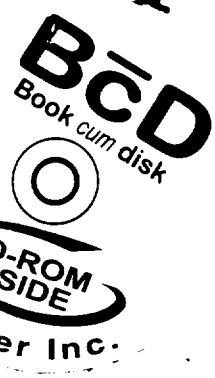
ORAL CANCER

Fourth Edition



Silverman

AMERICAN CANCER SOCIETY

Contents

Introduction xiii

1 **Epidemiology** 1
Sol Silverman Jr

2 **Etiology and Predisposing Factors** 7
Sol Silverman Jr
Edward J. Shillitoe (*Viruses*)

3 **Leukoplakia and Erythroplasia** 25
Sol Silverman Jr

4 **Diagnosis** 41
Sol Silverman Jr
William P. Dillon (*Imaging*)
Nancy J. Fischbein (*Imaging*)

5 **Spread of Tumor, Staging, and Survival** 67
Karen K. Fu
Sol Silverman Jr
Alan M. Kramer (*Chemoprevention*)

6 **Treatment** 75
Mark I. Singer (*Surgery*)
Theodore L. Phillips (*Radiation*)
Alan M. Kramer (*Chemotherapy*)
Karen K. Fu (*Chemotherapy*)

7 **Complications of Treatment** 91
Sol Silverman Jr

8 **Restoration of Palate, Tongue-Mandible, and Facial Defects** 103
John Beumer III
Ian M. Zlotolow
Arun B. Sharma

9 **Leukemia and Lymphoma** 127
Mark M. Schubert
Sol Silverman Jr

10 **Malignant Salivary Gland Tumors** 143
Joseph A. Regezi
Sol Silverman Jr

11 **Other Malignancies and Oral Oncology** 151
Sol Silverman Jr
Herbert H. Dedo (*Larynx*)
Catherine M. Flaitz (*Pediatric Oncology*)
Karen K. Fu (*Nasopharynx*)
Joseph A. Regezi (*Melanoma*)

12 **HIV-associated Oral Malignancies** 165
Catherine M. Flaitz
Sol Silverman Jr

Index 171

3

Leukoplakia and Erythroplasia

SOL SILVERMAN JR.

Decreasing morbidity and mortality from oral carcinoma in part depends upon improved understanding of precancerous lesions. White and red lesions of the oral mucosa are the most common precancerous clinical lesions. Although not all oral cancers are preceded by premalignant mucosal changes, such changes give a warning of risk and present an opportunity for preventive measures. Early cancer can even appear as an innocuous white and/or red lesion. Although white changes (leukoplakia) are the most common premalignant lesion, red changes (erythroplasia, erythroplakia) or white changes with a red component (speckled leukoplakia, erythroleukoplakia) carry a greater risk.

LEUKOPLAKIA

The term *leukoplakia* is used to designate a clinical white patch or plaque on the oral mucous membranes that cannot be removed by scraping and cannot be classified clinically or microscopically as another disease entity. Most of these lesions, which can occur in all areas of the oral cavity, are reflections of benign hyperkeratosis (Figures 3–1 to 3–6). Although tobacco or acute/chronic irritation may induce hyperkeratosis, causes of many leukoplakias are unknown.

EPIDEMIOLOGY OF LEUKOPLAKIA

The age range and the tobacco habits of patients with oral leukoplakia are similar to those of patients with oral carcinoma. These facts indicate possible biologic similarities and comparable risks. The relationship between smoking and leukoplakia is not always clear, since abstinence from tobacco may not lead to remission of the lesion, and some patients with leukoplakia have never smoked.

Figure 3–1. Leukoplakia, buccal mucosa.

Figure 3–2. Leukoplakia, tongue.

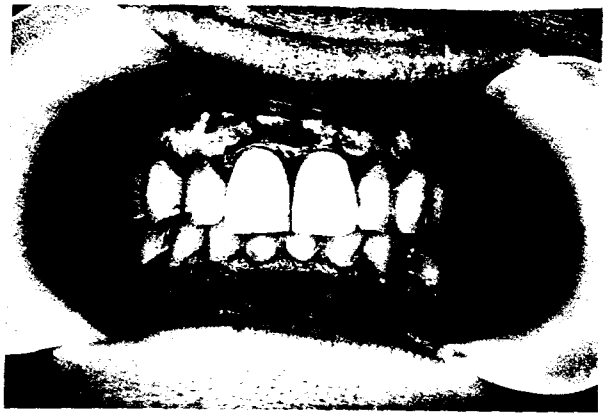


Figure 3–3. Leukoplakia, gingiva.

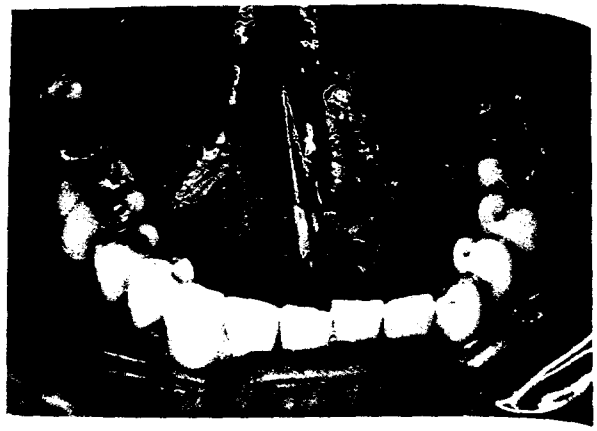


Figure 3–5. Leukoplakia, ventral tongue, floor of mouth.

Figure 3–4. Leukoplakia, alveolar mucosa, tongue.

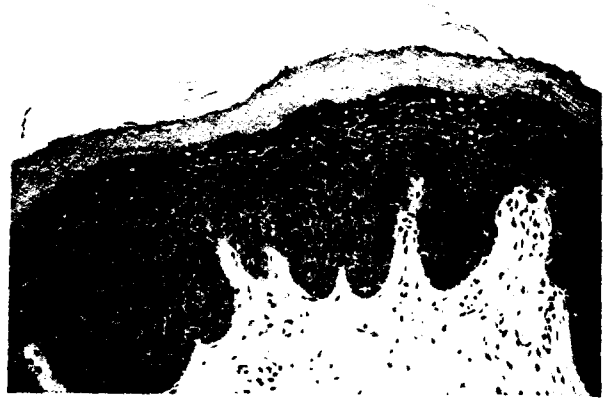


Figure 3–6. Hyperkeratosis, stratified squamous epithelium.

However, if associated with the use of smokeless tobacco, an induced leukoplakic change almost always reverses when the use of snuff or chewing tobacco stops (Figures 3–7 A, B, 3–8 A, B).

