efficacy of a class 3 corticosteroid, fluocinonide in an adhesive base, in the treatment of symptomatic oral lichen planus.

## PATIENTS AND METHODS

The study was randomized, double-blind and placebo-controlled, with the drug or placebo applied to the lesions of the oral mucosa for a period of 9 weeks. Forty consecutive patients with symptoms due to oral lichen planus seen in the Department of Oral and Maxillofacial Surgery and Oral Pathology, Free University Hospital, Amsterdam, were included in the study (Table 4.1). Twenty patients received the fluocinonide ointment and twenty patients received the placebo. Criteria for admission were based on clinical features, history of the disease and histopathologic and immunofluorescence microscopy for confirmation of the diagnosis (chapter 2 par. 6). Twelve patients were diagnosed as having erosive lichen planus, defined as a condition predominantly consisting of erosive and/or atrophic lesions of the oral mucosa. Thirteen patients showed reticular lichen planus, defined as a condition consisting of reticular changes in the absence of erosions. In the remaining 15 patients both clinical subtypes were present. Other criteria of inclusion in the study were: non-use of medication and the absence of oral mucosal lesions other than lichen planus. The aim of the study was explained to all patients in advance. They were only admitted, if they

gave their informed-consent. After completion of the study all patients received the fluocinonide ointment.

**Table 4.1.** Clinical data of the study group (N=40).

| | | Number of patients | Mean age at onset (range) * | Mean duration of disease (range) * |
|---|---|---|---|---|
| Clinical types of oral lichen planus | | Gender | | |
| | | M F ** | | |
| a. | Erosive | 2 10 (12) | 46.4 (20-66) | 4.5 (0.2-15) |
| b. | Reticular | 3 10 (13) | 47.5 (21-72) | 2.5 (0.1-18) |
| c. | Combination | 3 12 (15) | 46.7 (12-83) | 4.8 (0.3-20) |
| | Total | 8 32 (40) | 46.9 (12-83) *** | 4.0 (0.1-20) **** |

* in years
** M=male, F=female
*** mean age in years at onset of total study group (range)
**** mean duration of disease in years of total study group (range)

## Medication

The drug under study was fluocinonide 0.05% w/w (Topsyne$^R$ fatty ointment) 1:1 homogeneously incorporated in an adhesive base containing 40% hydroxy-propyl-methyl cellulose in white soft paraffin. The resulting concentration was 0.025% w/w of fluocinonide. The Topsyne$^R$ ointment also contained Amerchol CAB 5%, propylene carbonate 3.5%, propylene glycol 1.5%, Petrolatum ultima 36% and white soft paraffin 54%. To obtain two identical ointments, with or without fluocinonide, both the active medication and the placebo ointment were extemporaneously mixed in a 1:1 ratio with the adhesive ointment base in the Department of Pharmacy of the Free University Hospital, Amsterdam. Fluocinonide is a class 3 corticosteroid with anti-inflammatory and vasoconstrictive properties. The base is nontasting and had no biological properties. No additives like preservatives or colouring agents other than the aforementioned, were present. We choose this base, because of its good properties of adhesion to the oral mucosa, which increases the contact time of the drug. Additionally, the base itself had no pharmaceutical effect on the mucosa.



## Procedure and registration of signs and symptoms

At the first visit, the participants were instructed how to apply the ointment on dried lesions at least six times a day. They were instructed not to eat or drink for half an hour afterwards. After three weeks they were seen for the first follow-up visit. The second follow-up visit was scheduled six weeks after the first follow-up visit. At every visit clinical photographs of the mucosal lesions were made in a standardized way, for the scoring of signs (objective score). The response was subdivided in five scores: 1) 0%, no response, 2) up to 33%, partial response, 3) up to 66% good response, 4) up to 100%, complete remission, and 5) increase of signs (Table 4.2). The Visual Analogue Scale has been used for the scoring of symptoms (subjective score) also using five subgroups (Table 4.3).
Statistical analysis of the possible contrast between treatment and placebo group were assessed by means of the chi-square test for trend in proportions.[2] The data were summarized in 2x5-contingency tables. In tables where almost empty columns might cast some doubt on the validity of the chi-square test, it was checked that significant results could be confirmed in 2x3-tables, obtained by taking small columns together.

## RESULTS

The results are summarized in Tables 4.2 and 4.3. With regard to signs in the group of patients receiving the drug, four patients (20%) showed complete remission and 12 patients (60%) showed a good or partial response to the topical ointment. In the placebo-group, these figures were 0 (0%) and 6 (30%), respectively. The majority of the placebo-group (70%) did not respond at all. In the fluocinonide-group, only four patients (20%) did not respond to therapy; all four of them had erosive lesions of the mucosa. The best response to fluocinonide was recorded in the subgroup of reticular lichen planus (Table 4.2) (Fig 4.1). Figures 4.2 and 4.3 show the possible response to fluocinonide in the other subgroups.
As summarized in Table 4.3, we did not note a large difference between response with regard to signs or symptoms, although nine people in the fluocinonide-group had complete remission of their symptoms and, yet, had a few lesions left in the mouth. We did not note any adverse effects. The difference in results between the fluocinonide and placebo-group was statistically significant with regard to signs ($X_t^2=10.4$, $p=0.0013$) and symptoms ($X_t^2=6.97$, $p=0.008$).

**Table 4.2.** Results with regard to signs.

| Clinical type(s) | | Number of patients and response (signs) * | | | | | |
|---|---|---|---|---|---|---|---|
| | | +++ | ++ | + | 0 | - | Total |
| a. | Erosive OLP (N=12) | | | | | | |
| | Fluocinonide | 1 | 2 | 1 | 0 | 1 | 5 |
| | Placebo | 0 | 2 | 2 | 1 | 2 | 7 |
| b. | Reticular OLP (N=13) | | | | | | |
| | Fluocinonide | 2 | 3 | 1 | 0 | 0 | 6 |
| | Placebo | 0 | 0 | 0 | 4 | 3 | 7 |
| c. | Combination of erosive and reticular OLP (N=15) | | | | | | |
| | Fluocinonide | 1 | 4 | 1 | 2 | 1 | 9 |
| | Placebo | 0 | 2 | 0 | 3 | 1 | 6 |
| | All types (a+b+c) (N=40) | | | | | | |
| | Fluocinonide | 4 | 9 | 3 | 2 | 2 | 20 ** |
| | Placebo | 0 | 4 | 2 | 8 | 6 | 20 ** |

