

COMPREHENSIVE OVERVIEW OF ORAL PATHOLOGY

Ashley Clark, DDS, FACD, FICD, FAAOMP

Vice President, CAMP Laboratory

Diplomate, American Board of Oral and Maxillofacial
Pathology

AshleyClarkDDS@gmail.com

1

Conflicts of interest & disclaimers

- Conflict of interest: None, though I am in private practice and a pathology lab.
- The opinions expressed in this presentation are those of the speaker and not necessarily those of my lab
- The opinions expressed in this course should not be construed as advice to care for specific patients.

2

Course objectives

- Upon completion of this course, you will be able to:
 - Discuss potentially malignant disorders and malignancies of the oral cavity
 - Recognize common lesions of the oral cavity, including ulcerative conditions
 - Discuss how to manage patients who have oral pathologic lesions

3

Potentially malignant disorders

- The WHO adopted the phrase “potentially malignant disorders” to describe lesions with potential to progress to malignancy
- Terminology has changed; “pre-malignant” was formerly used
 - This term fell out of favor because it suggests these lesions eventually undergo malignant transformation, though some do not

Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;125:612-627.

4

Potentially malignant disorders

- Oral entities associated with an increased risk of squamous cell carcinoma are numerous and include:
 - Leukoplakia (and proliferative verrucous leukoplakia, or PVL)
 - Nicotine stomatitis in people who reverse smoke
 - Smokeless tobacco keratosis
 - Oral lichen planus
 - Erythroplakia (and erythroleukoplakia)
 - Actinic cheilitis
 - Oral submucous fibrosis
 - Dyskeratosis congenita
 - Fanconi anemia
 - Others!

Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;125:612-627.

5

Potentially malignant disorders

- Clinically, most of these are red patches or red and white patches
 - 2.5% of Americans will have leukoplakia
- Therefore, we will focus on these entities

Mehanna HM, Rattay T, Smith J, et al. Treatment and Follow-Up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck.* 2009;31(11):1600-1609.

6

LEUKOPLAKIA

7

Leukoplakia

- Defined by the World Health Organization as “a white plaque of questionable risk having excluded other known diseases or disorders that carry no risk”
 - This means tobacco pouch keratosis, leukoedema, lichen planus, and etc. are not leukoplakias
- Lesions tend to change overtime; they don't always remain white
 - The more “red” they get, the greater the chance of malignant transformation
 - The red lesions are more difficult to detect (IMO!)
- A clinical term; leukoplakia is never a diagnosis
 - This means you will not receive a biopsy report from me with “leukoplakia” on the diagnosis line

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8



9



10

Leukoplakia

- Leukoplakia comprises 85% of oral potentially malignant disorders, though not all progress to SCCa
- Dysplastic epithelium or squamous cell carcinoma (SCCa) is seen in 20% of biopsy samples of clinical leukoplakia
 - This means 80% are benign hyperkeratosis
- Malignant transformation potential is 5% to 50%, depending on clinical subtype
 - The overall malignant potential of leukoplakia is ~10%

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition, Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.
 Mehanna HM, Rattay T, Smith J, et al. Treatment and Follow-up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck*. 2009;31(12):1605-1609.
 Spright PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125(6):617-627.

11

Leukoplakia – Etiology

- Tobacco: 80% of patients with leukoplakia smoke
 - People who smoke are much more likely to have leukoplakia compared to people who do not smoke
 - People who smoke heavily tend to have a greater number of lesions and larger lesions
 - Leukoplakia can disappear after 1 year of smoking cessation

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition, Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.
 Woo S-B, Cashman EC, and Lerman MA. Human papillomavirus-associated oral intraepithelial neoplasia. *Modern Pathology*. 2013;26:1288-1297.

12

Leukoplakia – Etiology

- Most recent data states 34.2 million people age 12 or older are people who currently smoke (13.7%)
 - The good news: tobacco use is declining steadily
- It is estimated that smoking-related illnesses cost nearly \$300 billion per year in direct medical costs and loss of productivity

Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual Healthcare Spending Attributable to Cigarette Smoking: An Update. *American Journal of Preventive Medicine*. 2015. 49(3):326-33.

Creamer MR, Wang TW, Babb S, et al. Tobacco Product Use and Cessation Indicators Among Adults – United States, 2018. *MMWR*. 2019;68(45):1013-1019.

