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Potentially Malignant Oral Lesions and Oral Cancer

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Potentially malignant oral lesions (PMOL) and oral cancer (OC) are alterations of the oral mucosa that can be encountered by the dentist during routine clinical examination. It is important for the dentist to identify these abnormalities, and appropriately manage/counsel the patient upon the significance of the finding. These conditions are very complex in nature and associated with difficulty in fully predicting their behavior. The dentist also plays an important role in public awareness of these disorders and by doing so, may change the long term outcomes for patients diagnosed with these conditions. This monograph will explore the epidemiology, etiology/risk factors, pathogenesis, diagnosis and finally management of these disorders. We will limit our scope to leukoplakia, erythroplakia, dysplasia, oral submucosal fibrosis, lichen planus, actinic cheilitis and oral squamous cell cancers; and focus on those inside the oral cavity, mindful that other defined oral diseases have the potential to convert to cancer.

Common Potentially Malignant Oral Lesions*

Leukoplakia [1,2,3,4,5]

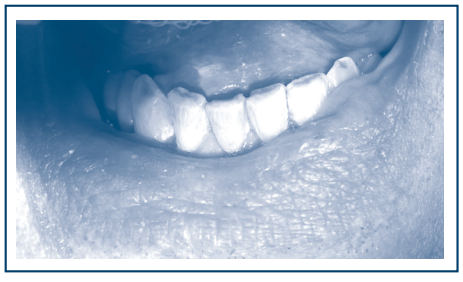

Figure 1: Leukoplakia

- Defined as a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer
- Very common oral finding
  - Approximately 8% of males over the age 70 will be affected by leukoplakia
  - Spontaneous regression is possible in some of the cases
- Risk of malignant transformation is approximately 5% to 17%
- Higher risk for non smokers, verrucous texture, mixed color and time
- Time related progression to malignancy is unclear
- Homogenous vs Non-homogenous
  - Homogenous white plaque less likely to transform to malignancy
  - Speckled white plaques with red component more likely to convert
  - Proliferative verrucal (warty appearance) variety is associated with a greater risk of malignant conversion
- Floor of mouth and posterior lateral tongue more likely to transform

Erythroplakia [3,4]

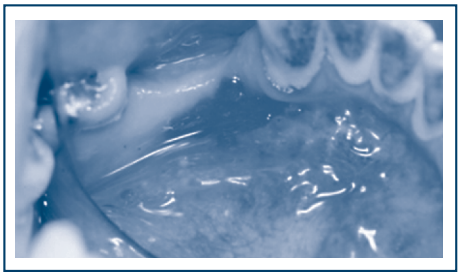

Figure 2: Erythroplakia

- Defined as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease
- Very high rate of malignant transformation
  - Risk of malignant transformation of erythroplakia is estimated to be 28%
- Often diagnosed as severe dysplasia or carcinoma when discovered

Dysplasia [3,4,5]

- Histologic description of the epithelium
- Described as mild, moderate or severe based on extent of epithelium involved
  - Mild dysplasia
    - Dysplastic cells are limited to the basal layer of the epithelium
  - Moderate/Severe dysplasia
    - Increasing cellular morphologic changes in increasing layers of epithelium
  - Carcinoma in situ
    - Abnormal cells involve the entire epithelium without invasion through the basement membrane

** Potentially malignant lesion as defined by WHO is morphologically altered tissue in which cancer is more likely to occur[1].*

- Carcinoma
  - Disruption of the basement membrane and invasion into connective tissue
- Presence of dysplasia implies an increased risk of malignant transformation
- Not all dysplastic lesions become malignant; not all non dysplastic lesions will remain benign
- Severe dysplasia has a high potential to transform to malignancy

Oral Submucosal Fibrosis [6]

- Associated with Betel/Areca nut usage
- Clinically associated with trismus from mucosal scarring
- High risk of malignant transformation

Oral Lichen Planus [7,8,9]

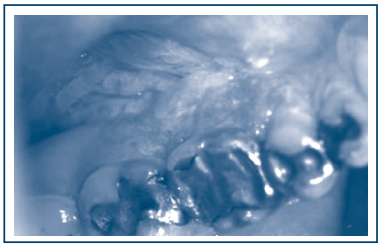

Figure 3:
Oral Lichen Planus

- Very common mucocutaneous disease affects 0.5%-2.2% of the population
- Various appearances including ulcerative, plaque like, atrophic, and reticular
- Plaque like and ulcerative may have higher transformation rate
- Rate of malignant transformation estimated at 0.04%-1.74%