* +++ = complete response, ++ = good response , + = partial response, 0 = no effect and - = increase of signs.
** Statistically significant ($X_t^2$ =10.4 ; p=0.0013)

**Table 4.3.** Results with regard to symptoms.

| Clinical type(s) | Number of patients and response (symptoms) * | | | | | |
|---|---|---|---|---|---|---|
| | +++ | ++ | + | 0 | - | Total |
| All types (a+b+c)(N=40) ** | | | | | | |
| Fluocinonide | 13 | 2 | 3 | 2 | 0 | 20 *** |
| Placebo | 6 | 1 | 5 | 6 | 2 | 20 *** |

* +++ = complete response, ++ = good response , + = partial response, 0 = no effect and - = increase of symptoms.
** a. erosive lichen planus, b. reticular lichen planus, c. combination of erosive and reticular changes.
*** Statistically significant ($X_t^2$ =6.97 ; p=0.008)



## DISCUSSION

Management of oral lichen planus is difficult because of lack of response to various palliative agents and either frequent resistance to low dose systemic corticosteroid therapy or bothersome side effects from more aggressive corticosteroids and vitamine-A-derivates.[3-6] Fluocinonide in an adhesive base appears to provide a reasonable successful alternative for this problem.[7] Futhermore, fluocinonide seems to remain effective also if it is used on an intermittent, symptom-related schedule. Other studies have mentioned a diminished effectiveness after repeated cutaneous application of fluocinonide or other topical corticosteroids.[8] However, these latter observations were based on extensive corticosteroid applications for prolonged periods of time. In our study the patients were told to use the drug less frequently if the signs had subsided after the first follow-up visit.

There is essentially no risk of undesirable systemic effects, such as pituitary-adrenal axis suppression, fluid retention and hyperglycemia, if corticosteroids are used topically in low dosages.[9]

Most parts of the oral mucosa are readily accessible for topical application of the drug. The effectiveness of topical treatment is enhanced by the use of an adhesive ointment that provides both transport medium of active drug and prolonged exposure time.

In a previous pilot study (data unpublished) we noticed that, if patients were using fluocinonide in an adhesive base without proper instructions how to use the ointment, there was a considerable difference in outcome. Only those who used the medication regularly and applied it on the mucosa after drying, obtained benefit from the drug.

The effect of the natural course of the disease on the results of treatment remains difficult to define. Both aforementioned factors may explain why not all patients experience a complete remission of lesions with topical application of fluocinonide; possibly more frequent and longer usage might induce a higher incidence of remission of signs and symptoms. In conclusion the results from this study suggest, that topical application of fluocinonide in an adhesive base is a safe and effective therapy to reduce signs and symptoms in oral lichen planus.

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# CHAPTER 5

## CYCLOSPORIN A IN AN ADHESIVE BASE FOR TREATMENT OF RECALCITRANT ORAL LICHEN PLANUS

### An open trial

This chapter is based on the following publication:
Voûte ABE, Schulten EAJM, Langendijk PNJ, Nieboer C, van der Waal I. Cyclosporin-A in an adhesive base for treatment of recalcitrant oral lichen planus; An open trial. Oral Surg Oral Med Oral Pathol 1994, in press.

## INTRODUCTION

Oral lichen planus (OLP) is a relatively common chronic inflammatory disease of unknown cause, affecting skin and mucosa of squamous cell origin. The reported prevalence of oral lichen planus varies from 0.7% to 2.2%.[1] The disease seems to be predominantly present in women in their later decades.

In comparison with the cutaneous form of lichen planus, oral lesions are more resistant to therapy and less likely to undergo spontaneous remission. Since the etiology of lichen planus is still to be unraveled, management is primarily concentrated on alleviation of symptoms, if present.

In general, the histopathological appearance in combination with immunohistochemical features of OLP is rather characteristic, one of the main characteristics being a band-like lymphocytic infiltrate, directly adjacent to and invading into the epithelium. Due to this infiltrate the overlying skin or mucosa can be damaged. Corticosteroids are known to reduce the formation of such a submucosal infiltrate and also reduce edema.[2] Some benefit may also be the result of anti-immunological properties of suppressing T-cell function.[3] Therefore, treatment with systemically or topically applied immunosuppressive drugs may be effective in decreasing signs and symptoms in lichen planus.

In recent literature the beneficial effect of topical cyclosporin-A (CsA) has been suggested.[4] CsA is a new generation immunosuppressive drug. It is highly effective in cell-mediated immunity and inhibits chronic inflammatory reactions.[5,6] CsA is, therefore, widely used to prevent rejection in clinical organ transplantation and appears to be rather promising in the treatment of several autoimmune diseases. The most important aspect of its immunosuppressive mechanism is inhibition of lymphokine production secreted by activated T-cells.[7]

The purpose of the present study was to investigate the efficacy of CsA in an oral adhesive base in the treatment of recalcitrant OLP accompanied by severe complaints.[8]

## PATIENTS AND METHODS

Out of a group of patients with symptoms due to OLP referred to the Department of Oral and Maxillofacial Surgery and Oral Pathology, Free University Hospital, Amsterdam, in the period 1991 - 1992, nine patients have been selected for the study. Five patients have been diagnosed as having erosive or atrophic OLP, one showed reticular OLP and the remaining three patients had a combination of these two clinical

subtypes (Table 5.1). The clinical criteria for subtypes has been described previously.[8] All patients, including the patient with reticular OLP, had severe complaints of chronic pain due to their oral lesions. Four of the nine patients had been previously treated with topical application of 0.025% fluocinonide in an adhesive base for at least 9 weeks. Three patients had been treated with topical triamcinolonacetonide between 3 months and 3 years, and two patients had been treated with systemic prednisone for 12 weeks without a satisfactory result. These patients were therefore described as having recalcitrant OLP. The time interval between the present and previous treatment was at least one month.

In all cases the clinical diagnosis was confirmed by histopathologic and immunofluorescence examination. Further criteria for admission were based on a long standing presence of the disease (Table 5.1), the extent of the oral lesions, and the history of complaints as recorded by the patient.

The aim of the study was explained to all patients in advance. They were only admitted, if they had given their informed-consent. At first visit each patient's complete blood count, blood urea nitrogen, creatinine, serum levels of electrolytes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin, triglycerides, cholesterol were obtained. All values had to be within the normal range according to the hospitals standard. Additionally, CsA serum levels were determined at every follow-up visit.

