ORAL CANCER BACKGROUND PAPERS

Chapter IV: Premalignant Lesions

Working Draft

Introduction

Classification schemes for lesions of the oral cavity typically have used the clinical appearance of lesions to determine which are premalignant.[1] Leukoplakia and erythroplakia are two clinical lesions widely considered to be premalignant. However, using clinical features to classify lesions is difficult because they vary in appearance and are likely to be interpreted subjectively by the clinician. A histopathologic diagnosis is generally more indicative of premalignant change than clinically apparent alterations.

A. State of the Science

Clinical Lesions Associated with Premalignancy

Leukoplakia

The term *leukoplakia* is sometimes used inappropriately to indicate a premalignant condition. In fact, the term describes a white plaque that does not rub off and cannot be clinically identified as another entity. Most cases of leukoplakia are a hyperkeratotic response to an irritant and are asymptomatic, but about 20% of leukoplakic lesions show evidence of dysplasia or carcinoma at first clinical recognition.[1] However, some anatomic sites (floor of mouth and ventral tongue) have rates of dysplasia or carcinoma as high as 45%. There is no reliable correlation between clinical appearance and the histopathologic presence of dysplastic changes except that the possibility of epithelial dysplasia increases in leukoplakic lesions with interspersed red areas. In one large study,[2] lesions with an erythroplakic component had a 23.4% malignant transformation rate, compared with a 6.5% rate for lesions that were homogeneous. The term *erythroleukoplakia* has been used to describe leukoplakias with a red component.

Erythroplakia

An *erythroplakia* is a red lesion that cannot be classified as another entity. Far less common than leukoplakia, erythroplakia has a much greater probability (91%) of showing signs of dysplasia or malignancy at the time of diagnosis.[3] Such lesions have a flat, macular, velvety appearance and may be speckled with white spots representing foci of keratosis.

Lichen planus

The premalignant or malignant potential of *lichen planus* is in dispute. Some believe that the occasional epithelial dysplasia or carcinoma found in patients with this relatively common lesion may be either coincidental or evidence that the initial diagnosis of lichen planus was erroneous.[4] It is frequently difficult to differentiate lichen planus from epithelial dysplasia; one study found that 24% of oral lichen planus cases had 5 of the 12 World Health Organization (WHO) diagnostic criteria for epithelial dysplasia, and only 6% had no histologic features suggestive of that disorder.[5] However,

as many reports on lichen planus patients followed over time indicate a higher than expected rate of malignant transformation,[6] it is prudent practice to biopsy the lesion at the initial visit to confirm the diagnosis and to monitor it thereafter for clinical changes suggesting a premalignant or malignant change.

Other Lesions

Premalignant changes arising in other oral lesions are uncommon. White lesions such as linea alba, leukoedema, and frictional keratosis are common in the oral cavity but have no propensity for malignant transformation. The health professional can usually identify them by patient history and clinical examination.

Clinical Features of Oral Premalignancy

A diagnostic biopsy should be considered for any mucosal lesion that persists for more than 14 days after obvious irritants are removed; simply noting the clinical appearance or presentation of a lesion is not enough to determine premalignant changes. The following overview describes clinical features generally but is insufficient to identify premalignancy in a specific patient.

Anatomic Location

Studies relating premalignant tissue changes to anatomic sites have produced varying results. One study found that 21.8% of oral epithelial dysplasias occurred on the buccal mucosa, 13.7% on the palate, and 12.3% on the floor of the mouth.[7] A study of leukoplakia by Shafer and Waldron[8] found that the mandibular mucosa and sulcus were involved in 25.2% of their cases and on the buccal mucosa in 21.9%. Because many oral premalignancies present as leukoplakias, the similar findings are not unexpected. Interestingly, the distribution of locations is much different from that of squamous cell carcinomas of the oral cavity, for which the tongue, oropharynx, lip, and floor of mouth are the most common sites.[9] Perhaps there is a subset of epithelial dysplasias, such as those that occur on the buccal mucosa, that have a lower rate of malignant transformation than those found at other sites.