Substance Abuse and Mental Health Services Administration. (2019). *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data>

13

Leukoplakia – Etiology

- Tobacco is the leading cause of death and disability in the world
- People who smoke are more likely to successfully quit if they are aware of health risks
- Most adults know smoking can cause heart disease and lung cancer (n = 9058)
 - Only 75% knew smoking can cause a stroke
 - Less than half knew smoking can cause impotence
 - My unpublished data: 30% of people knew it could cause oral cancer

Hammond D, Fong GT, McNeill A, et al. Effectiveness of cigarette warning labels in informing smokers about the risks of smoking: findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*. 2006; 15:19-25.

US Department of Health and Human Services. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. – Atlanta, GA.: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

14

Leukoplakia – Etiology

- Alcohol:
 - Acts synergistically with tobacco
 - No current evidence that continued use of alcohol is a risk factor for lesion progression

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15

Leukoplakia – Etiology

- The role of high-risk HPV in the development of oropharyngeal carcinoma is well-established, but less is known about high-risk HPV in potentially malignant lesions and the risk of malignant transformation
- Microorganisms: High-risk HPV (16, 18, 31, 33, 45, etc.) is found up to 4 times more in leukoplakia than in unaltered mucosa
 - Low-risk strains causing squamous papilloma, verruca vulgaris, condylomas, etc. are not associated with oropharyngeal SCCa

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Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125:612-627.

16

Leukoplakia

- Clinical features:
 - Most commonly found in patients over 40 years old; the prevalence increases rapidly with age
 - 10% of men over age 70 are affected
 - 70% of leukoplakias are found on:
 - Lip vermillion
 - Buccal mucosa
 - Gingiva
 - 90% with dysplasia or carcinoma are found:
 - Lip vermillion
 - Lateral/ventral tongue
 - Floor of mouth

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17

Leukoplakia

- Thin leukoplakia represents the earliest lesions and it presents as slightly elevated gray or white plaques
 - Most have sharply demarcated borders
 - The lesions may appear fissured or wrinkled
- Thin leukoplakia seldom shows dysplasia on biopsy
- The malignant potential is probably less than 5%
 - Exception: If the lesion is positive for a high-risk strain of HPV

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18

Thin leukoplakia; hyperkeratosis



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19

Thin leukoplakia; hyperkeratosis



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Thin leukoplakia; hyperkeratosis with atypia



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Thin leukoplakia; mild dysplasia



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Thin leukoplakia; mild dysplasia



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Thin leukoplakia; mild dysplasia



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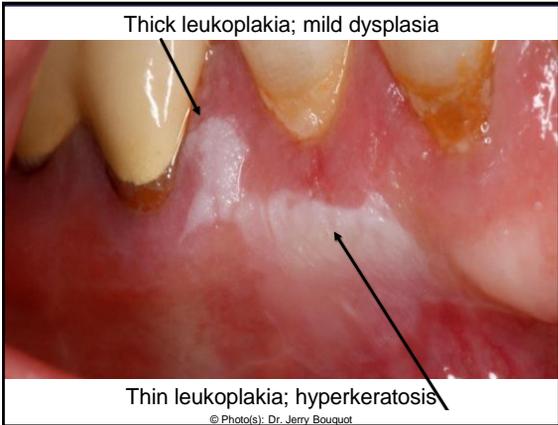
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Leukoplakia

- Thin leukoplakia can progress to become thicker, more distinctly white, and fissured
 - This is termed homogeneous or thick leukoplakia
- Most leukoplakias remain at this stage; up to 1/3 may regress

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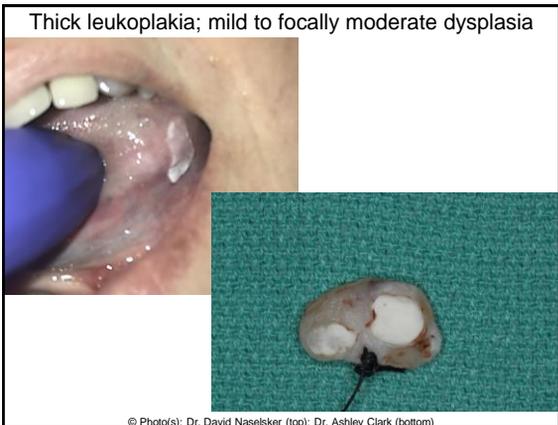
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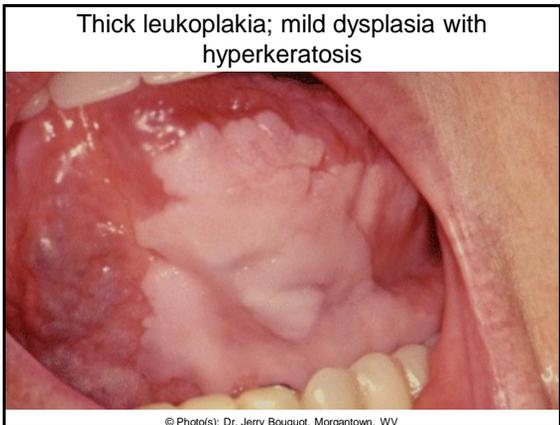
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28



