Premalignant Conditions of the Oral Cavity

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Overview

Oral cavity cancer accounts for approximately 3% of all malignancies and is a significant worldwide health problem.[1, 2] Most oral malignancies occur as squamous cell carcinomas (SCCs); despite remarkable advances in treatment modalities, the 5-year survival rate has not significantly improved over the past several decades and still hovers at about 50-60%.[3]

Many oral SCCs develop from premalignant conditions of the oral cavity.[4, 5] A wide array of conditions have been implicated in the development of oral cancer, including leukoplakia, erythroplakia, palatal lesion of reverse cigar smoking, oral lichen planus, oral submucous fibrosis, discoid lupus erythematosus, and hereditary disorders such as dyskeratosis congenital and epidermolysis bullosa.[6]

Despite the general accessibility of the oral cavity during physical examination, many malignancies are not diagnosed until late stages of disease. In order to prevent malignant transformation of these precursor lesions, multiple screening and detection techniques have been developed to address this problem. The early detection of cancer is of critical importance because survival rates markedly improve when the oral lesion is identified at an early stage.[3]

Epidemiology

Much of the published information describing the prevalence of potentially malignant disorders varies by geographic location and population studied. Despite this limitation, a generally accepted prevalence rate ranges between 1% and 5%.[7] Most affected patients are middle-aged or elderly men. Potentially malignant disorders are discovered most commonly on the buccal mucosa, lower gingiva, tongue and floor of mouth, with the remaining cases distributed throughout the remainder of the oral cavity.[7]

Oral cancer accounts for approximately 3% of all malignancies in the United States, and approximately 25,000-30,000 cases of oral cancer are diagnosed each year.[8] In addition, oral cancer is one of the most common malignancies in Southeast Asia, accounting for up to 30-40% of all malignancies in India.[9] Oral cancer occurs most commonly in middle-aged and elderly individuals; however, recent evidence suggests these demographics may be changing.

Surveillance Epidemiology and End Results (SEER) data demonstrated an increase in the incidence of tongue cancer in young individuals (< 40 years old), from 3% in 1973 to approximately 6% in 1993, and many of the affected individuals are without traditional risk factors.[9] Additionally, research indicates that the traditional male

predominance is less overt in young individuals with oral SCC. This trend is thought to be a reflection of the general acceptance of social habits such as smoking and drinking by both sexes.[9]

Tobacco-related disease is a prevalent source of death in African American men. A recent study in rural Alabama showed that cigarettes are the most-used tobacco product in that area, with marijuana as the second most-used product. Additionally, participation in education and religion lead to a decrease in tobacco use amongst this particular demographic.[10]

Risk Factors and Pathophysiology

The use of tobacco has been well established as a significant risk for the development of oral squamous cell carcinoma (SCC) and premalignant lesions. Up to 80% of patients with oral SCC have used tobacco products,[11] and the risk of developing malignancy is 5-9 times greater for smokers than nonsmokers.[12, 13]

Alcohol use has also been implicated as a risk factor for the development of oral SCC and premalignant lesions. Although not uniformly accepted to have a role in the development of oral cancer, studies have shown that moderate to heavy drinkers have a 3-9 times greater risk of developing cancer.[14] In fact, the heavy use of alcohol and tobacco combined may convey a risk greater than 100 times the general population.[15]

The role of human papillomavirus (HPV) in the development of oral premalignant disorders and SCC continues to undergo investigation. HPV types 16 and 18 may be found in approximately 22% and 14% of oropharyngeal tumors,[16] and a recent study demonstrated HPV DNA in 17.6% of oral leukoplakic lesions and 19.7% of oral lichen planus samples.[17] Although evidence substantiating the role of HPV in oropharyngeal tumors is more definitive, the implication of the presence and integration of HPV in oral cavity lesions requires further clarification.[18]

Despite the association between tobacco and alcohol and the development of persistent oral lesions, a definitive etiology is seldom identified in many of these lesions. In addition, the lack of distinctive histopathologic features in many of the potentially malignant disorders supports the multifactorial pathogenesis of these lesions.

Terminology and Definitions

The World Health Organization classifies oral precancerous/potentially malignant disorders into 2 general groups, as follows:[19]

- A precancerous lesion is “a morphologically altered tissue in which oral cancer is more likely to occur than its apparently normal counterpart.” These precancerous lesions include leukoplakia, erythroplakia, and the palatal lesions of reverse smokers.
- A precancerous condition is “a generalized state associated with significantly increased risk of cancer.” The precancerous conditions include submucous fibrosis, lichen planus, epidermolysis bullosa, and discoid lupus erythematous.

Premalignant Lesions

Leukoplakia

The term leukoplakia describes a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.[19] The precise definition of leukoplakia continues to undergo refinement in an attempt to distinguish benign from premalignant lesions, and leukoplakia remains a clinical diagnosis of exclusion. Leukoplakia occurs most often in middle-aged and older men and arises most frequently on the buccal mucosa, alveolar mucosa, and lower lip.