Age

The mean age at diagnosis of oral premalignancy is 50-69; less than 5% of diagnoses are in patients under 30 years of age.[7,10,11] Thus, the aging process itself is the greatest risk factor for premalignant and malignant changes.

Sex

Studies have shown that epithelial dysplasia has a predilection for males, but the decrease in the male:female ratio for oral squamous cell carcinoma suggests the picture may be changing.[7,10,11] This may be due to increased use of tobacco and alcohol among women (see Chapter I).

Clinical Appearance

Although most premalignant lesions are white (leukoplakia), they vary considerably in their initial presentation. These lesions are usually asymptomatic; the development of pain or soreness may be associated with a malignant change.

Probability of Malignant Change

About 5-18% of epithelial dysplasias become malignant.[7,11,12] Although expecting a greater probability of malignant change for dysplasias with a greater histologic degree of epithelial dysplasia seems intuitive, that relationship is hard to prove because only a few cases of epithelial dysplasia have been diagnosed but not excised, then monitored to see whether malignant change occurred. A greater risk of malignant change in an epithelial dysplasia has been associated with the following factors: (1) erythroplakia within a leukoplakia, (2) a proliferative verrucous appearance, (3) location at a high-risk anatomic site such as the tongue or floor of mouth, (4) the presence of multiple lesions, and, paradoxically, (5) a history of not smoking cigarettes.[2]

Transition Time from Epithelial Dysplasia to Malignancy

Although most oral carcinomas have adjacent areas of epithelial dysplasia, some carcinomas may not evolve from epithelium with top-to-bottom dysplastic changes but rather arise from basilar keratinocytes. Silverman and colleagues[2] monitored 257 patients with oral leukoplakia; 22 had a diagnosis of epithelial dysplasia, the remaining 235, hyperkeratosis. Eight of the 22 (36.4%) with epithelial dysplasia developed carcinoma. Of the 107 patients with a homogeneous leukoplakic lesion and a diagnosis of hyperkeratosis, 7 (6.5%) developed carcinoma. However, 30 (23.4%) of the 128 patients with erythroplakic lesions and a diagnosis of hyperkeratosis were eventually diagnosed with carcinoma. The time from initial diagnosis of either epithelial dysplasia or hyperkeratosis to carcinoma ranged from 6 months to 39 years. In another study, reported by Lumerman and colleagues,[11] 7 (15.9%) of 44 patients with oral epithelial dysplasia identified in a biopsy service developed carcinoma; mean time from biopsy to cancer diagnosis was 33.6 months.

Epithelial dysplasia has been more extensively studied in association with the uterine cervix than with the oral cavity. Based on clinical reviews, approximately 12% of cervical epithelial dysplasias progress to carcinoma in situ.[13] The estimated median time for this progression depends on the histologic severity of the epithelial dysplasia: 58 months for mild, 38 months for moderate, and 12 months for severe.[14] Approximately 73% of carcinoma in situ cases evolve into full-blown carcinoma.[15] How important this information is for understanding progression to oral cancer is unclear, but it is consistent with observations that not all oral epithelial dysplasias evolve into carcinoma in situ or full-blown carcinoma and that this transition—when it does occur—takes months or years.

Diagnosis

Verifying the premalignant status of an oral lesion requires a biopsy. However, there is a noninvasive clinical test—the topical application of toluidine blue to a suspicious area—that helps identify the

presence of dysplastic or carcinomatous lesions.[16] Mashberg and Samit reported that proper use of toluidine blue yielded false-positive and false-negative rates less than 10%;[17] the agent is believed to bind selectively to the DNA and RNA in cells. Clinicians can use toluidine blue to help identify lesions more likely to have premalignant or malignant changes, select an appropriate biopsy site within a large lesion, or monitor high-risk patients who have been previously diagnosed with a premalignant or malignant lesion. They must still exercise clinical judgment, however, when evaluating the results of the toluidine blue stain. In almost all cases in which they encounter an unexplained leukoplakic or erythroplakic lesion, they should perform a biopsy to diagnose the patient. Toluidine blue is an adjunct to biopsy, not a replacement for it.