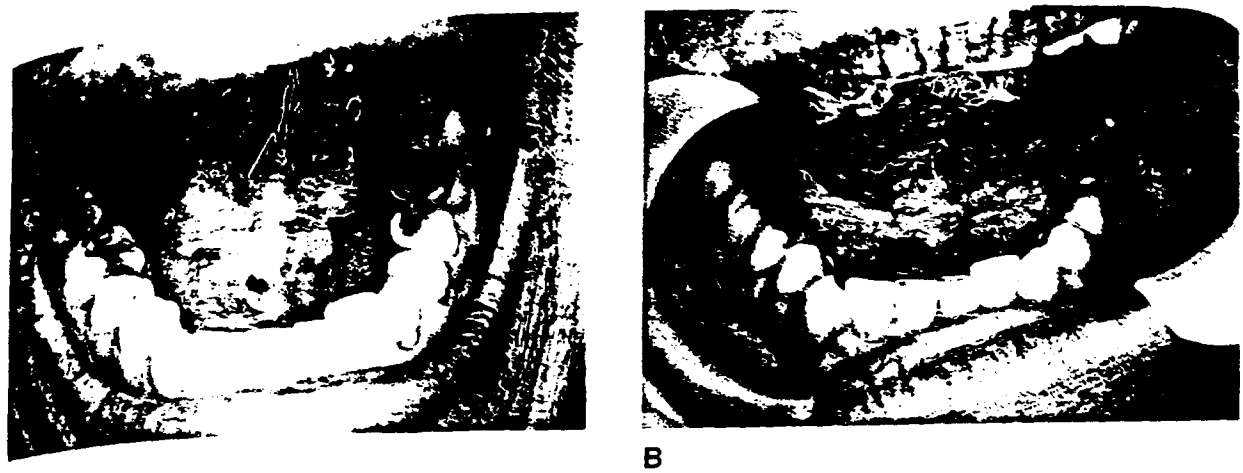
The prevalence of oral leukoplakia in the general population is unknown. Prevalence studies have been attempted in certain parts of the world, but the results are variable and do not support any generalizations as to rates. In a Minnesota study of 27,443 adults, the occurrence of leukoplakia was found to be 0.1%; yet in a study of more than 180,000 army recruits ranging in age from 17 to 26 years, 1.5% had oral leukoplakia. A study of 51,000 villagers in southern India found that the prevalence rates in four states ranged from 0.2% to 5%. On the other hand, a study from Ahmedabad, in northwest India, indicated that the occurrence of leukoplakia was close to 12%. However, this study examined a selected population of 57,518 textile-mill workers over 35 years of age who belonged to a lower socioeconomic class.

PRECANCEROUS CLASSIFICATION

Oral leukoplakia is a premalignant lesion. This conclusion is based on the following: (1) a large number of oral carcinomas have been associated with leukoplakic changes (Tables 3–1, 3–2), and (2) in prospective studies, occurrences of malignant transformations in oral leukoplakias exceed the number of oral cancers expected in the general population (Tables 3–3 to 3–6) (Figures 3–9 to 3–12).

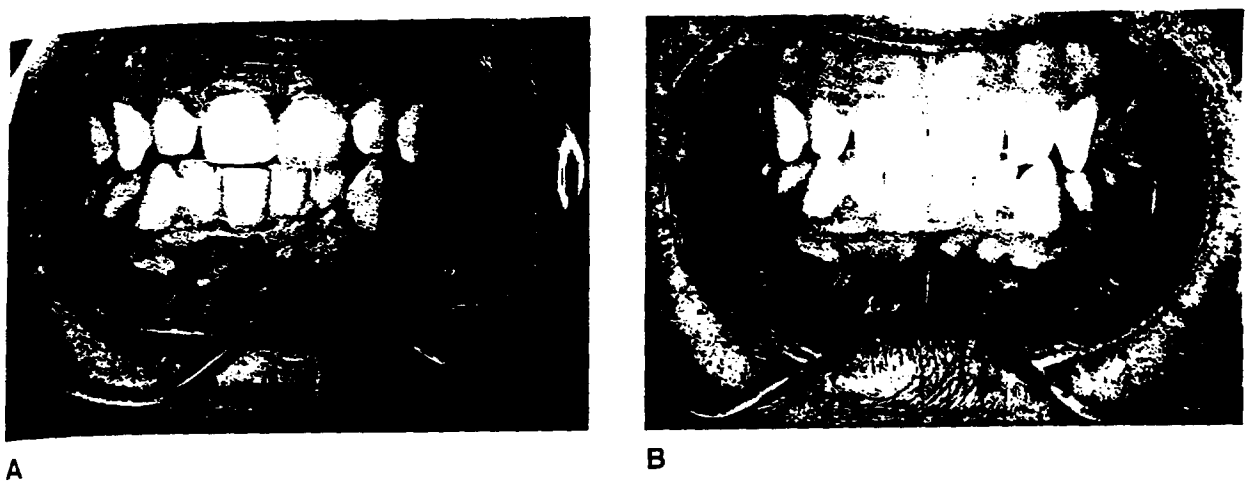
TOBACCO-INDUCED RISKS

Tobacco usage increases the risk for individuals of developing oral cancer. Paradoxically, in patients with oral leukoplakia, nonsmokers are at higher risk. This finding was shown in a study of patients from the University of California at San Francisco (UCSF) Oral Medicine Clinic (Table 3–7) and has also been reported by others. Einhorn (Sweden) cited an eightfold risk, and Roed-



A B

Figure 3–7 A, B. Leukoplakia and smoking cessation.
A. Leukoplakia, floor of mouth, associated with years of smoking one pack of cigarettes daily.
B. Four months after discontinuation of smoking, the leukoplakia is regressing with complete disappearance in 6 months.



A B

Figure 3–8 A, B. A 16-year-old athlete who held snuff between his lower lip and anterior teeth for almost 4 years.
A. Asymptomatic gingival leukoplakia.
B. Complete disappearance 1 month after discontinuing the use of snuff.

Petersen (Denmark) cited a fivefold risk of developing a carcinoma for nonsmoking leukoplakic patients. Although no one has proposed a clear explanation for this finding, it might be speculated that patients without tobacco as a causative irritant may have more lethal initiating or potentiating factors. Banoczy (Hungary) confirms this increased risk in nonsmokers in her long-term reports on leukoplakic patients.

DYNAMIC NATURE OF ORAL LEUKOPLAKIA

The possibility of spontaneous regression of oral leukoplakia was confirmed in a two-year follow-up study of 4762 persons with oral leukoplakia, in Gujarat, India. Although essentially no one changed habits during the two-year interval, almost one third experienced complete regression of their lesions. However, the prevalence rates for oral leukoplakia in the entire Gujarat study group at the beginning and end of the two-year period were similar, 11.7% and 12.0%, respectively. These results indicate that development and regression rates were comparable, so that the occurrence of oral leukoplakia in this population was relatively constant. The incidence was 2.6% per year.

