

From: The Dental Department and the Department of Head and Neck Surgery, the University Hospital and the Departments of Oral Pathology and Surgery, the Royal Dental College, Copenhagen, Denmark.

STUDIES IN ORAL LEUKOPLAKIAS

V. CLINICAL AND HISTOLOGIC SIGNS OF MALIGNANCY

by

J. J. PINDBORG,

GRETE RENSTRUP,

H. E. POULSEN,

S. SILVERMAN, JR.

For many years, leukoplakia has been recognized as an important precancerous condition of the oral cavity. Figures for estimating the rate of malignant transformation of these lesions may be obtained in either of two ways: 1) *i n d i r e c t l y* by a) establishing the number of leukoplakias associated with oral carcinoma in large series of patients (*Silverman, Renstrup & Pindborg, 1963*) or b) by determining the number of carcinomas found in a series of histologic material, which was clinically classified as leukoplakias, or 2) *d i r e c t l y* by following a number of leukoplakias over a period of time and determining the incidence of malignant transformation.

Supported by a research grant, DE-1358, from the National Institute of Dental Research, U. S. Public Health Service.

Dr. Silverman's stay in Copenhagen was supported in part by the Danish Cancer Society.

Table I. Percentage of malignancies and premalignant changes occurring in materials of leukoplakias from various countries.

Author	Country	Year	Size of Material	Incidence of Malignancy or Premalignant Changes
Renstrup	Denmark	1958	80	2.2 % premalignant changes
King & Hamilton	U.S.A.	1931	80	6.3 %
Hahn et alii	Germany	1961	152	10 %
Winiker-Blanck	East-Germany	1961	66	10 %
Sovadina	Czechoslovakia	1955	55	7.3 % premalignant 7.3 % malignant
Present Investigation	Denmark	1963	185	14.6 % 12.4 % epithelial atypia 3.2 % carcinoma 15.6 %
Shafer & Waldron	U.S.A.	1961	332	7.8 % focal atypia 1.8 % carcinoma in situ 8.1 % carcinoma 17.7 %
Bredy	East Germany	1955	15	20 %
McKown	U.S.A.	1949	100	30 %

The percentage of malignancies occurring in various materials of leukoplakias is tabulated in Table I. Table II compiles available reports on malignant transformation of oral leukoplakias, that have been followed over a period of time. The figures within each table cannot be directly compared due to the fact that the criteria for the diagnosis of leukoplakias and the sampling of material vary from one investigation to the other. For figures before 1930 the reader is referred to *Haase, 1931* who compiled all data up till that time.

The sources of material for the present study were patients with oral leukoplakias seen in the Department of Oral Surgery, Royal Dental College and Dental Department, University Hospital, Copenhagen. The lesions were classified as leukoplakia if the

Table II. Incidence of malignant transformation in oral leukoplakias observed over a longer period of time.

Author	Country	Year	Size of Material	Incidence of Malignant Transformation	Observation Period
Skach, Svoboda & Kubat	Poland	1960	71	1.4 %	3—6 yrs.
Sugar & Banóczy	Hungary	1959	86	6 %	11 yrs.
Sturgis & Lund	U.S.A.	1934	298	12 %	5 yrs.
Leonardelli & Talamazzi	Italy	1950	268	20 %	1 month— 15 yrs.
Weisberger	U.S.A.	1957	22	36 %	4 yrs.

white patches could not be scraped off and they could not be attributed to any other diagnosable disease. In examining the patients it became apparent that some leukoplakic lesions had characteristics of white patches on an erythematous background giving a "speckled" appearance. These clinical changes were often associated with epithelial atypia and some were carcinomas. The purpose of this report is to discuss the clinical and histologic features in this group of leukoplakias.

FINDINGS

In a material of 185 oral leukoplakias examined histologically, 35 lesions in 29 patients (6 occurred bilaterally) were biopsied from clinical changes resembling speckled type of leukoplakias. Table III gives information as to location of the lesions. The commissures were the sites for the lesions in almost two-thirds of the cases. The average age of the patients was 54 years and 59 per cent were men.

The clinical appearance of the leukoplakias revealed the same basic pattern in all patients. The affected mucosa showed the presence of white patches, sometimes nodules, on an erythematous background. This simultaneous occurrence of white and red

Table III. Location of speckled type of leukoplakia.

Location of Speckled Leukoplakia	Number
Commissures	23
Alveolar sulcus	4
Alveolar process	1
Dorsum of tongue	2
Buccal mucosa	2
Floor of mouth	2
Palate	1
Total	35

areas endowed the lesions with a speckled appearance, Figure 4, A--F.