**Table 5.1.** Clinical data of the study group (N=9).

| Clinical type of oral lichen planus | | Number of patients | | Mean age at onset (range) * | Mean duration of disease (range) * |
|---|---|---|---|---|---|
| | | Gender | | | |
| | | Male | Female | | |
| a. | Erosive | 0 | 5 | 55.8 (43.2-63.8) | 8.2 (3-14.5) |
| b. | Reticular | 0 | 1 | 56.0 | 4.0 |
| c. | Combination | 2 | 1 | 38.9 (32.8-48.3) | 5.3 (3.5-7.5) |
| | Total | 2 | 7 | 50.2 (32.8-63.4) | 6.8 (3-14.5) |

* in years



### Medication

The drug under study was CsA 0.05% w/w in vegetable oil (Sandimmune®) 1:1 homogenously incorporated in an adhesive ointment base, containing 40% hypromellose in white soft paraffin, resulting in a CsA-concentration of 0.025% w/w. The ointment was prepared in the Department of Pharmacy of the Free University Hospital, Amsterdam. The ointment-base is nontasting and has no biological properties. No additives like preservatives or colouring agents were incorporated.

### Procedure and registration of signs and symptoms

At the first visit the participants were instructed how to apply the ointment on dried lesions at least four times a day. They were instructed not to eat or drink for half an hour afterwards. After three weeks the patients were seen for the first follow-up visit. The second follow-up visit was scheduled six weeks thereafter. At every visit colour pictures of the mucosal lesions were made in a standardized way, for the scoring of signs (objective score). Clinical examination of the oral mucosa and evaluation of the colour pictures was used for scoring. The response was subdivided in four scores: 1) 0 %, no response ,2) up to 50 %, partial response, 3) over 50 % good response, 4) increase of signs. The Visual Analogue Scale[9] has been used for the scoring of symptoms (subjective score) also using these four subgroups. Statistical analysis of the scores with regard to signs and symptoms, before and after treatment, was performed by means of a Student t-test. The results were considered statistically significant if the p value was less than 0.01.

## RESULTS

The results are summarized in Tables 5.2 and 5.3. Four patients showed partial response (Fig.5.1) and five patients showed no response or even an increase of signs (Fig.5.2) to the topical ointment. As summarized in Table 5.3, we did not note much difference between response to signs or response to symptoms, although four patients (mentioned in Table 5.3) had the same complaints before and after treatment and, yet, had more severe lesions in the mouth. The difference in scores before and after treatment was not statistically significant with regard to signs and symptoms.

No local adverse side effects like gingival hyperplasia[10] were noted, and the drug was

well tolerated by the patients. In none of the nine patients, CsA was detectable in the serum. In patient's complete blood count, blood urea nitrogen, creatinine, serum levels of electrolytes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin, triglycerides and cholesterol no clinically relevant changes were found.

**Table 5.2.** Results with regard to signs.

| | Number of patients and response (signs) * | | | | |
|---|---|---|---|---|---|
| Clinical type(s) of OLP | ++ | + | 0 | - | Total |
| a. Erosive | 0 | 1 | 1 | 3 | 5 |
| b. Reticular | 0 | 1 | 0 | 0 | 1 |
| c. Combination of erosive and reticular | 0 | 2 | 0 | 1 | 3 |
| All types (a+b+c) | 0 | 4 | 1 | 4 | 9 |

* ++ = good response, + = partial response, 0 = no effect, - = increase of signs.

**Table 5.3.** Results with regard to symptoms.

| | Number o patients and response (symptoms) * | | | | |
|---|---|---|---|---|---|
| Clinical type(s) of OLP | ++ | + | 0 | - | Total |
| All types (a+b+c)** | 0 | 4 | 4 | 1 | 9 |

* ++ = good response, + = partial response, 0 = no effect, - = increase of symptoms.
** a. erosive lichen planus, b. reticular lichen planus, c. combination of erosive and reticular changes.

## DISCUSSION

Management of OLP might be difficult because of lack of response to various palliative agents and/or frequent resistance to low dose systemic corticosteroid therapy or bothersome side effects from more aggressive corticosteroids and vitamine-A-derivatives.[11-14] Fluocinonide in an adhesive base is a reasonable successful alternative for treatment of OLP.[8]
For patients with recalcitrant OLP, not responding to topical fluocinonide treatment,



topical and in some cases systemic CsA is suggested to be an alternative as reported in literature.[4,15,16] Eisen et al.[4] observed a marked improvement in all of their 8 patients with OLP after treatment with topical CsA. The patients swished and expectorated 5 ml of medication (100mg CsA/ml) three times daily. In several patients systemic concentrations were encountered, which could have therapeutic effects. In the present study in none of the nine patients CsA was detected in the blood. These findings are supported by a few authors, also reporting negative results of topical CsA treatment.[17,18]
In the selection of CsA for treatment of OLP a few problems are encountered: 1) the drug is not readily available for topical use on the oral mucosa, and 2) CsA is an expensive drug. Therefore, the drug was chosen as an alternative in selected cases only. The present group, indeed, consisted of patients with recalcitrant OLP.
If used topically in low dosages, CsA carries essentially no risk of undesirable systemic side effects, such as renal dysfunction and hypertension, paraesthesia, hypertrichosis, gingival hyperplasia and gastrointestinal disorders.[19] In the literature the risk of neoplasms is reported if CsA is used over prolonged periods.[20] Although no serum abnormalities were encountered in the present study, laboratory monitoring of patients with OLP treated with topical CsA is recommended.
Most parts of the oral mucosa are readily accessible for topical application of the drug. The efficacy of topical treatment might be enhanced by the use of an adhesive substance that provides both transport medium of active drug and reasonable exposure time. We chose the present indifferent base, because of its good properties of adhesion to the oral mucosa, in order to increase the contact time of the drug, when compared to rinsing. Still the efficacy of the topical treatment appeared to be insufficient. Optimized drug delivery and release are certainly an important issue of modern topical therapy. The permucosal absorption of large cyclopeptides may not be the only key to a variable clinical response to topical therapy. Whether the release of CsA from a topically applied ointment or the concentration of CsA is sufficient to inhibit molecular and cellular interactions or to inactivate already activated T-cells remains unclear. Assuming that the T-lymphocyte is the target cell for CsA, local therapy probably only reaches a small fraction of the T-cell population. Perhaps a systemic inhibition of helper/inducer T-lymphocyte function is needed for successful therapy.[21] The possible benefit and adverse side effects of systemic treatment with CsA should be considered for each patient individually.
The results of this study indicate that topical application of CsA in the present form, does not offer advantage over the use of topical corticosteroids in the treatment of recalcitrant OLP.