Since others have found cases of complete regression in oral leukoplakia in different Indian pop-

Table 3–1. MALIGNANCIES AND PREMALIGNANT CHANGES FOUND IN BIOPSY SPECIMENS CLINICALLY DIAGNOSED AS LEUKOPLAKIA

Author (Country), Year	No. of Patients	Frequency of Malignancy or Premalignant Changes	
Pindborg (Denmark), 1963	185	3% Carcinoma	12% Dysplasia
Silverman (USA), 1968	117	10% Carcinoma	
Waldron (USA), 1975	3256	3% Carcinoma	17% Dysplasia
Banoczy (Hungary), 1976	500	10% Carcinoma	24% Dysplasia

Table 3–2. PROGRESSION OF DYSPLASIA IN CLINICAL LEUKOPLAKIA TO CARCINOMA

Author (Country), Year	No. of Patients	No. (%) of Malignancies	Time Span (yr)
Mincer (USA), 1972	45*	5 (11)	1–8
Banoczy (Hungary), 1976	68†	9 (13)	1–20
Pindborg (India), 1977	21	3 (14)	7
Silverman (USA), 1984	22	8 (36)	1–39

*22 persisted; 3 disappeared spontaneously; and 20 were excised, of which 7 recurred.
†45 of the 68 lesions were excised; 8 of the 9 malignant changes occurred in the 23 lesions not treated.

Table 3–3. MALIGNANT TRANSFORMATION IN ORAL LEUKOPLAKIAS OBSERVED OVER A PERIOD OF TIME*

Author (Country), Year	No. of Patients	Malignant Transformation (%)	Observation Period	
			Years	Mean
Silverman (Gujarat, India), 1976	4762	0.13	2	
Gupta (Bhavnagar, India), 1980	360	0.3	1–10	7
Gupta (Ernakulam, India), 1980	410	2.2	1–10	7
Roed-Petersen (Denmark), 1971	331	3.6	>1	
Einhorn (Sweden), 1967	782	4.0	1–20	
Pindborg (Denmark), 1968	248	4.4	1–9	
Kramer (England), 1969	187	4.8	1–16	
Banoczy (Hungary), 1977	670	5.9	1–30	9.8
Silverman (USA), 1968	117	6.0	1–11	3.5
Silverman (USA), 1984†	257	17.5	1–39	7.2

*Number of transformations varied according to selection of patients and duration of observation. A larger number of patients with leukoplakic lesions, selected at random and followed up over a longer period of time, would be necessary to determine a transformation rate in a given population.
†*See Tables 3–4 through 3–6.*

Table 3–4. TRANSFORMATION RATES OF LEUKOPLAKIC FORMS*

Leukoplakia	No. of Patients	Subsequent Carcinoma	Transformation Rate (%)
Homogeneous†	107	7	6.5
Erythroleukoplakia‡	128	30	23.4
Dysplasia§	22	8	36.4
Total	257	45	17.5

*Source: Silverman, 1984.
†All-white appearance.
‡Red component.
§20/22 appeared clinically as erythroleukoplakia.

Table 3–5. OCCURRENCES OF CARCINOMAS RELATED TO FOLLOW-UP PERIODS IN 257 PATIENTS WITH LEUKOPLAKIA*

Follow-Up (yr)	Occurrences of Carcinoma in 45 Patients (%)	Patients Followed up for Each Period (%)	Rate of Carcinoma in Patients Followed (%)	Rate of Carcinoma Per Year (%)
0.5–1	9	100	2	4
1–2	24	84	5	5
2–5	20	70	5	1.6
5–10	22	46	8	1.6
10–20	16	27	10	1
20–39	9	8	19	1

*Source: Silverman, 1984.

Table 3–6. PROFILE OF 45 PATIENTS WITH TRANSFORMATION OF LEUKOPLAKIA TO CARCINOMA*

Transformation Site	F	M	% of Lesions	Age at Onset of Leukoplakia (yr)		Transformation Time (yr)		Pre-existing Dysplasia	Tobacco Usage†		
				Range	Mean	Range	Mean		Cigarette	Pipe	Cigar
Tongue	9	4	28.9	37–79	55	1–18	6.4	1	2		1
Gingiva	6	5	24.4	46–84	66	1–21	8.6	3	2	1	
Floor	2	5	15.6	30–69	50	1–30	10.2	2	6	1	
Buccal	3	2	11.1	48–71	60	1–16	8.8	1	1	1	
Palate	4	1	11.1	38–76	54	2–39	9.3	1	2		1
Lip	2	2	8.9	45–65	54	3–11	6.6	0	3		
Total	26	19	100.0	30–84	57	1–39	7.2	8	16	3	2

*Source: Silverman, 1984.
†Of the 24 nonsmokers, 18 had never smoked, and 6 stopped smoking when diagnosed.

ulations, at rates ranging from 26 to 45% in five-year intervals, this remission phenomenon appears to be real. Similarly, a Danish study found that 37% of 214 leukoplakic lesions were totally or partially reversed without any intervention during a follow-up period that ranged up to 15 years, and a study of 520 Hungarian patients with oral leukoplakia observed from 1 to 25 years found regressive changes in 9%.

DYSPLASIA AND MALIGNANT TRANSFORMATION

The risk of transformation increases when a biopsy specimen reveals an associated epithelial dysplasia. However, specific data regarding the correlation between degrees of oral epithelial dysplasia, time-related progression, and the influences of a variety of cofactors remain uncertain. Well-designed studies to collect and evaluate this type of information have not been conducted.

In a retrospective review from a large New York City biopsy service, Lumerman and colleagues reported a follow-up study of oral epithelial dysplasia in 44 patients for whom they were able to obtain adequate follow-up material. These patients represented 14% of a pool of 308 recorded epithelial dysplasia cases in their service. Obviously, the question arises as to whether this small group of evaluable cases is representative of all their cases, or even of similar patients at other centers. Thirty-nine (89%) presented with white and/or red lesions, indicating the probable clinical diagnosis of leukoplakia and/or erythroplakia. The mean age was 61 years, and 55% were women. While most reports indicate a similar age-grouping, this preponderance of women was unusual. After the biopsy diagnosis and management, 7 (16%) developed oral carcinomas 7 to 78 months later (mean, 34 months); the average age was 63, and 4 were men. Two of the 7 had microscopic descriptions consistent with the high-risk type of leukoplakia termed "proliferative verrucous leukoplakia."

From a prospective study of 257 oral leukoplakia patients followed up for a mean time of 8.1 years in

Figures 3–9 to 3–12. Some varying appearances of squamous cell carcinomas associated with pre-existing areas of long-standing leukoplakia.