29



30

Leukoplakia

- Some lesions of thick leukoplakia can progress to develop increased surface irregularities
 - This is called granular or nodular leukoplakia; those with wartlike projections are termed verruciform leukoplakia

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31

Verruciform leukoplakia; severe dysplasia



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Verruciform leukoplakia; atypical epithelial proliferation



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33

Leukoplakia

- If granular, nodular, or verruciform leukoplakia progresses, the lesion begins to demonstrate scattered red patches (erythroplakia)
- The erythroplakia found in areas of leukoplakia represents sites in which epithelial cells are so immature they can no longer produce keratin
- Red and white intermixed lesions are termed erythroleukoplakia
- Erythroplakia and erythroleukoplakia frequently reveal advanced dysplasia on biopsy

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34

Erythroleukoplakia; moderate dysplasia



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Erythroleukoplakia – severe dysplasia



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36

Leukoplakia - PVL

- Proliferative verrucous leukoplakia (PVL) is a special high-risk form of leukoplakia
- It is characterized by multiple keratotic plaques with roughened surface projections
- Lesions slowly spread throughout the mouth; the gingiva is typically involved
- Lesions nearly always transform into verrucous carcinoma or SCCa if left untreated; the average time of transformation is 8 years after initial diagnosis

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37

Leukoplakia - PVL

- PVL is difficult to treat because lesions nearly always recur; the only treatment is to repeatedly destroy tissue
- PVL is unusual because there is a 4:1 F:M predilection
- There is no known etiology (it is not associated with tobacco use, etc.)

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38



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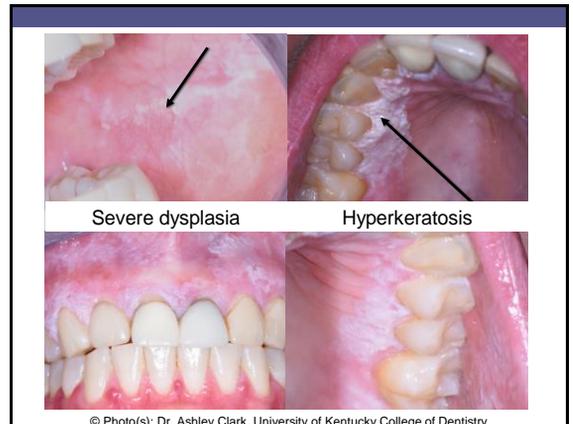
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Leukoplakia

- The first step in the treatment of leukoplakia is arriving at a definitive diagnosis
- Therefore, biopsy is mandatory and should be taken from most severe looking areas of involvement

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43

NICOTINE STOMATITIS

44

Nicotine stomatitis

- White keratotic change on the palate
 - Due to heat (long-term hot beverage use can cause the same clinical changes)
 - Not premalignant
- Reverse smoking:
 - Hand-rolled cigarettes and cigars are smoked with the lit end in the mouth
 - Produces a palatal change termed "**reverse smoker's palate**"
 - Significant potential for malignant transformation

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45

Nicotine stomatitis

- Most commonly found in white males, older than age 45
- Long-term exposure to **heat**
- Diffusely gray or white palate
- Numerous, slightly elevated papules are present; typically have punctate red centers
 - Represent inflamed minor salivary glands and their ductal orifices
- May appear like "dried mud"

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46

Nicotine stomatitis

- Nicotine stomatitis:
 - Completely reversible
 - NOT premalignant unless due to reverse smoking
 - Palate returns to normal within 2 weeks of habit cessation
 - Any white lesions on the palate that persists 1 month after habit cessation requires biopsy
- Reverse smoker's palate is premalignant and demands biopsy