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# CHAPTER 6

## LONG TERM FOLLOW-UP OF 153 PATIENTS WITH ORAL LICHEN PLANUS

This chapter is based on the following publication:
Voûte ABE, Schulten EAJM, Nieboer C, van der Waal I. Long term follow-up of 153 patients with oral lichen planus. (submitted for publication).

## INTRODUCTION

Lichen planus (LP) is a chronic inflammatory disease of unknown cause, affecting skin and mucosa of squamous cell origin. In general its histopathological appearance in combination with immunohistochemical features can be rather characteristic.
The reported female:male ratio in the literature is approximately 2:1. The disease is most frequently seen between the age of 40 and 70 years. The reported prevalence of oral lichen planus (OLP) varies between 0.7% and 1.89%.[1] Several studies of large populations report percentages of 6% up to 44% on the concomitant presence of cutaneous lesions.[2] Although individual lichenoid skin eruptions are generally cleared in one year,[3] OLP is usually chronic in nature.
Clinically, various subtypes of OLP can be distinguished, the most common being the erosive (or atrophic) and reticular (including papular and plaque-like) subtypes. Both forms may be present at the same time. The lesions are often present in more than one site of the mouth. OLP is most commonly observed bilaterally on the buccal mucosa and adjacent areas; other frequently involved sites are the tongue and gingiva. If present, the symptoms may range from mild discomfort to a severe burning sensation. No proven correlation exists with other diseases.[4,5]
Previous follow-up studies showed various rates of spontaneous healing of OLP, ranging from 6.5 to 17%.[4,5] Malignant transformation of OLP as being reported in the literature varies from 0.1% up to 10% in a mean period of five years; the most likely range varies between 0.1% and 3%,[6-8] although the premalignant character of OLP still remains subject for discussion.[9,10]
The purpose of the present study was to describe the clinical follow-up data of 153 patients with OLP in a selected Dutch population.

## PATIENTS AND METHODS

From a group of 225 patients, who had been initially referred to the Department of Oral and Maxillofacial Surgery of the Free University Hospital, Amsterdam, for diagnosis and management of OLP in the period 1970-1992, a total number of 71 patients (31.7%) were lost for follow-up: 11 patients (4.9%) have been deceased, 18 patients (8.1%) refused recall examination, 6 patients (2.7%) moved to another country, and 34 patients (15.2%) were lost track off because of administrative reasons. Three patients (1.4%), who had developed squamous cell carcinoma, were not included in this follow-up report either and have been described in more detail in chapter 3.

In all remaining 153 patients the initial diagnosis was confirmed by histopathological examination and in 51 patients (33%) also by immunofluorescence investigation, using criteria that have been previously described in chapter 2 paragraph 6. At last follow-up visit duration of disease, dental status, medical history and medication, as well as the use of tobacco, alcohol and periods of increased emotional stress as reported by the patient, were recorded. Only patients with a minimal follow-up of six months have been included in this study.

In Table 6.1 the characteristics of the study group are shown. Ninety percent were of Caucasian origin. Forty-seven patients (30.7%) gave a history of LP of the skin, nails and/or genital area.

**Table 6.1.** Characteristics of 153 patients with oral lichen planus (103 females and 50 males)

| Signs * | + | + | - |
|---|---|---|---|
| Symptoms * | + | - | - |
| Mean age at onset (range) ** | 49.6 (10.5-79.5) | 47.2 (21-78) | 48.3 (11-80) |
| Mean duration of disease (range and median) ** | 7.6 (1-18) (6.2) | 7.3 (1-22) (6.2) | 7.5 (1-16) (6.3) |
| Use of tobacco | | | |
| Smokers | 17 | 8 | 3 |
| Non-smokers | 53 | 48 | 24 |
| Use of alcohol | | | |
| none | 38 | 12 | 10 |
| intermittent | 26 | 30 | 9 |
| daily <4 units | 4 | 13 | 7 |
| daily ≥4 units | 2 | 1 | 1 |
| General health *** | | | |
| ASA I | 41 | 37 | 15 |
| ASA >I | 29 | 19 | 12 |
| Total no patients | 70 | 56 | 27 |

* + = presence of signs or symptoms, - = absence of signs or symptoms
** in years
*** ASA classification of physical health state according to the American Society of Anaesthesiologists



In Table 6.2 the various oral sites affected by OLP are given. Almost all patients had more than one oral site involved. The buccal mucosa and adjacent areas were the most commonly affected localisations, followed by the lateral border of the tongue, and gingiva. Lesions in the aforementioned sites often occurred bilaterally.

For registration of signs and symptoms, three groups were distinguished: (1) the reticular type, mainly characterised by white striated lesions; (2) the erosive (or atrophic) type, with predominantly erosions and/or ulcerations or erythema of the oral mucosa, and (3) a combination of these two subtypes. Lesions of the lips, including the vermillion border were considered part of the oral cavity.

Remission was defined as absence of oral lesions at the time of intraoral examination and a negative history of oral lesions over the last six months as reported by the patient.

If oral lesions and symptoms were present at any follow-up visit, therapy was offered depending on patients' discomfort and willingness to be treated, and usually consisted of topical application of corticosteroids (fluocinonide in an adhesive base).[11]

**Table 6.2.** Sites of oral lichen planus in 126 patients *

| | Number of patients | | |
|---|---|---|---|
| Oral Sites | Bilateral | Unilateral | Total |
| Buccal mucosa | 80 | 16 | 96 |
| Lateral border of the tongue | 39 | 11 | 50 |
| Upper gingiva | 25 | 10 | 35 |
| Lower gingiva | 31 | 9 | 40 |
| Upper lip | 8 | 2 | 10 |
| Lower lip | 18 | 5 | 23 |
| Dorsum of tongue | 16 | 0 | 16 |
| Palate | 5 | 4 | 9 |
| Floor of mouth | 6 | 1 | 7 |

* At the last follow-up visit no signs of OLP in 27 patients were observed.

## RESULTS

At the time of the last follow-up visit, 83 patients (55%) were free of symptoms, while 27 patients (18%) also had complete absence of oral lesions for a period of six months or longer (Table 6.3). In total 52 patients had been treated with topical fluocinonide and showed good response, part of these patients are described in more detail in chapter 4. In 63% the clinical diagnosis OLP during the last follow-up visit matched the initial clinicopathological diagnosis of OLP.