Figure 3–11.

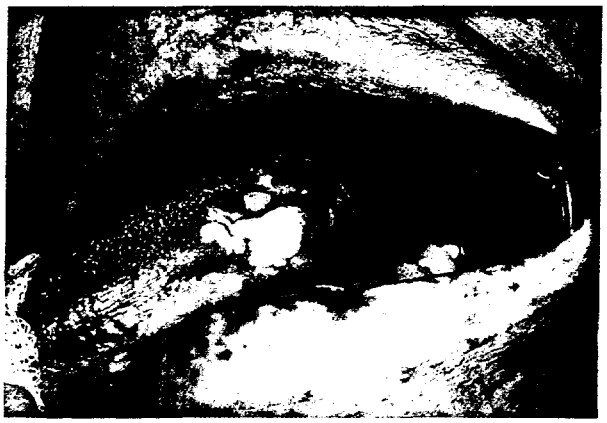


Figure 3–10.

Figure 3–12.

the author's clinic in San Francisco, 22 of these patients with oral leukoplakia also had microscopic dysplasia. In the time frame of this study, 37 of 235 patients (15.7%) without biopsy evidence of epithelial dysplasia developed oral carcinomas; however, 8 of the 22 patients (36.4%) with epithelial dysplasia developed oral carcinomas. (See Tables 3–4 and 3–6.) No evident factors distinguished these 8 patients and the 14 who had epithelial dysplasia but did not develop oral carcinomas. A

Table 3–7. ASSOCIATION BETWEEN TOBACCO HABITS AND FOLLOW-UP CHANGES IN LEUKOPLAKIA IN 257 UNTREATED PATIENTS*

	Tobacco Use		Leukoplakia		
No. of Patients	At Diagnosis	After Diagnosis†	Unchanged or Extended (%)	Improved or Disappeared (%)	Transformed to Carcinoma (%)
74	–	–	73	3	24
133	+	+	47	37	16
50	+	–	44	44	12

*Source: Silverman, 1984.
†More than 1 year.
+ Current tobacco users.
– Never smoked or stopped permanently at time of diagnosis.

longer follow-up may well have shown more malignant transformations.

The mean age of the 8 patients was 59 years (range, 30–77), and 5 were women. Four smoked; 6/8 had a red component in their leukoplakic lesion; and microscopic candidiasis was found in 4/8. While oral leukoplakia is generally asymptomatic, half of the patients had complaints of discomfort. The overall follow-up time from when the 8 patients first noticed their clinical leukoplakia was 9.5 years (range 1–29). Obviously, no one knows when the dysplastic changes actually occurred.

These findings prompt the following conclusions regarding the clinical recognition and diagnosis of oral leukoplakia, the development of epithelial dysplasia, and subsequent malignant transformation:

1. In oral leukoplakia, the occurrence and time of dysplastic changes are uncertain. De novo transformation from hyperkeratosis to carcinoma may occur without recognizable dysplasia.
2. An erythematous component and discomfort should raise suspicion of dysplastic or malignant transformation. (See below.)
3. Since epithelial dysplasia increases the risk of the development of a malignant tumor, surgical removal of dysplastic lesions is indicated. This limits prospective follow-up studies.
4. Proliferative verrucous forms of leukoplakia (PVL) have a high risk of dysplasia and malignant transformation and should be treated aggressively. (See below.)
5. While the severity of the degrees of dysplasia has clinical significance regarding neoplasia, patients with mild dysplasia, or even without evidence of dysplasia, are at risk of transformation. Therefore, all patients with chronic white and/or red lesions, whether treated or not, should be followed carefully. This advice holds true even after surgical intervention, since recurrences are common.
6. Reproducible interexaminer agreements in diagnosing oral epithelial dysplasia are difficult to achieve, adding to the confusion regarding treatment approaches and aggressiveness. Therefore, the development of biologic markers (e.g., monoclonal antibodies, DNA/RNA probes, special stains) emerge as extremely important, and even critical, in producing fundamental advancements in the diagnosis, prognosis, and treatment parameters of precancerous lesions.

ERYTHROLEUKOPLAKIA AND ERYTHROPLASIA

Leukoplakia that clinically has an erythematous or red component (erythroleukoplakia) is far more likely to undergo dysplastic or malignant epithelial changes than other forms of leukoplakia (Figures 3–13 to 3–16, 3–17 A–D). Since red lesions without a white component may also represent either dysplasia or carcinoma, such lesions must be carefully evaluated. (See Chapter 4.) In our Oral Medicine Clinic, the risk of malignant transformation in the patients with erythroleukoplakia was shown to be almost fourfold that of the patients with homogeneous leukoplakia. (See Table 3–4.) With this in mind, clinicians should take biopsy specimens which include erythematous areas. In our study group, 53% of the patients with leukoplakia had an associated erythematous area.

Figures 3–13 to 3–16. Erythroleukoplakias associated with transformations to dysplasia and carcinoma.
Figure 3–13. Dysplasia, buccal mucosa.

Figure 3–14 Carcinoma, oropharynx.

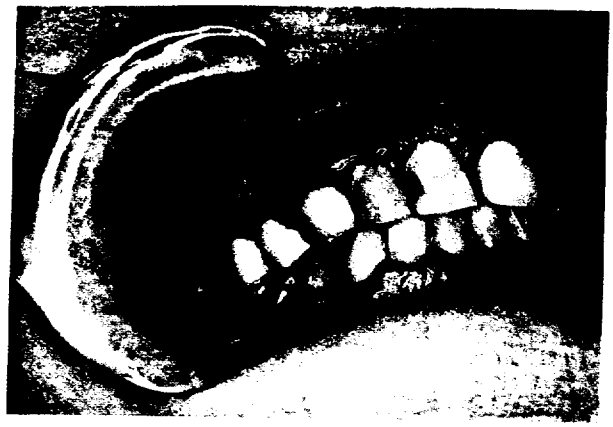


Figure 3–15. Gingival dysplasia (areas 6–9) and carcinoma (areas 3–5).