However, note that lesions arising on the floor of mouth, lateral tongue, and lower lip are the most likely to harbor dysplasia or progress to malignancy.[20] The rate of progression to malignancy has been reported to be between 3.6% and 17.5%,[5, 21] and as many as 19.9% of leukoplakic lesions may demonstrate some degree of dysplasia, with 3.1% showing frank carcinoma.[20] Please see the Medscape Reference article Oral Leukoplakia for further discussion.

Erythroplakia

Erythroplakia is a clinical term used to describe a fiery red patch that cannot be clinically or pathologically distinguished as any other definable disease.[22] Similar to leukoplakia, the erythroplakic lesion is considered as a diagnosis of exclusion because numerous other disease entities must be excluded before erythroplakia is considered as the diagnosis. The clinical appearance of erythroplakia is described as a red macule or patch with a soft, velvety texture most often occurring on the floor of mouth, lateral tongue, retromolar pad, and soft palate.[14]

Although far less common than leukoplakia, erythroplakia is a worrisome clinical condition that often harbors dysplasia. Upon histological analysis, 51% of erythroplakic lesions have been shown to demonstrate invasive squamous cell carcinoma (SCC), with 40% demonstrating carcinoma in situ, and 9% exhibiting mild-moderate dysplasia.[23]

Proliferative verrucous leukoplakia

Proliferative verrucous leukoplakia (PVL) is a unique form of aggressive disease considered to be within the continuum of leukoplakia and erythroplakia. Most patients with PVL are women, and many do not have a history of tobacco use. PVL generally appears on the oral mucosa as an irregular white patch or plaque with a varying surface. The disease is often characterized by resistance to treatment, recurrence, multifocal proliferation, and a progression to carcinoma in up to 87% of patients.[24]

Palatal lesion of reverse smokers

The palatal lesion of reverse smokers is unique to individuals who place the lit end of a cigarette inside the mouth. The resulting palatal lesion may appear clinically as a red, white, melanotic patch or papule. Up to 84% of palatal lesions have been demonstrated to harbor dysplasia upon histologic analysis.[25]

Premalignant Conditions

Oral submucous fibrosis

Oral submucous fibrosis (OSF) is a chronic progressive condition found predominantly in people of Asian decent. OSF is considered to be the result of the use of the Areca nut product with resultant disruption of the extracellular matrix. The disease often manifests with diffuse involvement of the oral cavity, pharynx, and upper esophagus that appears clinically as whitish mucosa lacking elasticity. Epithelial dysplasia has been described in 7-26% of OSF tissues, and long-term studies suggest a malignant transformation rate in approximately 7% of these lesions.[26]

Lichen planus, discoid lupus erythematous, and epidermolysis bullosa

Although classified as potentially malignant conditions, the data regarding progression to malignancy for these conditions is controversial. Because of the difficulty in classifying and clinically distinguishing the varied lesions associated with these conditions, the potential for malignant transformation remains unclear.[6]

Relevant Anatomy and Physical Examinations

The oral cavity extends from the vermilion border of the lips to the junction of the hard and soft palates in the roof of the mouth superiorly, and to the circumvallate papillae on the tongue. The oral cavity consists of the lips, commissures, lingual tonsil, gums, floor of mouth, hard palate, buccal mucosa, and retromolar trigone, and most of the tongue with the exception of the base.

Although the oral cavity can be physically examined in a variety of approaches, a general examination should contain the following features:[1]

- Extraoral
    - Inspect the head and neck.
    - Palpate cervical lymph nodes and salivary glands.
- Lip: Inspect and palpate inner and outer surfaces of the upper and lower lip.
- Buccal mucosa
    - Inspect and palpate buccal mucosa and cheek.

    - Inspect and palpate parotid duct to express saliva.
- Gingival and alveolar ridge: Inspect and palpate gingival and alveolar ridge on facial and lingual aspects.
- Tongue
    - Inspect and palpate dorsal and ventral surfaces with accompanying retraction of the tongue with gauze.
    - Inspect and palpate lateral borders from anterior to posterior with manual retraction.
- Floor of the mouth
    - Inspect and palpate floor of the mouth.
    - Inspect and palpate submandibular ducts to express saliva.
- Hard palate: Inspect and palpate.
- Soft palate and oropharynx: Depress the dorsal surface of the tongue and inspect soft palate and anterior oropharynx.
- Salivary glands: Palpate the parotid, submandibular, sublingual, and minor salivary glands. Ensure clear salivary flow.

Work-up and the Early Detection of Oral Cancer

With the development and success of screening programs for breast, cervical, and colon cancer, the potential to reduce the morbidity and mortality of oral cancer through early detection modalities is of critical importance. Data indicates that the diagnosis of oral squamous cell carcinoma (SCC) at an early stage of disease allows for less aggressive treatment, improves quality of life, and improves the overall 5-year survival rate when compared with SCCs diagnosed at late stages.[3]

The criterion standard for diagnosis and identification of oral lesions is histopathologic analysis via the procurement of a tissue sample by surgical biopsy. Because of the invasive nature of surgical biopsy, early detection techniques are designed to provide a minimally invasive assessment of the malignant potential of the lesion that guides the approach to diagnosis and treatment of these lesions.