During last follow-up visit one female patient showed a suspicious change within a white lesion on the margin of the tongue (Fig 6.1). Four years earlier this lesion had been diagnosed, both clinically and histopathologically as OLP. Excisional biopsy of the present lesion was performed for histopathological examination, which showed "verrucous carcinoma". In two other patients frank squamous cell carcinoma developed in 7 and 9 years, respectively, in the lower lip, and in the buccal mucosa. One patient developed a "verrucous carcinoma" on the dorsum of the tongue after 5 years. These three patients have been described in more detail in chapter 3.

The recorded use of tobacco, alcohol, medication, and the presence of other illnesses did not correlate with the presence or subtype of OLP. In addition, no relation was found between the coexistence of restoration materials, such as amalgam fillings, golden crowns and bridges and the wearing of (partial) dentures and the presence of OLP. Fourteen patients (9%) reported a strong relationship with stress. During stressful periods they all noticed an exacerbation of their disease. The distribution of healthy and non-healthy patients is shown in Table 6.1. With regard to medical history and use of medication, 93 healthy patients (61%) excluded, the noted diseases had a wide variation from high blood pressure (n=16), cardiovascular diseases (n=12), endocrine disturbances like diabetes mellitus (n=8), mentally depressed (n=6), chronic aspecific respiratory diseases (n=5), gastro-intestinal disorders (n=5), chronic hepatitis (n=4), arthritis (n=3), hypothyroïdism (n=3), neuro-muscular disorders (n=2) to various other disorders (n=8). Treatment for the above-mentioned diseases was different per individual, except for the use of insuline and levothyroxine, in diabetes mellitus and hypothyroïdism, respectively.



Table 6.3. Symptoms of 153 patients with oral lichen planus according to subtype as recorded at last follow-up *

| | Number of patients | Symptoms | |
|---|---|---|---|
| Subtype of OLP | | Yes | No |
| Erosive | 37 | 22 | 15 |
| Reticular | 61 | 32 | 29 |
| Combination of erosive and reticular | 28 | 16 | 12 |
| Healed mucosa | 27 | 0 | 27 |
| Total | 153 | 70 | 83 |

* Symptoms: from mild discomfort to severe burning.

## DISCUSSION

Despite the partial retrospective character, the relatively large number of drop-outs and the possible selective nature of the studygroup due to referral bias, the present survey of 153 patients may provide an interesting complement to other follow-up studies.[2-5] In the continuous search for etiological factors of OLP, various correlations between OLP and drugs, dental restoration materials and medical history have been discussed. The results of this study do not support any particular relation between OLP and any of these factors. For example, no statistical difference was noted between those patients wearing dentures and those having amalgam restorations. The relation between dental restoration materials and OLP, as suggested in the literature, could hardly explain the history or coexistence of cutaneous LP in 30.7% of the patients. Maybe the term "lichenoid" lesions would be a more appropriate diagnosis in these cases.[12] The use of tobacco and alcohol as noted in Table 6.1 give no reason for discussion, but are noted merely as additional information.

Although the literature reports on the chronic nature of OLP, we found a relative large percentage of patients (18%) with remission. In 63% the clinical diagnosis at the last follow-up visit matched the initial diagnosis of OLP. In the remaining 19% of the

patients, there was some doubt about the concurrence of the diagnosis of the mucosal lesion(s) at the last follow-up visit and the initial diagnosis of OLP. In the latter group more atrophic features seemed to be present than at the time of onset of the disease (Fig.6.2).

In one patient "verrucous carcinoma" has been diagnosed during last follow-up visit, while frank squamous cell carcinoma in two other patients (0.9%) and a "verrucous carcinoma" in one other patient (0.5%) had developed, previously.

Unless a demographic study is carried out in The Netherlands, it remains difficult to determine whether our study group is representative for The Netherlands or consists of a selection of patients with OLP. If the prevalence of OLP is set at 1% in the population over the age of 15 years, and if the rate of malignant transformation is also set at 1% in a mean period of five years, 1 : 10.000 population would develop oral cancer in a period of five years, which results in a incidence of oral cancer on the basis of malignant transformation of OLP only, of two per 100.000 population per year. For the Dutch population, in which the incidence of oral cancer in the population above 15 years amounts approximately two per 100.000, this would mean that all oral cancer cases develop on the basis of OLP, which is extremely unlikely. Therefore, either the rate of malignant transformation, the time span, or the prevalence figure of OLP need adjustment.

Therefore we still feel reluctant to routinely inform every patient with OLP about the possible premalignant nature of their lesions. Histopathological examination should be performed when there is doubt about the clinical diagnosis. Nevertheless, bi-annual dental check-ups are recommended with thorough inspection of the oral mucosa. Although spontaneous remission of oral lesions in this study group occurred more often than has been described in other studies and although more than half of the patients were free of symptoms, the more or less chronic nature of the disease probably requires a life time follow-up.



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# CHAPTER 7

## SUMMARY AND CONCLUSIONS

## SAMENVATTING EN CONCLUSIES

## SUMMARY AND CONCLUSIONS

In this thesis a clinical study of oral lichen planus (OLP) in a Dutch population is described. An introduction on the study and the major aims of the study are outlined in **chapter 1**: (1) to study the theory of OLP being a premalignant condition, using the 21-years experience with patients having OLP in the Department of Oral and Maxillofacial Surgery/Oral Pathology, Free University Hospital, Amsterdam, (2) to investigate the efficacy of fluocinonide in an adhesive base for treatment of patients with symptomatic OLP, (3) to study whether topical application of cyclosporin-A is a useful alternative in recalcitrant, corticosteroid-resistant OLP, (4) to describe the results of longterm follow-up of untreated and treated patients with OLP.

In **chapter 2** an overview of the literature on oral and cutaneous lichen planus is given.

Lichen planus (LP) is a chronic inflammatory disease of unknown cause, affecting skin and mucosa of squamous cell origin. The disease seems to be predominantly present in women; the female:male ratio is approximately 2:1. The disease is most frequently seen between the age of 40 and 70 years. The prevalence of OLP varies between 0.7% and 1.89%, the prevalence of cutaneous lichen planus (CLP) is estimated at less than 1%. Percentages of 6% up to 44% on the concomitant presence of cutaneous lesions are reported. Although individual lichenoid skin eruptions are generally cleared in one year, OLP is usually chronic in nature.

The etiology and pathogenesis of LP is still to be unraveled. Recent evidence has shown that gamma-interferon, produced by T-cells, may induce monocyte expression of lymphocyte function associated antigen-1 that helps these cells attaching to keratinocytes. The apposition of activated immune cells and keratinocytes could then lead to destruction of the latter. Intercellular adhesion molecule-1 (ICAM-1), an keratinocyte antigen is mentioned in this context as well. The role of immunoglobulins in the pathogenesis of LP is speculative. The association of LP and HLA-antigens needs further investigation. Emotional stress is suggested to influence the course of OLP more than of CLP. There is still no proof for an infectious etiology.