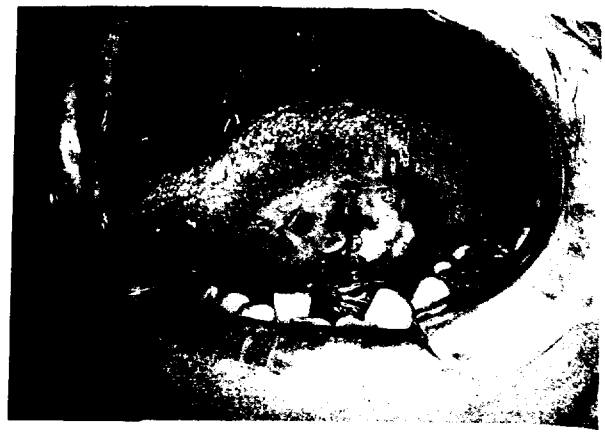
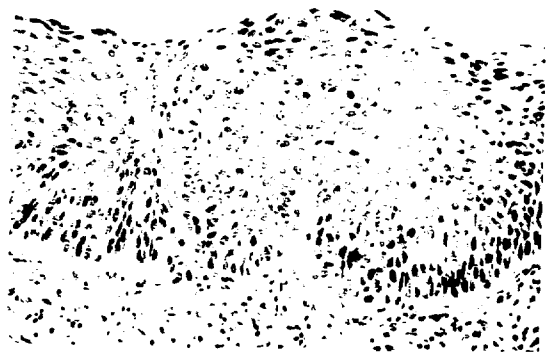


Figure 3–16. Carcinoma, tongue.

A

B



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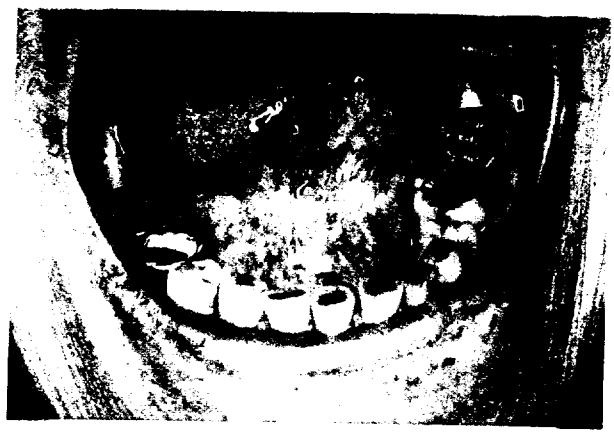


D

Figure 3–17 A–D.

A. Patient complained of floor-of-mouth irritation of 1 month's duration.

B. The red and white lesion was painted with 1% toluidine blue and decolorized with 1% acetic acid. Note retention in red area.

C. A biopsy from the red area showed carcinoma in situ.

D. Two months after carbon dioxide laser excision. The lesion had not recurred at 5 years, and the patient was asymptomatic.

whereas 82% of the patients who eventually developed a carcinoma demonstrated a red component. Other investigators have also found this increased risk associated with erythroleukoplakia. Roed-Petersen reported a sevenfold risk of malignant transformation in Danish patients whose leukoplakia had an erythematous component. His patients showed a 1.3% transformation rate in homogeneous leukoplakia, versus a 9.1% rate in red-and-white lesions. In a study limited to leukoplakias of the tongue and mouth floor, Kramer (England) reported a 15% transformation rate in an average period of 4.3 years. The risk of formation of carcinoma in the red-and-white lesions was five times that of the homogeneous leukoplakias. Banoczy (Hungary) described an erosive form of leukoplakia with an erythematous component, which had a fivefold greater risk of malignant transformation than other leukoplakias.

The high risk of malignancy in erythroplasia was reaffirmed further by Waldron in a microscopic review of more than 3000 leukoplakias. Fifty-eight were described as clinically red lesions, of which 91% were found to be either invasive carcinoma, carcinoma in situ, or severe dysplasia. Mashberg directed another series of studies of high-risk patients (older men, high tobacco and alcohol consumption) in a Veterans Administration Hospital. These studies showed that persistent erythroplasia rather than leukoplakia in high-risk sites is the earliest and predominant sign of oral carcinoma. In his prospective study of 222 asymptomatic oral carcinomas, 28% were red only; 62% were red and white; 97% occurred in the mouth floor, oral tongue, and oropharynx; and 84% were less than 2 cm at their largest diameter.

ERYTHROPLASIA WITH ULCERATION

Another rare but high-risk premalignant lesion is the chronic erythematous change associated with constantly recurring erosive changes. These lesions are often mistaken for "recurrent aphthous stomatitis of the herpetiform variety" or a "nonspecific inflammatory vesiculoerosive disease" (Figure 3–18). A biopsy of the early lesion may show only hyperkeratosis and inflammation not suggestive of any specific disease. Clinical responses to empirical corticosteroid therapy may help rule out a premalignant status by indicating a benign inflammatory response associated with a vesiculo-erosive disease. However, even a nondysplastic pattern in this type of lesion that cannot be classified deserves close follow-up, or even attempted removal, because of the risk that it may eventually develop into a carcinoma.

Figure 3–18. Squamous cell carcinoma presenting as a symptomatic erosive erythematous lesion of 3 months' duration.

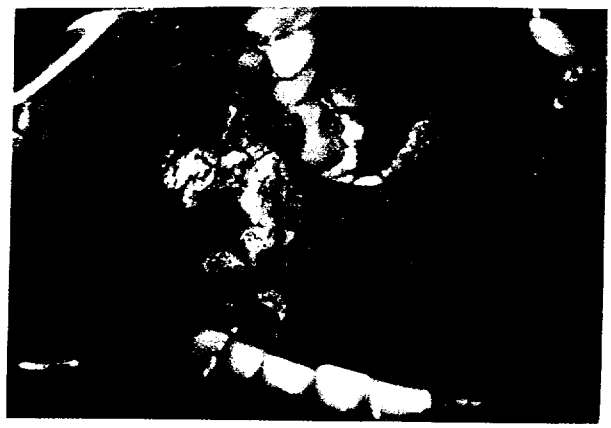
PROLIFERATIVE VERRUCOUS LEUKOPLAKIA (PVL)

In 1985, we first described a unique form of leukoplakia found in 30 patients. This group of lesions had a high risk of malignant transformation. Because of the characteristic appearance—an expanding, exophytic/fissured white lesion—we coined the name "proliferative verrucous leukoplakia" (PVL) (Figures 3–19 A–D, 3–20 A–B).

To complicate matters, these growths displayed variable histologic appearances even within the same patient specimen, variations that could range from a benign hyperkeratosis through degrees of epithelial dysplasia to verrucous or squamous carcinoma (Figure 3–21). The inflammatory infiltrate also appeared quite variable, ranging from a mild, diffuse, white-cell appearance to a dense, subepithelial clustering.