Actinic Cheilitis [10]

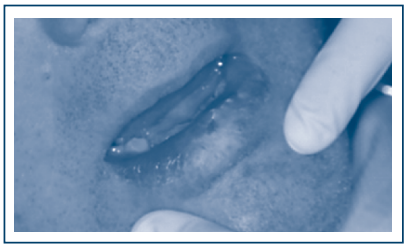

Figure 4:
Actinic Cheilitis

- Associated with solar UV light to lip
- Clinically resembles non-healing chapped lips and often associated with ulceration, erythema and thickened texture
- Variable risk of malignant transformation

Epidemiology of Oral Cancer [8,11,12]

- Over 40,000 new cases of oral and oropharyngeal cancer annually in the United States
- ~ 8000 deaths annually
  - More common than, esophageal, stomach, brain, and liver
- Overall 5 year survival rate approximately 60%
- Mortality rate: only slight improvement over past several decades
- Accounts for 3% of the approximately 1 million new cancers diagnosed per year in the United States
- Males 3% of total body cancers
- Females 2% of total body cancers
- Majority of cases occur in patients over 40 years old - average age of diagnosis is 60 years old
- Male: Female 2:1
- Increased incidence in younger individuals emerging due to HPV

Etiology [11,12]

- Accumulation of genetic changes from exposure to initiators and promoters without adequate DNA repair.
- Risk Factors include:
  - Tobacco
  - Using smokeless tobacco, including snuff and chewing tobacco
  - Alcohol
  - Combined use of tobacco and alcohol are associated with an increased risk of more than 30-fold
  - Human Papilloma Virus (HPV) - especially HPV Type 16
  - Immunosuppression/being immunologically compromised (e.g., after bone-marrow transplantation)
  - Increased age
  - Chewing betel quid, areca nut and paan
  - Fanconi's anemia
  - History of prior oral or oropharyngeal cancer

Clinical Presentation [11,12]

- Majority of oral cancers involve the following sites:
  - Tongue
  - Oropharynx
  - Floor of mouth
- Dysplasia more prevalent:
  - Tongue
  - Lips
  - Floor of mouth
- Symptoms
  - Precancerous and early cancerous lesions have no distinctive clinical features and are rarely associated with symptoms
- Prognosis
  - TNM system of cancer classification used for staging
    - Higher the stage - prognosis decreases (EXCEPT with HPV positive tumors)
  - OC occurring in the posterior aspect of the oral cavity and oropharynx is typically associated with a poorer prognosis
  - Incidence of spread is influenced by tumor size

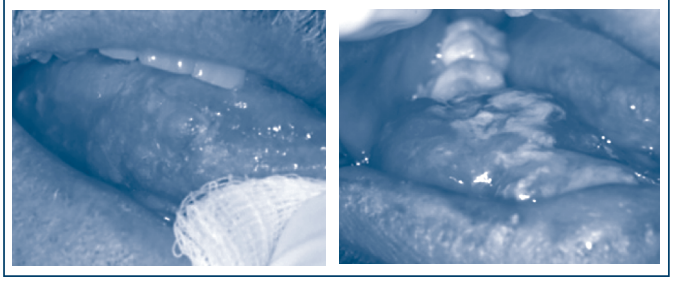

Figure 5 & 6: (Left) Squamous cell carcinoma of right lateral border of the tongue. (Right) Squamous cell carcinoma of right alveolar ridge.

- Localized tumors of the oral cavity and pharynx have an overall survival rate of 70-95%
- Patients with distant metastases demonstrated an overall survival rate of 33%

Pathogenesis [13,14,15]

- Multistage process that does not seem to follow a linear progression pattern
- Several potential markers of molecular changes in oral cancer and premalignant lesions have been studied
- Transformation from a benign to a malignant disease is a genetic process that occurs at the cellular level, which later becomes histologically evident at the tissue level and finally becomes clinically evident on examination
- Recent studies have identified a molecular (genetic) profile for risk of malignancy. In premalignant lesions the risk of progression to cancer is:
    - **Low** when no genetic change is seen
    - **Intermediate** if there is genetic loss on the short arms of chromosome at sites 3p & 9p
    - **High** if there is 3p & 9p loss accompanied by genetic loss on additional chromosome arms (including 4q, 8p, 11q, 13q, and 17p)

Diagnosis [13,15,16]

- Biopsy of the abnormal tissue results in a histologic diagnosis
- Currently the gold standard for predicting the malignant potential of premalignant lesions is the presence and degree of dysplasia
- Various techniques to identify cancer transformation – genetic/molecular markers are emerging