The cutaneous lesions of LP consist of faintly erythematous to violaceous papules. They are flat topped and occasionally take on a polygonal form. Involved nails show longitudinal ridging and grooving. Oral lesions of LP often show the characteristic striae of Wickham. However, white confluent plaques do occur. Also

erythematous lesions are often seen in OLP, with atrophic or ulcerative features. A combination of the afore-mentioned features is frequently seen in OLP. Genital lesions of LP show concurrence with the clinical features of OLP.
LP has been reported to be associated with a variety of other disorders, such as gastrointestinal diseases and malignancies. It is difficult to determine, whether there is a causal or a purely fortuitious association.
In general, the histopathological appearance in LP is usually characteristic. The stratum corneum usually shows hyperkeratosis, rete ridges sometimes form a "sawtooth" pattern, degenerative changes in the basal cell layer and a bandlike subepithelial inflammatory infiltrate that consists of lymphocytes and histiocytes, that hug the basal layer.
Clinically, the erosive, ulcerative and plaque-like lesions of OLP are sometimes difficult to differentiate from other oral entities, such as erythroplakia and leukoplakia.
Malignant transformation in CLP is rare. The reported malignant transformation rate in OLP varies from 0.1 to 10.
In general, treatment is palliative and the most successful with local or systemic administration of corticosteroids.

In **chapter 3** the results of a study on the possible premalignant character of OLP are described. The 21-years experience of the Department of Oral and Maxillofacial Surgery/ Oral Pathology and the Department of Otorhinolaryngology of the Free University Hospital, Amsterdam, is reported. The study consisted of two parts: 1) the follow-up of 113 patients with histopathologically proven OLP, and 2) a search for OLP in 727 patients who had been admitted for oral squamous cell carcinoma. Three patients with histopathologically proven OLP developed squamous cell carcinoma in an average follow-up period of seven years. Of the 727 patients with oral squamous cell carcinoma, two additional patients with the simultaneous occurrence of OLP were observed. It is concluded from this study that our experience gives some but not very strong support to the hypothesis that OLP is a premalignant condition.

In **chapter 4** a study on topical treatment of OLP with fluocinonide is described. In a randomised, double-blind, placebo-controlled study, the efficacy was evaluated of topical application of 0.025% fluocinonide in an adhesive base. Forty consecutive patients with histopathologically and by immunofluorescence proven, symptomatic



OLP participated in this study. All patients were followed for three to seventeen months. During follow-up no adverse effects were noted. In the group of 20 patients that received the drug, four patients (20%) showed a complete remission, and twelve patients (60%) had a good or partial response to topical treatment. In the placebo-group, these figures were 0 and 6 (30%), respectively. The majority of the placebo-group (70%) did not respond at all with regard to signs ($X_t^2=10.4$; $p=0.0013$) and symptoms ($X_t^2=6.97$, $p=0.008$). The results from this study suggest, that topical application of fluocinonide in an adhesive base is a safe and effective drug to reduce signs and symptoms in OLP.

In **chapter 5** the results of a study with cyclosporin-A (CsA) in the treatment of corticosteroid-resistant OLP are described. In this open study the efficacy of CsA was evaluated, being applied as a topical drug, containing 0.025% CsA, four times daily. The study group comprised nine symptomatic patients in whom the diagnosis of OLP was confirmed by histopathological examination, including immunofluorescence. All patients had unsuccesfully undergone previous treatment with topical or systemic corticosteroids. The minimum follow-up period in the present study was four months. Four patients showed partial response with regard to signs and symptoms. None of the patients had a complete remission. Five patients showed no response or even complained of an increase of signs and symptoms. During follow-up no adverse side effects of the drug were recorded. Although the number of patients has been small, the results of this study indicate that topical application of CsA (0.025%) in the treatment of recalcitrant OLP does not offer a distinct advantage over the use of topical corticosteroids.

In **chapter 6** the clinical findings of untreated and treated patients with OLP during follow-up are described and discussed. Out of a group of 225 patients, who had been initially referred to the Department of Oral and Maxillofacial Surgery/Oral Pathology, Free University Hospital, Amsterdam, for diagnosis and management of OLP in the period 1970-1992, a study group was formed consisting of 153 patients. For those patients who had been lost for follow-up, recalls have been arranged. The mean duration of follow-up was 7.5 years (range: 0.8 - 22 years; median 6.2 years). In all patients the diagnosis of OLP was confirmed by histopathological examination and in 51 patients (33%) also by immunofluorescence investigation. The age, gender, signs and symptoms, duration of disease, presence of skin lesions, medical history and medication were recorded.
At last follow-up visit, 27 patients (18%) showed complete absence of oral lesions,

hich is rather high but in accordance with most other studies. Eighty-three tients (55%) were free of symptoms, which is a much higher rate of relief of mptoms than reported in other studies. One patient (0.6%) has been encountered, whom malignant transformation was diagnosed at last follow-up. Three patients .9%) had developed squamous cell carcinoma.

he present study confirms, that OLP is chronic in nature, but may show ontaneous resolution in about one fifth of the patients during a mean follow-up of 5 years. On the other hand, some patients with OLP seems to be at risk of veloping oral squamous cell carcinoma.



## SAMENVATTING EN CONCLUSIES

In dit proefschrift wordt een klinisch onderzoek beschreven naar lichen planus van het mondslijmvlies (OLP) bij een geselecteerde Nederlandse groep patiënten. In **hoofdstuk 1** wordt een inleiding en een uiteenzetting van de belangrijkste doelstellingen van het onderzoek gegeven: (1) de bestudering van de theorie dat OLP een premaligne conditie zou zijn; hierbij werd gebruik gemaakt van 21 jaar ervaring met patiënten met OLP op de afdeling Mondziekten en Kaakchirurgie/Pathologie van de Mondholte van het VU ziekenhuis te Amsterdam, (2) het onderzoeken van de bruikbaarheid van fluocinonide in een adhesieve mondzalf bij de behandeling van patiënten met klachten ten gevolge van OLP, (3) de evaluatie van het gebruik van cyclosporin-A als alternatieve behandeling bij patiënten met hardnekkige OLP, welke therapieresistent bleken voor behandeling met corticosteroïden, (4) het beschrijven van de resultaten van een follow-up onderzoek van onbehandelde en behandelde patiënten met OLP.