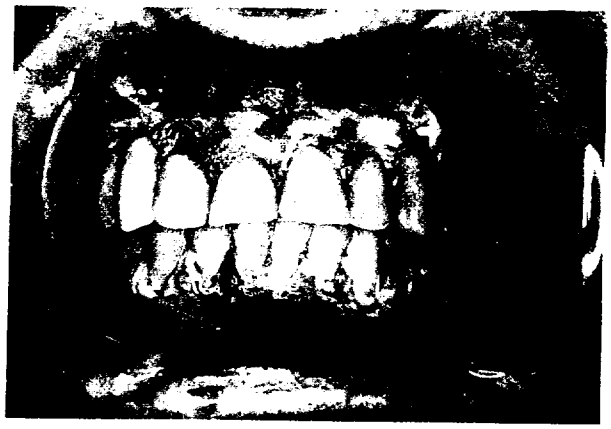
Our recent follow-up study of 54 PVL patients confirmed our initial findings and present impressions: (1) PVL is a very high-risk precancerous lesion with high transformation and mortality rates; (2) women outnumber men; (3) less than one third smoke; and (4) there is usually multisite oral involvement (Tables 3–8 and 3–9).

Therapeutic approaches have not been encouraging, although surgery utilizing laser technology offers some hope. This procedure includes photodynamic therapy with cell-sensitizing compounds, e.g., photofrin or 5-aminolevulinic acid, followed by applications of laser energy of specific wave-



A

B



C

D

Figure 3–19 A–D. Proliferative verrucous leukoplakia.

A

B

Figure 3–20 A, B. A. Proliferative verrucous leukoplakia of 5 years' duration in a nonsmoking 78-year-old woman. **B.** A biopsy revealed characteristic changes of hyperorthokeratosis, surface papillary projection, epithelial hyperplasia, and an inflammatory infiltrate. There was a malignant transformation during the sixth year.

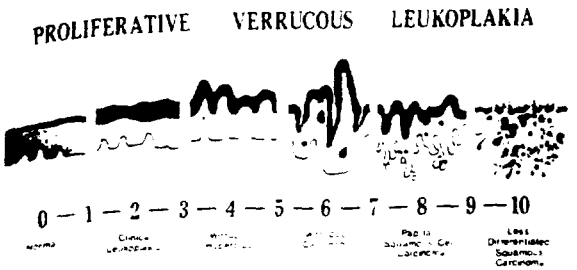


Figure 3–21. Varying histologic findings in proliferative verrucous leukoplakia specimens.

lengths. The surgical failures appear to be related to early changes in subcellular elements that are not clinically or microscopically evident, thereby leading to recurrences because of "inadequate margins." Radiation does not appear to be effective in controlling these biologic factors of epithelial cell behavior.

Biomarkers have not as yet been identified. Human papillomaviruses (HPV) have been isolated from some PVL lesions, but their role in the occurrence and/or progression of PVL remains speculative. However, the known effects of HPV E6 protein, which is capable of inactivating p53 suppressor protein, may account for ineffective epithelial suppression of growth factors and subsequent neoplasia.

Because of the extreme variations in PVL appearance, natural history, histopathology, and outcome, it logically seems to be a multifactorial condition. Additionally, factors such as smoking and the presence of *Candida* have not demonstrated any influence on either occurrence or progression. At the present time, then, careful clinical and microscopic assessment combined with surgical techniques, clinical judgment, and close follow-up offer the best approaches to management.

Table 3–8. HISTOLOGIC PROGRESSION OF PROLIFERATIVE VERRUCOUS LEUKOPLAKIA (PVL) IN 54 PATIENTS*

Microscopic Diagnosis†	Initial Biopsy	Last Biopsy
Hyperkeratosis/hyperplasia	28	11
Epithelial dysplasia	16	5
Carcinoma	10	38

*Source: Silverman, 1997. Mean follow-up, 11.6 years (range, 1–39) after PVL first seen/diagnosed.

†Most severe cellular change found in biopsy(-ies). Note that 10 patients had a carcinoma initially in one of their PVL sites.

Table 3–9. SITES OF SQUAMOUS CARCINOMA IN 38 OF 54 PATIENTS WITH PROLIFERATIVE VERRUCOUS LEUKOPLAKIA*

Site	No. of Carcinomas: Both Sexes (%)	Women (n = 43)	Men (n = 11)	Smokers
Gingiva	11 (29)	9	2	1
Tongue	10 (26)	8	2	5
Buccal	6 (16)	5	1	3
Floor	5 (13)	5	0	1
Palate	5 (13)	4	1	2
Lip	1 (3)	1	0	0
Total	38 (100)	32 (74.4)	6 (54.5)	12 (31.6)

*Source: Silverman, 1997.

CANDIDIASIS (CANDIDOSIS), LEUKOPLAKIA, AND ERYTHROPLASIA

Candidiasis (thrush, moniliasis) is caused almost always by an overgrowth of the fungus *Candida albicans*. Although this fungus is found in more than one third of normal-appearing mouths, overgrowth does not occur unless the normal balance of the oral flora is disturbed, for example, by debilitating or acute illness, immune suppression, xerostomia, or antibiotic therapy. The following factors support clinical manifestations of candidal colonization: (1) adherence mechanisms between fungi and oral epithelial cells; (2) yeast overgrowth (which is probably dependent upon and reflective of proteins expressed by *Candida*), host-cell and extracellular matrix proteins, host cation influence on adhesion, and possible coaggregation between fungi and bacteria; and (3) host immune incompetence. The diagnosis of candidiasis is suspected with the observation of creamy-white and/or erythematous mucosal changes (Figure 3–22). Candidiasis can be confirmed by smear, culture, biopsy, or response to antifungal therapy.

Our studies indicate that candidiasis may add a potential risk factor for malignant transformation of leukoplakia (Figures 3–23 A, B, 3–24 A, B). Although cultures showed that 31% of our leukoplakia patients fostered *Candida* as part of their oral flora, a rate similar to the occurrence in the normal populations, 53% of the leukoplakia patients who developed carcinomas were *Candida*-positive prior to tumor formation. However, mutagenicity and carcinogenicity of *C. albicans* have not been shown. Formation of nitrosamines (potential carcinogens) by *Candida* species in vitro has been implicated.

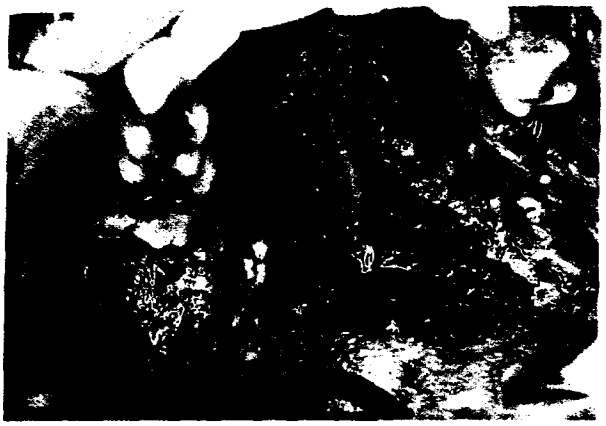


Figure 3–22. Candidiasis presenting as a red-and-white lesion.