Histopathologic Diagnosis

Defining "epithelial dysplasia" as an entity with histologic abnormalities suggests that the lesion has a greater probability of undergoing malignant change than does normal tissue. However, histopathologic diagnosis reflects cellular changes that are visibly apparent but does not necessarily predict biologic behavior. The histomorphologic changes of epithelial dysplasia consist of the following:[18]

- Loss of basal cell polarity
- Parabasilar hyperplasia
- Increased nuclear:cytoplasmic ratio
- Drop-shaped rete ridges
- Abnormal epithelial maturation
- Increased mitotic activity
- Mitoses in the superficial half of the surface epithelium
- Cellular pleomorphism
- Nuclear hyperchromaticity
- Enlarged nucleoli
- Loss of cellular cohesiveness
- Individual cell keratinization in the spinous cell layer.

Usually, the diagnosis of epithelial dysplasia indicates that most of these factors are present; but rarely does one lesion have all of them. The histologic grade reflects the degree of involvement: mild cases of epithelial dysplasia are those in which changes are seen within the lower third of the epithelium; moderate cases, those in which at least half the epithelium is involved; and severe cases, those in which most of the epithelium is affected. Carcinoma in situ is similar in appearance to severe epithelial dysplasia, and some authorities do not attempt to distinguish between the two. Perhaps fewer than 20% of oral epithelial dysplasias are severe.[7,10,19]

Hyperkeratosis is an increased thickness of the parakeratin or orthokeratin layer of the epithelium. Interestingly, most epithelial dysplasias show parakeratinization, which might reflect cellular

immaturity. Although most solid tumors and hematologic malignancies are monoclonal in origin, in the oral mucosa it is not uncommon to histologically identify multiple foci of dysplastic change separated by normal cell fields.

Treatment

Surgical excision, which can be accomplished with a scalpel or a CO_2 laser,[20,21] is the treatment of choice for epithelial dysplasia of the oral cavity. The laser provides a relatively bloodless surgical field and in one report actually reduced recurrences.[20,21] However, to date neither technique has been shown to be better than the other in preventing recurrence. Once an incisional biopsy has established the diagnosis of epithelial dysplasia, the remainder of the lesion should be removed completely, as the probability of malignant change, although unknown, must be considered substantial.

Reported recurrence rates for premalignant lesions are as high as 34.4%.[2] One study found an 18% recurrence rate in cases of severe epithelial dysplasia or carcinoma in situ in which the lesion had been excised with a 3-5 mm margin of normal tissue.[22] Whether recurrence relates to continued exposure to risk factors or to an underlying mechanism that initiated the original lesion is unclear, but patients should be closely monitored for recurrence regardless.

The hyperkeratotic lesion is difficult to manage because it has potential for malignant change but is not yet considered dysplastic; Silverman and colleagues found that 37 out of 235 hyperkeratotic lesions (15.7%) underwent malignant change.[2] As a first step, the clinician should remove any local irritants. If after 2 weeks the hyperkeratosis is still present, excision should be considered, especially if the lesion is in a high-risk site (e.g., floor of mouth and ventral tongue) or if the patient has been exposed to established risk factors for oral cancer.

Chemoprevention

If the size of the lesion, its location, or the medical status of the patient would make surgical removal difficult, use of antioxidant supplements should be considered as "chemoprevention" to try to prevent progression to carcinoma.[23,24] Beta-carotene and the retinoids are the most commonly used antioxidant supplements for chemoprevention of oral cancer.[25] However, although antioxidant supplements have shown promise, they have an uncertain success rate and no long-term results. Still, antioxidant supplementation may be appropriate if there is recurrence after surgical excision but concern that a second excision would not prevent another recurrence. Patients with leukoplakia involving a large area of the oral mucosa might also be candidates for antioxidants, as might patients with extensive medical problems that increase their surgical risk.