In **hoofdstuk 2** wordt een literatuuroverzicht gegeven van lichen planus van het monslijmvlies en de huid. Lichen planus (LP) is een chronische inflammatoire ziekte met een onbekende oorzaak. De afwijking kan voorkomen op slijmvliezen en huid, welke zijn opgebouwd uit plaveiselcellen. De ziekte komt voornamelijk voor bij vrouwen; de vrouw:man-ratio is ongeveer 2:1. De leeftijd waarop de ziekte het meest voorkomt ligt tussen 40 en 70 jaar. De prevalentie van OLP varieërt tussen 0.7% en 1.89%, de prevalentie van lichen planus van de huid (CLP) wordt geschat op minder dan 1%. Er wordt beschreven dat 6% tot 44% van de patiënten met OLP ook CLP hebben. Huidafwijkingen zijn meestal binnen één jaar genezen, slijmvliesafwijkingen zijn veelal chronisch van aard.
De etiologie en pathogenese van LP zijn tot op heden nog niet geheel duidelijk. Recentelijk is aangetoond dat gamma-interferon, een product van T-cellen, betrokken is bij monocyten-expressie van het lymfocyten-antigeen-1, zodat deze cellen gemakkelijker binden aan de keratinocyten. Keratinocyten kunnen hierdoor beschadigd raken. Het intercellulaire adhesie molecuul-1 (ICAM-1) wordt in dit verband ook genoemd. De rol van immunoglobulines in de pathogenese van LP is speculatief. De relatie van LP met bepaalde HLA-antigenen moet nog verder worden onderzocht. Het beloop van OLP lijkt meer dan CLP door stress te worden beïnvloed. Bewijs voor een infectieus agens als oorzaak voor LP ontbreekt.
Huidafwijkingen worden gekenmerkt door licht rode tot paarsachtige, vlakke verheven, soms polygonale papels. Indien de nagels zijn aangedaan, tonen zij een

duidelijk in de lengterichting verlopende groeven en richels. Afwijkingen van het mondslijmvlies worden meestal gekenmerkt door de striae van Wickham. Soms worden witte, confluerende, plaques gezien. Tevens wordt OLP klinisch vaak gekenmerkt door erythemateuze afwijkingen met een ulceratief of atrofisch aspect. Combinaties van voornoemde kenmerken komt veelvuldig voor. Afwijkingen aan de uitwendige geslachtsorganen tonen een grote overeenkomst met het klinische beeld van OLP.
Een associatie van LP met een aantal ziektebeelden is beschreven (maag-darm-lever afwijkingen, kwaadaardige tumoren). Tot op heden is het onduidelijk of er in deze gevallen sprake is van een toevallig, dan wel een causaal verband.
In het algemeen is het histopathologische beeld van LP karakteristiek. Hyperkeratose is meestal zichtbaar in het stratum corneum, soms zijn "zaagtand-vormige" retelijsten zichtbaar, evenals degeneratieve veranderingen van de basale cellen, en een bandvormig ontstekingsinfiltraat van lymfocyten langs de basale membraan.
Klinisch zijn erosieve, ulceratieve en plaque-vormige mondslijmvliesafwijkingen bij OLP vaak moeilijk te onderscheiden van erythroplakie en leukoplakie.
Slechts zelden treedt maligne ontaarding van CLP op. De gerapporteerde percentages van maligne ontaarding in OLP liggen tussen 0.1 en 10.
In het algemeen is de behandeling palliatief meest succesvol met lokale of systemische toediening van corticosteroïden.

In **hoofdstuk 3** worden de resultaten van een onderzoek naar het mogelijke premaligne karakter van OLP beschreven. De ervaringen, opgedaan gedurende 21 jaar, op de afdeling Mondziekten en Kaakchirurgie/Pathologie van de Mondholte en de afdeling Keel, Neus-en Oorheelkunde in het VU ziekenhuis te Amsterdam, zijn weergegeven. Het onderzoek bestond uit twee delen: 1) De follow-up van 113 patiënten met een histopathologisch bevestigde diagnose van OLP en 2) In een groep van 727 patiënten, bekend met een plaveiselcelcarcinoom in de mondholte, is gezocht naar het voorkomen van OLP. In de eerste groep ontwikkelden drie patiënten een plaveiselcelcarcinoom in een gemiddelde periode van zeven jaar. In de tweede groep werden nog twee extra patiënten gevonden met OLP. Uit dit onderzoek wordt enerzijds geconcludeerd, dat OLP een premaligne conditie is, maar dat anderzijds enige reserve blijft bestaan.



In **hoofdstuk 4** wordt een onderzoek naar het lokale gebruik van fluocinonide bij de behandeling van OLP beschreven. In een gerandomiseerd, dubbel-blind, placebo-gecontroleerd onderzoek is gekeken naar de effectiviteit van lokaal aangebrachte fluocinonidezalf (0.025%). Veertig opeenvolgende patiënten met klachten ten gevolge van OLP werden, na histopathologisch en immunofluorescentie onderzoek in de studie opgenomen. Alle patiënten werden over een periode van drie tot zeven maanden gevolgd. Gedurende deze periode werden geen bijwerkingen van het onderzochte middel gezien. Twintig patiënten ontvingen het verum; vier patiënten (20%) toonden een volledige remissie van de mondafwijkingen, twaalf patiënten (60%) reageerden goed of redelijk op de behandeling. In de placebo-groep waren deze aantallen respectievelijk 0 en 6 (30%). De meerderheid van de placebo-groep (70%) reageerde in het geheel niet, wat betreft het klinische beeld ($X_t^2=10.4$; $p=0.0013$) en wat betreft klachten ($X_t^2=6.97$; $p=0.008$). Dit onderzoek geeft aan dat locaal gebruik van fluocinonide in een adhesieve basis, bij OLP, een veilig en effectief middel is om klachten te verminderen en het klinische beeld te verbeteren.