The histologic sections of these 35 lesions were evaluated with regard to hyperorthokeratosis, hyperparakeratosis, epithelial hyperplasia, atrophy, epithelial atypia and carcinoma. Epithelial atypia is a histologic term used to designate an epithelium that displays premalignant characteristics. Epithelial atypia is featured by a disorderly maturation of the epithelium. The changes comprise one or more of the following features: irregular epithelial stratification, increased density of the basal layer or spinal cell layer or both, thickening of the basal cell layer, increased number of mitotic figures, alterations in the nuclear-cytoplasmic ratio, loss of polarity of cells, hyperchromatism and nuclear atypism, Figure 1, A--B. Abnormal mitoses are never observed in epithelial atypia and the basement membrane is always intact.

In 5 (14 %) of the 35 lesions of the speckled type leukoplakia, the histologic findings revealed a carcinoma. Eighteen (51 %) of the lesions showed histologically the occurrence of epithelial atypia. The histologic examination disclosed, in all 35 cases of the speckled type leukoplakia, a simultaneous occurrence of hyperparakeratosis, epithelial hyperplasia and epithelial atrophy, Figure 2, A--B. All biopsies revealed inflammatory reactions in the connective tissue.

Cytologic scrapings were obtained from 5 patients with speckled type leukoplakia. Smears from two of these patients showed nuclear changes that were interpreted as suspicious for malignancy, Figure 3, A—B. Histopathologic sections from both of these patients demonstrated epithelial atypia. The smears from the other three patients yielded nucleated cells which showed no abnormalities except for increased cytoplasmic acidophilia. The morphologic appearance of these cells was consistent with the tissue sections, which showed normal individual cellular characteristics superimposed on a maturation pattern of hyperplasia, atrophy and hyperparakeratosis.

DISCUSSION

While the majority of investigators have not been able to correlate the histologic changes with the clinical aspects of leukoplakias, as pointed out by *Silverman, Renstrup & Pindborg*, 1963, a few authors (*Rotter*, 1957, *Sharp*, 1948, *Hahn*, *Morgenroth & Themann*, 1961) are of the opinion that verrucous leukoplakias are often associated with epithelial atypia. Other authors (*Ackermann & Johnson*, 1952 and *Shafer & Waldron*, 1961) have emphasized that leukoplakic lesions exhibiting a pinkish-gray or a red granular appearance are often associated with carcinoma in situ. The present investigation confirms the point of view that leukoplakias characterized by the presence of white patches, either in a nodular form or as more diffuse, white lesions interspersed with erythematous areas, are often associated with epithelial atypia or carcinoma. Therefore, the speckled type of oral leukoplakia should be excised or followed with the utmost care. A great number (Table III) of the speckled type leukoplakia was located to the commissures. This is remarkable, as the latter location is not a common site for oral carcinomas.

Since exfoliative cytology has proved to be a reliable reflector of abnormal cellular changes, it should be utilized as an adjunct to clinical observations and biopsies, *Silverman & Ware*, 1960. This is particularly emphasized because of the innocuous appearance of some of these speckled-type lesions, which may not encourage frequent or adequate follow-up biopsies.

In the oral cavity, the majority of the lesions with epithelial atypia are speckled leukoplakias clinically. In the uterine cervix, however, which possesses an epithelial structure similar to that of the oral mucosa, epithelial atypia is not associated with leukoplakic changes. Here, the clinical picture is one of erosion or normally looking mucosa.

According to *Schiller*, 1938, leukoplakias on the cervix, which histologically show either hyperorthokeratosis or hyperparakeratosis are not related to the genesis of cervical carcinoma. However, *Friedell*, 1960 has reported one cervical leukoplakia exhibiting foci of early invasive grade I squamous cell carcinoma. Moreover, all gradations of epithelial atypia may be seen in biopsies of clinical leukoplakia on collum uteri.

SUMMARY

The literature is reviewed with regard to prevalence figures for malignancy and malignant transformation of oral leukoplakias (Tables I and II). In a material of 185 oral leukoplakias, 35 lesions revealed a picture of white, nodular patches intermingled with erythematous areas (a speckled appearance). 51 % of these cases were associated with epithelial atypia and 14 % with carcinoma.

RÉSUMÉ

ÉTUDES SUR LES LEUCOPLASIES BUCCALES

V. SIGNES CLINIQUES ET HISTOLOGIQUES DE MALIGNITÉ

Les auteurs passent en revue la littérature concernant les images de malignité et de transformation maligne des leucoplasies buccales (Tableaux I et II). Sur 185 cas de leucoplasies buccales, les lésions présentaient dans 35 des cas la configuration de plaques nodulaires blanches entremêlées à des zones érythémateuses (aspect moucheté). Ces cas étaient associés à un épithélium atypique dans la proportion de 51 % et à un carcinome dans la proportion de 14 %.