Other reports have demonstrated a higher prevalence of *Candida* in speckled leukoplakia as compared to homogeneous (all-white) leukoplakia. In one study of 235 Danish patients with leukoplakia, 23.4% were *Candida*-positive. However, while in the homogeneous group, 4 of 152 (2.6%) were *Candida* positive. in the speckled leukoplakia group, 51 of 83 (61.4%) were positive. Our experience confirms the greater risk of fungal infection in the red-and-white lesion. It seems that the *Candida* organisms in these situations are secondary residents, since treatment will most often only convert erythroleukoplakia into the homogeneous form. It is possible, but infrequent, that *Candida* organisms stimulate hyperkeratosis leading to hyperplastic candidiasis, since adequate antifungal treatment of the *Candida* infection may lead to disappearance of the clinical lesion.

These reports show that candidiasis may complicate the observation and management of oral leukoplakia, but no studies have documented a cause-and-effect relationship between *Candida*-associated leukoplakia and malignant transformation.

HAIRY LEUKOPLAKIA

Oral *hairy leukoplakia* (HL) describes white-appearing lesions that almost always occur unilaterally or bilaterally on the borders of the tongue. The significance of HL is that it serves as a marker for human immunodeficiency virus (HIV) infection. HL frequently appears as hairlike projections and/or corrugations, but it may also have a plaque-like appearance (Figure 3–25 A, B). It appears occasionally on other oral sites such as the buccal mucosa, oropharynx, and mouth floor. No evidence suggests that HL shares biologic similarities with hyperkeratotic leukoplakia, which has premalignant connotations.

The diagnosis is confirmed by biopsy and/or serology if the HIV status is unknown. Microscopically, HL appears as an epithelial hyperplasia with a parakeratotic surface and vacuolated cells often referred to as koilocytes (cells suggestive of viral infection). The presence of Epstein-Barr virus (EBV) in these vacuolated cells has been shown by electron microscopy and DNA probes. Since

A

B

Figure 3–23 A, B. *Candida*-associated leukoplakia.
A. Uncomfortable lesion of 6 months' duration. Biopsy showed hyperkeratosis, inflammation, and *Candida* hyphae in the surface cell layers.
B. Antifungal medication transposed the lesion to an asymptomatic homogeneous leukoplakia. The patient suffered recurrent bouts of candidiasis and, after almost 2 years, the lesion transformed into a squamous cell carcinoma.

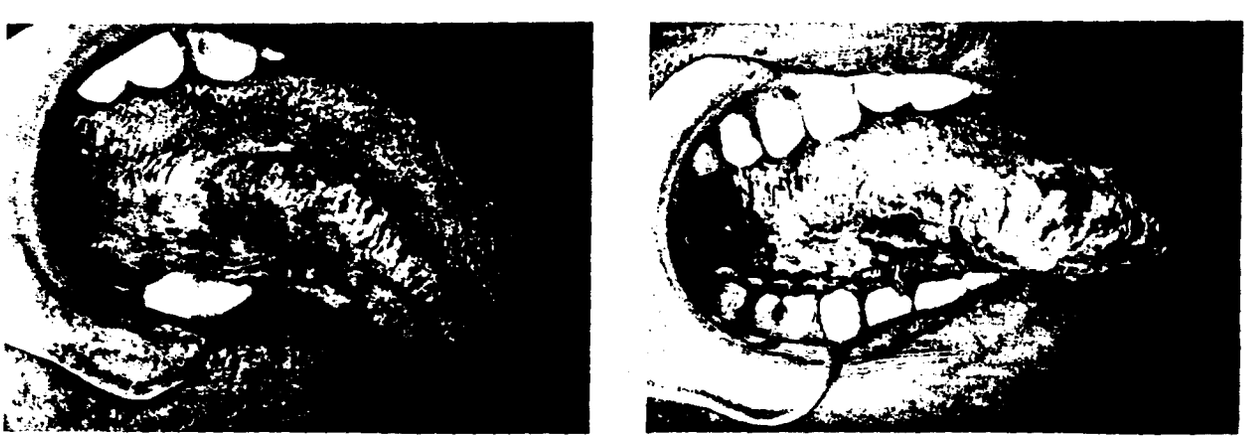
A B

Figure 3–24 A, B. *Candida*-associated leukoplakia.
A. Biopsy of this painful, longstanding leukoplakia showed hyperkeratosis, inflammation, and surface *Candida* organisms.
B. Antifungal treatment led to control of symptoms and a marked reduction in the leukoplakia. Years later this 60-year-old nonsmoking woman developed a squamous cell carcinoma in this area.

sometimes non-HL lesions can have a similar clinical or even microscopic appearance as HL. ultimate confirmation may depend upon the demonstration of EBV or HIV-positive serology. Connective-tissue inflammation may vary from moderate white-cell infiltrates to the appearance of a noninflammatory lesion. The keratotic surface appears to comprise immature keratin, since it is not preceded by keratohyaline granules. In about half the cases, *Candida* organisms can be demonstrated in the epithelial surface; however, antifungal treatment does not appreciably alter HL.

Whether EBV is a cause or result is as yet not clear. HL can occur in all HIV-infected groups, although far more often in homosexual men than in heterosexual men or women. This finding suggests a cofactor or cofactors that possibly may be transmitted more readily by oral and anal sexual practices.

Treatment is elective, since these lesions are usually asymptomatic, but chronic. They are treated only if they bother the patient in some way, or by coincidence when another disease is the target of treatment. HL may disappear following high doses



A B

Figure 3–25 A, B. Hairy leukoplakia (HL). HL is not related to dysplasia or carcinoma.
A. Mild, asymptomatic lesion in a 38-year-old HIV-positive homosexual male.
B. Marked, asymptomatic lesion in a 32-year-old HIV-positive male.

of antiviral drugs (acyclovir, zidovudine), which interrupt viral replication; topical tretinoin solution; sulfa-type antibiotics given for controlling *Pneumocystis* pneumonia; or topical applications of a podophyllum solution (a keratinolytic agent). HL usually recurs when treatment is modified or discontinued. In any event, HL augurs a poor prognosis and is most definitely a sign of acquired immunodeficiency syndrome (AIDS)-related complex (ARC).

DIAGNOSIS AND MANAGEMENT

Patients with leukoplakia are usually asymptomatic. The lesion is often discovered by a clinician during a routine examination or by patients because of roughness in their mouths. No consistent or reliable clinical signs and symptoms associated with oral leukoplakia allow differentiation between or accurate prediction of a premalignant or early malignant change. Since the clinical appearance of oral leukoplakia—thick or scant, large or small—does not reliably indicate its biologic potential, clinicians should be suspicious of all white lesions and should carefully evaluate and observe these patients.