Adjunctive Diagnostic Techniques [15,17,18,19, 20]

- Tissue staining with toluidine blue
  - Toluidine blue is effective as a diagnostic adjunct for use in high risk populations and suspicious lesions
- Computer assisted cytology
  - Useful in assessment of identifying disaggregated dysplasic cells in clinically suspicious lesions
- Optical Visualization Techniques
  - Insufficient evidence at this time to support or refute the use of visually based adjunctive techniques - further studies are necessary
- Salivary Biomarkers
  - May in future result in improved diagnostic and predictive capabilities
- Tissue Biomarkers
  - Genomic Profiling - Detection of multiple genes/gene variants that have been associated with a greater risk or predisposition to a particular disease or condition. Already being done in various diseases
  - Ultimately used to modify and reduce risk by changing certain controllable parameters with the ability to prevent disease or more adequately treat the condition
  - In future, patterning of genetic/epigenetic and molecular profiling, may result in improved predictive capabilities

Management of PMOL [21,22]

- Eliminate risk factors: return in 2-4 weeks
- Biopsy, if lesion still present, for definitive diagnosis
- Lifelong follow-up
- Clinical studies failed to provide evidence based recommendations regarding treatment of dysplastic lesions
- If lesions determined to be severe dysplasia or frank oral cancer, referral to a head and neck cancer specialist is recommended

Management of Oral Cancer [14,23]

- Usually treated by surgery, radiation and/or chemotherapy solely or in combination
- Surgical excision is often the treatment of choice for accessible well defined tumors
- Transoral robotic surgery (TORS) is a novel surgical approach resulting in fewer side effects
- Radiotherapy could be an effective alternative to surgery but most often is an adjunct in regional control
- Chemotherapy (neoadjuvant) has been shown to improve regional control and long term survival
- Complications of surgery include disfigurement, dysphagia, trismus and speech impairment
- Complications of radiotherapy include both immediate (mucositis, dysphagia/odynophagia) and delayed (salivary dysfunction, trismus, dysgeusia, dental disease, potential for osteoradionecrosis) effects
- Complications of chemotherapy include mucositis, pain and dysgeusia
- Since patients that have had a history of prior oral or oropharyngeal cancer are at high risk for developing another, lifelong follow-up with particular attention to the oral clinical exam is warranted

Conclusion

Potentially malignant oral lesions and oral cancer are alterations of the oral mucosa that will be encountered by the dentist during routine clinical examination. The dentist maybe the first healthcare provider to identify these abnormalities and initially manage/counsel the patient upon the significance of the finding. It is important to have an understanding of the risk factors associated with these disorders and an understanding regarding the detection of them as well. At this time, predicting the behavior of these lesions is difficult and incomplete. In the future, as the understanding of genetic/molecular signatures found in the patient's tissue or salivary samples improves, so will our ability to predict the behavior of the lesion and our ability to better manage the patient's disease. The dentist plays an important role in changing the long-term outcomes for patients diagnosed with these conditions as well as maintaining the oral health in those who have been treated for oral cancer. ■

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Dr. Sollecito graduated from the University of Pennsylvania, School of Dental Medicine in 1989. He completed a general practice residency and a fellowship in oral medicine at the University of Pennsylvania Health System. He is board certified by the American Board of Oral Medicine and the American Board of Special Care Dentistry. He is a Fellow in Dental Surgery, Royal College of Surgeons of Edinburgh and a Fellow of the International College of Dentists, USA Section. He is currently Professor and Chair of Oral Medicine at the University of Pennsylvania, School of Dental Medicine and Professor of Oral Medicine in Otolaryngology: Head and Neck Surgery, University of Pennsylvania School of Medicine. He is also an Attending in Oral Medicine at the Hospital of the University of Pennsylvania and a University Associate at the Children's Hospital of Philadelphia. Dr. Sollecito is an expert in oral mucosal diseases, facial pain as well as in the dental treatment of the medically complex patient. He is a member of the University of Pennsylvania Health System's Abramson Cancer Center. He is currently Section Editor, Oral Medicine for the Compendium of Continuing Education in Dentistry. He serves on the Council on Scientific Affairs of American Dental Association and is a Regional Dental Advisor, N.A. for the Royal College of Surgeons of Edinburgh. He is a Past President of the American Academy of Oral Medicine. His research interests include oral cancer and pre-cancer. Dr. Sollecito has authored numerous papers and chapters related to various topics in Oral Medicine.