ZUSAMMENFASSUNG

UNTERSUCHUNGEN VON LEUKOPLAKIEN DER MUNDSCHLEIMHAUT
V. KLINISCHE UND HISTOLOGISCHE MALIGNITÄTSANZEICHEN

Es wird eine Übersicht gegeben über das Schrifttum im Hinblick auf Frequenzangaben der Malignität und der bösartigen Entartung von Leukoplakien der Mundschleimhaut (Tabellen I und II).

Aus einem Material von 185 Leukoplakien der Mundschleimhaut zeigten 35 ein Bild von weissen, knotigen Flecken mit eingemischten erythematösen Bereichen (ein 'fleckiges' Aussehen). 51 % der Fälle wiesen Epithelatybie und 14 % die Entstehung von Karzinomen auf.

REFERENCES

- Ackermann, L. V. & R. Johnson*, 1952: Present-day concepts of intraoral histopathology. Proc. 2nd nat. Cancer Conf. Vol. 1: 403—414.
- Bredy, E.*, 1955: Beitrag zur Kenntnis der Leukoplakie der Mundhöhle. Dtsch. Stomat. 5: 88—96.
- Friedell, G.*, 1960: Tumors of the female sex organs. Atlas of Tumor Pathology, Section IX, Fascicle 33, p. 99.
- Haase, G.*, 1931: Zur Kenntnis der Leukoplakia oris und der Lippen- und Zungenkrebses bei Rauchern. Dtsch. Mschr. Zahnheilk, 49: 881—913 and 929—976.
- Hahn, W., K. Morgenroth & H. Themann*, 1961: Pre-cancerous changes in the oral cavity. Int. dent. J. 11: 343—362.
- Hobwk, A.*, 1946: Leukoplakia oris. Acta odont. scand. 7: 61—91.
- King, H. & C. M. Hamilton*, 1931: Leukoplakia buccalis: A study of eight cases. Sth. med. J. (Bgham, Ala.) 24: 380—383.
- Leonardelli, G. B. & F. Talamazzi*, 1950: Leucoplasie del cavo orale e pre-cancerosi, Nota I. Arch. ital. Otol. 61: 107—114.
- McKown, J. L., Jr.*, 1949: Leukoplakia, a pre-cancerous condition, statistical analysis of 100 cases. Bull. U. S. Army med. Dep. 9: 620—623.
- Renstrup, G.*, 1958: Leukoplakia of the oral cavity. A clinical and histopathologic study. Acta odont. scand. 16: 99—111.
- Rotter, W.*, 1957: Zur speziellen Pathologie der Tumoren der Mundhöhle. Dtsch. zahnärztl. Z. 12: 161—171.
- Schiller, W.*, 1938: Leukoplakia, leucokeratosis and carcinoma of the cervix. Amer. J. Obstet. Gynec. 35: 17—38.
- Shafer, W. G. & C. A. Waldron*, 1961: A clinical and histopathologic study of oral leukoplakia, Surg. Gynec. Obstet. 112: 411—420.

- Sharp, G. S.*, 1948: Cancer of the oral cavity. *Oral Surg.* 1: 614—631.
- Silverman, S., Jr., G. Renstrup & J. J. Pindborg*, 1963: Studies in oral leukoplakias. III. Effects of vitamin A, comparing clinical, histopathologic, cytologic and hematologic responses. *Acta odont. scand.* 21: 271—292.
- Silverman, S., Jr. & W. H. Ware*, 1960: Comparisons of histologic, cytologic, and clinical findings in intraoral leukoplakia and associated carcinoma. *Oral Surg.* 13: 412—422.
- Skach, M., Svoboda & K. Kubat*, 1960: Príspevek k problému leukoplakie. *Acta Univ. Carol. Ser. Med. Suppl.* 10: 363—371.
- Sovadina, M.*, 1955: Ad Leukoplacia oris. *Cs. Stomat.* 55: 116—120.
- Sturgis, S. N. & C. C. Lund*, 1934: Leukoplakia buccalis and keratosis labialis. *New Engl. J. Med.* 210: 996—1006.
- Sugar, L. & J. Bánóczy*, 1959: Untersuchungen bei Präkanzerose der Mundschleimhaut. *Dtsch. Zahn-, Mund- u. Kieferheilk.* 30: 132—140.
- Weisberger, D.*, 1957: Precancerous Lesions. *J. Amer. dent. Ass.* 54: 507—508.
- Winiker-Blanck, E.*, 1961: Die Leukoplakia oris als Präkanzerose. *Dtsch. Stomat.* 11: 368—373.

Address: *Dr. J. J. Pindborg*
4, *Universitetsparken*
Copenhagen Ø, Denmark.