The approaches to the screening and detection of malignant and potentially malignant conditions have the potential to drastically alter the course of oral cavity disease but have yet to effectively reduce the overall morbidity and mortality of oral cancer. The major modalities designed to reduce this burden include oral cavity examination, supravital staining, oral cytology, chemoluminescent technique, and optical detection systems.

Oral cavity examination

The examination of the oral cavity has traditionally been the preferred approach for the detection of oral mucosal abnormalities. As a noninvasive technique, the oral cavity examination can be performed quickly, is without additional diagnostic expense to the patient, and may be performed by health care professionals across a multitude of disciplines.

The evidence regarding oral examination as an effective screening technique, however, remains controversial. In a recently published randomized clinical trial with nearly 130,000 participants, investigators concluded that the evidence to support or refute the use of oral examination as a screening program was insufficient. However, this study, performed by the “Kerala” group in India, demonstrated improved survival rates at 9 years among males with high-risk habits (tobacco use).[27] Although an increase in survival for the overall population was not seen, this study was the first to clearly support the efficacy of an oral cancer screening program in a high-risk population.

Supravital staining

Toluidine blue (TB) is an acidophilic dye designed to stain acidic cellular components such as DNA and RNA. Its use in the detection of precancerous/cancerous tissue is based on the fact that dysplastic tissue contains quantitatively more DNA and RNA than nondysplastic tissue. To perform the staining, a 1% solution is placed on the oral mucosa and removed after 1-2 minutes with 2% acetic acid. The clinician then examines the oral mucosa for areas of increased cellular staining.[28]

In the evaluation of potentially malignant oral lesions, TB staining may provide better demarcation of lesion margins, may guide biopsy site selection, and may be valuable in the identification and visualization of lesions in high-risk patients.[29, 30, 31] Although useful as an adjunct to clinical examination, the specificity of TB staining is limited because cells undergoing inflammatory changes and benign hyperplasia may also retain dye leading to false-positive results. Overall, the sensitivity of TB staining ranges from 0.78 to 1.00, and the specificity ranges from 0.31 to 1.00.[29]

Oral cytology

Oral cytology describes a diagnostic technique used to sample oral tissue for histomorphological analysis. To obtain a tissue sample, the clinician applies a stiff brush to the oral mucosa with enough pressure to induce pinpoint bleeding, which ensures a full-thickness or trans-epithelial tissue sample. These cellular samples can then be analyzed by a variety of unique diagnostic measures, including cytomorphometry, DNA cytometry, and immunocytochemical analysis.[28, 32]

Computerized image analysis of brush biopsy samples (OralCDx) uses a computer program to perform morphological and cytological analysis of tissue samples. The computerized analysis ranks cells based on the amount of abnormal morphology, which are then presented to a pathologist for further distinction and classification. The sensitivity of the OralCDx ranges from 0.71 to 1.00, and the specificity is as low as 0.32.[28]

DNA cytometry uses a DNA-specific Feulgen dye to quantify and identify deviations in DNA content in sampled tissue. Although data are still limited, the addition of DNA measurements to cytological analysis has been shown to increase the sensitivity and specificity of brush biopsies.[28]

The use of oral cytology in the detection of dysplastic lesions shows considerable promise but has been limited thus far by variable false-positive and false-negative results.[28, 29, 31, 32]

Chemiluminescent light

Chemiluminescent light based systems (ViziLite Plus, MicroLux DL) use the application of a diffuse chemiluminescent light source to visualize abnormal oral mucosa not visible under normal incandescent light. A 1% acetic acid oral rinse is used to remove surface debris and slightly desiccate the oral mucosa before direct examination with the light source. Under illumination, normal epithelium absorbs the light (appearing light blue) while abnormal tissue reflects the light (appearing white, with sharper, distinct margins). The ViziLite system then uses a toluidine blue stain to aid in further lesion assessment.

As of 2008, insufficient evidence supports the use of chemiluminescent light modalities in discovering pathology that would not have been identified using incandescent light alone. However, the potential ability to identify pathologic tissue not visible under conventional examination may support the use of chemiluminescent light as a screening technique.[28, 29, 31, 33, 34]

Tissue autofluorescence

Tissue autofluorescence describes the exposure of epithelial tissue to specific wavelengths of light that results in the excitation of cellular fluorophores and emission of energy in the form of fluorescence. With the disruption of normal tissue morphology in dysplastic lesions, tissue fluorescence is scattered and absorbed, resulting in characteristic alterations in color that can be visually interpreted.[35]

The VELscope is an early detection device based on these principles. Under excitation with the VELscope device, normal mucosa emits a pale green light, whereas abnormal mucosa appears dark. The initial evidence suggests that the VELscope may be useful as both an adjuvant method of margin determination during surgical procedures as well as a screening technique to identify premalignant lesions not visualized during conventional examination.[29, 31]

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