The first step in management of leukoplakia is the removal of all irritants. If the leukoplakia is not reversible, excision is the most effective treatment. However, since these lesions may spread over a large area, they cannot always be surgically excised. In addition, recurrence after excision is common, due possibly to continuation of an irritant or the biologic potential in adjacent tissue that morphologically appears normal. The use of the carbon dioxide laser has proved extremely useful and effective (Figures 3–26 A–C, 3–27 A–C). Preceding the laser procedure, a diagnostic biopsy in part determines the extent and aggressiveness of removal. Removal, then, is usually accomplished by vaporization under local anesthesia in single or serial operations (depending upon extent of the leukoplakia). Healing occurs without suturing by secondary intention. Recurrences are infrequent and, essentially, no complications occur. Electrodesiccation and cryosurgery have not been uniformly effective in permanently removing keratotic lesions. Proteolytic enzymes have been of no value, since keratin resists them.

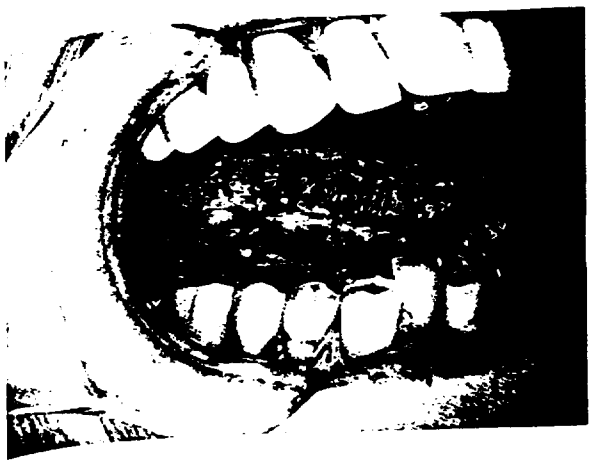
The use of vitamin A in attempts to control cancer and leukoplakia is often termed "chemoprevention." The benefit of vitamin A was surmised from animal studies in which vitamin A deficien-

A

B

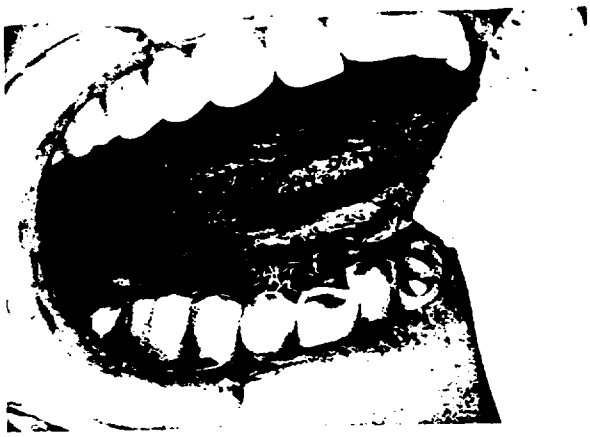
C

Figure 3–26 A–C. Laser removal of leukoplakia associated with mild dysplasia.
A. Before surgery.
B. Immediately after surgery.
C. Healed and asymptomatic at 3 weeks.



A

B



C

Figure 3–27 A–C. Leukoplakia with mild dysplasia.
A. Before laser surgery.
B. Immediately after CO_2 laser removal.
C. Completely healed at 3 weeks. There was no recurrence at 4 years of follow-up.

cies led to epithelial hyperkeratosis. Vitamin A in high dosages (more than 300,000 units per day in troche form) has been effective in some patients in reversing oral leukoplakia associated with hyperkeratosis. The mechanism of action is unknown but is probably related to effects on epithelial growth and suppressor proteins. However, upon withdrawal of vitamin A, the leukoplakia returns. Vitamin A tolerance is short lived with the required high dosages because of limited liver storage and subsequent toxicity. The most common side effects are dry skin, rash, and pruritus. Reports have shown that oral squamous carcinomas have developed during or shortly following vitamin A regimens in some patients. These reports suggest the possibility that, in some instances, high dosages of vitamin A associated with poorly understood host or other cofactors may increase the risk of carcinogenesis. Chemoprevention of oral leukoplakia is still experimental (see Chapter 5).

In attempts to increase effectiveness and diminish toxicity, an analogue of vitamin A (13-*cis* retinoic acid) was developed. While intake of moderately high dosages will control some lesions, toxicity still limits its usefulness. Beta-carotene, a precursor to vitamin A possessing very few adverse side effects, has not been effective. Combinations of antioxidant vitamins and nutrients are inconclusive in the control of oral leukoplakia. These include beta-carotene, vitamin A, ascorbic acid (vitamin C), and alpha-tocopherol (vitamin E). Their potential biologic actions include (1) quenching of cellular free radicals, which can affect chromosome integrity, mutagenesis, and carcinogenesis; and/or (2) promoting a balanced function between epithelial growth and suppressor proteins. Retinoic acid solution as well as 13-*cis* retinoic acid (Accutane®) have been approved for use in acne. In our experience, daily topical applications of 0.05% retinoic acid solution to oral leukoplakia have achieved partial remissions. Applications can produce inflammation and irritation, and long-term implications are unknown.

Since many methods of managing leukoplakia are not always feasible or effective, these patients must be observed periodically. The follow-up examination includes careful clinical observation and an occasional biopsy. Follow-up biopsy is indicated when changes in signs and/or symptoms occur. Exfoliative cytology and vital staining with toluidine blue help supplement clinical judgment and serve as an adjunct to biopsy (see Chapter 4). Negative smears or stains must be balanced with

clinical judgment. Therefore, if clinical suspicion persists, a biopsy must be considered.

SUMMARY

The risk of malignant transformation in oral leukoplakia always remains. Because leukoplakia and carcinoma can occur simultaneously, and no established prognostic clinical guide exists, all white lesions characterized as leukoplakia must be microscopically diagnosed and either removed or monitored with care. Biopsy is the only definitive way to establish the exact nature of oral leukoplakias.

When seeking dysplastic or malignant areas in leukoplakic lesions, it is important to remember that erythematous and speckled regions are more likely to be dysplastic or cancerous than thick and homogeneous white regions. It must also be remembered that the diagnosis of a previously biopsied benign white patch must be periodically reaffirmed, since a leukoplakia may unpredictably transform into malignancy. Moreover, although a leukoplakic lesion may regress and disappear when an irritant is reduced or removed, it can recur and may subsequently become cancerous.

In determining the aggressiveness of treatment, consideration of the following potential risk factors is essential: (1) an erythematous component or red lesion, (2) microscopic dysplasia, (3) a clinical appearance of proliferative verrucous leukoplakia, (4) associated candidiasis seen microscopically, (5) a nonsmoking patient, and (6) pain or irritation (leukoplakia is usually asymptomatic).

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