Beta-carotene is a carotenoid found primarily in dark green, orange, or yellow vegetables. Several clinical trials have found that treating oral leukoplakia solely with beta-carotene supplements is associated with clinical improvement; rates have ranged from 14.8% to 71%.[26-30] No side effects have

been reported in patients given beta-carotene supplements; but there is little information about recurrence following discontinuation of this substance.

Retinoids are compounds consisting of natural forms or synthetic analogues of retinol.[31] Of the more than 1,500 synthetic analogues of vitamin A, 13-*cis*-retinoic acid (13-cRA), also known as isotretinoin or Accutane®, has generated the most interest. 13-cRA has been shown to cause temporary remission of oral leukoplakia, but it also causes side effects in a high percentage of patients. A study at M.D. Anderson Hospital in Houston followed 44 patients with oral leukoplakias who were treated with 1-2 mg/kg/day of 13-cRA for 3 months;[32] nearly 67% of the patients had more than a 50% reduction in lesion size, but 79% experienced a variety of side effects. Other studies have noted that lowering the 13-cRA dose reduced the incidence and severity of side effects, but there have been numerous reports of recurrence after discontinuation. A rise in serum triglycerides has also been reported with use of 13-cRA.

To date, no combination of antioxidants has demonstrated its clear superiority. Beta-carotene with ascorbic acid and/or alpha tocopherol is attractive because of a lack of side effects, but clinical improvement typically takes several months. 13-cRA requires a shorter time to produce a clinical response, but use of this substance necessitates baseline and periodic serologies and close monitoring for side effects; women using it must also avoid becoming pregnant.

B. Emerging Trends

Many human papillomaviruses (HPVs) are associated with papillary and verrucous lesions of skin and mucous membranes. HPV types 16 and 18 present in 90% of cervical carcinomas, and the E6 and E7 early gene products of these viruses are considered to be oncogenes, as they can transform heratinocytes in cultures.[33,34] The E6 and E7 oncoproteins are able to bind the p53 tumor suppressor protein, facilitate its degradation, and inhibit normal apoptotic pathways in these cells; the last feature may favor overproliferation.[35,36] Mutations in p53 are also found in many tumors.

Oncogenic HPVs have been identified in many oral precancerous dysplastic and squamous carcinoma tissues; HPV 16 has been localized in normal oral mucosa as well.[37-44] In an investigation of head and neck squamous cancers using polymerase chain reaction (PCR) methods, over 80% were found to harbor HPV 16.[45] Mutations in p53 are also prevalent in both precancerous and overtly malignant oral tumors.[46-48] However, both determining the role these gene products and other oncogenes play in oral cancer causation and understanding their interplay with other carcinogens such as tobacco products require further investigation.

Finally, identifying an accurate biomarker for the premalignant state would aid in diagnosis and also allow premalignancy rather than carcinoma to be an endpoint in clinical trials.[49] Discovery of a

biomarker to identify those lesions likely to progress to cancer would represent a considerable advancement in patient care.

C. Opportunities and Barriers to Progress

Research opportunities include the following:

- Validating histopathologic criteria or biomarkers that would accurately identify premalignant lesions and those with an enhanced propensity for malignant change.
- Identifying the clinical factors of premalignancy that predict a higher probability of malignant change.
- Clarifying the premalignant risk of lichen planus.
- Comparing the efficacy of conventional scalpel excision with laser excision for control of oral leukoplakias.
- Determining the value for prevention of malignant transformation of completely removing hyperkeratotic lesions.
- Establishing the role of chemoprevention in the primary and/or adjunctive treatment of oral premalignancy.
- Clarifying the role of HPV in the development of oral premalignancy and determining whether presence of the virus has prognostic significance.
- Identifying specific biomarkers such as oncogenes, tumor suppressor gene mutations, cell cycle proteins, or DNA transcription factors that could provide both useful prognostic information on oral carcinogenesis, as well as guidance on where to set margins for surgical excision.

To achieve further progress, a substantial number of suitable patients must be brought together under a unified protocol so that histopathologic, clinical, and treatment factors can be properly evaluated. At present, the small number of suitable patients are divided among numerous centers.

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