In **hoofdstuk 5** worden de resultaten van behandeling met cyclosporine-A (CsA) bij corticosteroïde-resistente OLP beschreven. In een open studie werd gekeken naar de effectiviteit van vier maal daags, lokaal aangebrachte CsA zalf (0.025% CsA). De onderzoeksgroep bestond uit negen patiënten met klachten ten gevolge van OLP. De diagnose OLP was in alle gevallen door histopathologisch onderzoek, inclusief immunofluorescentie, bevestigd. Alle patiënten waren voorheen zonder succes met corticosteroïden, locaal of systemisch, behandeld. De follow-up was minimaal vier maanden. Vier patiënten reageerden met een gedeeltelijke verbetering ten aanzien van hun zichtbare afwijkingen en hun klachten. De overige vijf patiënten toonden geen reactie of zelfs een toename van de afwijkingen en/of klachten. Geen van de patiënten werd geheel klachtenvrij. Tijdens de controles werden geen bijwerkingen van het gebruikte middel gezien. Ondanks het geringe aantal patiënten, geeft dit onderzoek aan dat lokaal gebruik van CsA (0.025%) geen zinvol alternatief is voor het lokaal gebruik van corticosteroïden bij de behandeling van therapie-resistente OLP.

In **hoofdstuk 6** worden de klinische bevindingen tijdens follow-up van onbehandelde en behandelde patiënten met OLP beschreven en besproken. Uit een groep van 225 patiënten, die oorspronkelijk verwezen waren naar de afdeling Mondziekten en Kaakchirurgie /Pathologie van de Mondholte in het VU ziekenhuis

voor diagnostiek en behandeling van OLP in de periode 1970-1992, werd een onderzoeksgroep gevormd van 153 patiënten. Een aantal patiënten moest worden opgeroepen. De gemiddelde periode van follow-up was 7.5 jaar (spreiding: 0.8 - 22 jaar; mediaan 6.2 jaar). De diagnose OLP was bij alle patiënten bevestigd middels histopathologisch onderzoek en in 51 gevallen (33%) tevens ondersteund door immunofluorescentie-onderzoek. Leeftijd, geslacht, klinisch beeld, klachtenpatroon, duur van de ziekte, aanwezigheid van huidafwijkingen, medische voorgeschiedenis en medicijngebruik werden geregistreerd.

Bij het laatste controlebezoek bleken 27 patiënten (18%) geen afwijkingen meer te hebben, hetgeen ongeveer overeen komt met andere in de literatuur gepubliceerde onderzoeken. Drieëntachtig patiënten (55%) waren klachtenvrij. Deze bevinding is veel gunstiger dan in andere studies wordt gerapporteerd. Bij één vrouw (0.6%) werd, ten tijde van het laatste follow-up bezoek, een maligniteit in de mond aangetroffen. Drie patiënten (1.9%) ontwikkelden een plaveiselcarcinoom in de mondholte.

Dit onderzoek bevestigt het chronische karakter van OLP, maar laat ook zien dat ongeveer één vijfde van de patiënten spontane remissie ondergaat in een gemiddelde periode van 7.5 jaar. Verder lijkt het zo te zijn dat patiënten met OLP een iets verhoogd risico lopen een plaveiselcelcarcinoom in de mondholte te ontwikkelen.



## LIST OF ABBREVIATIONS

| | |
|---|---|
| ANA | - Anti-nuclear antigen |
| BMZ | - Basal membrane zone |
| BP | - Bullous pemphigoid |
| CAH | - Chronic active hepatitis |
| CLP | - Cutaneous lichen planus |
| CsA | - Cyclosporin-A |
| DM | - Diabetes mellitus |
| GVHD | - Graft-versus-host disease |
| HLA | - Human leucocyte antigen |
| ICAM-1 | - Intercellular adhesion molecule-1 |
| LE | - Lupus erythematosus |
| LN | - Lichen nitidus |
| LP | - Lichen planus (OLP + CLP) |
| LPE | - Lichen planus erythematosus |
| LPSA | - Lichen planus-specific antigen |
| LSA | - Lichen sclerosus et atrophicus |
| OLP | - Oral lichen planus |
| PBC | - Primary biliary cirrhosis |
| PUVA | - Psoralen-ultraviolet-A |
| SCC | - Squamous cell carcinoma |
| UC | - Ulcerative colitis |

## CURRICULUM VITAE

De auteur van dit proefschrift werd op 22 oktober 1961 geboren te Bergen (NH).
In 1981 behaalde hij het eindexamen aan het Murmellius Gymnasium te Alkmaar, waarna hij de opleiding tot officier volgde bij de Koninklijke Luchtmacht.
In 1982 werd begonnen met de studie tandheelkunde aan de Universiteit van Amsterdam. Het tandartsexamen werd in 1987 behaald.
In 1989 is hij gestart met het promotieonderzoek op de afdeling Mondziekten en Kaakchirurgie/Pathologie van de Mondholte, Vrije Universiteit / ACTA te Amsterdam (hoofd: Prof. dr I. van der Waal).
In 1992 behaalde hij het doctoraalexamen van de studie geneeskunde aan de Universiteit van Amsterdam.
Sinds 1 januari 1992 is hij in opleiding tot specialist in de Mondziekten en Kaakchirurgie (opleider: Prof. dr I. van der Waal).

**Stellingen behorende bij het proefschrift**

**ORAL LICHEN PLANUS**

**A clinical study**

A.B.E. Voûte

september 1994

1. Onvolledige diagnostiek leidt er toe dat lichen planus van het mondslijmvlies vermoedelijk te sterk wordt geassocieërd met het ontstaan van een plaveiselcel-carcinoom in de mondholte.

2. Het gebruik van de term lichenoïde dysplasie dient te worden vermeden.

3. "Lichen planus" met een oorzaak is waarschijnlijk geen lichen planus.

4. Lichen planus van het mondslijmvlies is vermoedelijk een "self-limiting disease".

5. Het aantal ligdagen van een schisispatiënt bij wie een bottransplantaat in de kaak moet worden aangebracht, wordt niet bepaald door de donorplaats.

6. Verzekeraars baseren de premies voor dekking van tandheelkundige hulp op ontoereikende gegevens, de overheid haar beleid ook.

7. Het beleid van de overheid in zake sluiting van faculteiten tandheelkunde heeft vreemd genoeg opening tot gevolg.

8. Voor een aangenaam verblijf op het strand is een strandhuisje wenselijk.

9. Jacques Perk was toen hij in 1881 op 22-jarige leeftijd stierf reeds een bekend dichter.

10. Met het klimmen der jaren doven kaakgewrichtsklachten meestal uit en vlamt het "mondbranden" op.

11. Voortplanting zonder manipulatie dreigt een uitzondering te worden.

12. Nederlandse driebaans snelwegen hebben in het midden een paarse strook. Links en rechts inhalen zal binnenkort mogelijk zijn.

13. Ergens in de evolutie hebben vrouwen een voorsprong genomen.

14. Linkshandigheid is een bron voor "onhandige" uitspraken. Het tegenovergestelde is minder waar.