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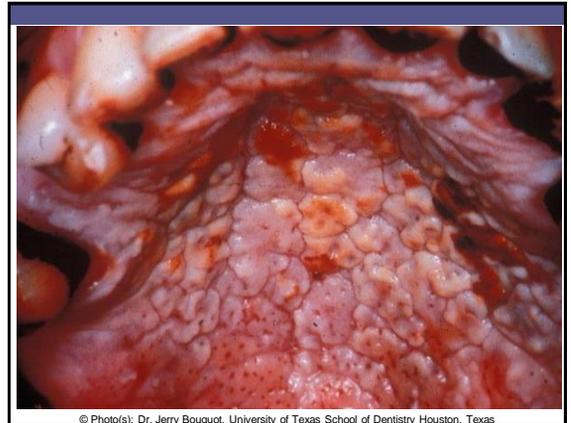
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50



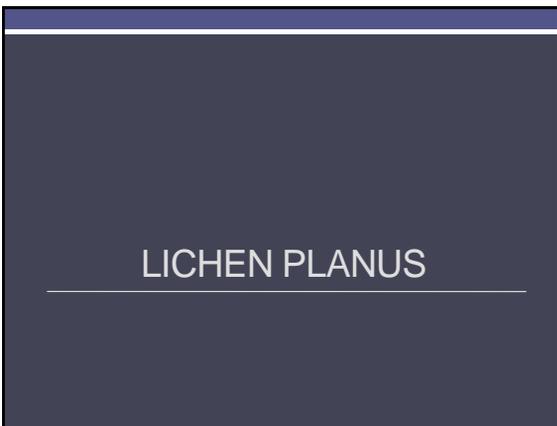
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51



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52



53

Lichen planus

- We will limit our discussion now to the malignant transformation potential of lichen planus (will discuss more in-depth tomorrow)
- Determining the malignant potential of lichen planus is challenging and somewhat controversial
 - Features overlap with lichenoid lesions and dysplasia
 - Most studies have not used strict diagnostic criteria, so the data is difficult to interpret
- In her systematic review published in *JADA*, Dr. Sarah Fitzpatrick and colleagues determined around a 1% risk for malignant transformation

Fitzpatrick SG, Hirsch SA, and Gordon SC. The malignant transformation of oral lichen planus and oral lichenoid lesions. *JADA*. 2014;145(1):45-56.
Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125:612-627.

54

Lichen planus

- Risk factors associated with a greater risk for malignant transformation:
 - Erosive lesions
 - Smoking & alcoholism
 - Atrophic mucosa is more susceptible to carcinogens, so the presence of tobacco and/or alcohol in someone with erosive lesions may increase risk even more
 - Hepatitis C virus infection
 - Female sex
 - Located on the tongue

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55

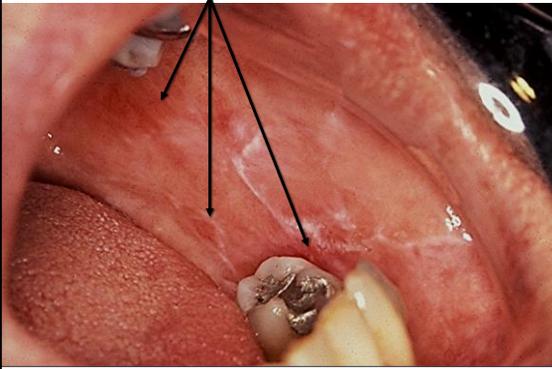
Lichen planus

- Patients with erosive lichen planus have a higher risk for high-risk HPV infection
 - This may also be a potential etiologic factor in malignant transformation

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56

Risk getting greater in atrophic areas



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57

SCCa until proven otherwise



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58

SMOKELESS TOBACCO KERATOSIS

Smokeless tobacco keratosis

- Three main types of smokeless tobacco used in the US:
 - Chewing tobacco – men during outdoor activities
 - Moist snuff – most popular
 - Dry snuff – southern women
- Moist snuff's sales have increased over the last few decades and comes in small, pre-packaged pouches
- Users typically start between ages 8-14; it is rare for the habit to start after age 20

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59

60

Smokeless tobacco keratosis

- Smokeless tobacco keratosis is a characteristic white or gray plaque produced on the mucosa in direct contact with the smokeless tobacco
- Affects 60% of moist snuff users
- Lesion development is influenced the most by habit duration
 - Brand, amount used daily, age when habit started, and number of sites used for placement will also affect lesion development
- Lesions develop shortly after heavy tobacco use begins; new lesions seldom arise in persons with long history of use

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61

Smokeless tobacco keratosis

- Lesion appears as a thin, gray or white plaque with a border that blends into surrounding mucosa
 - There may be mild erythema of the periphery
 - Lesion may feel soft or velvety upon palpation
- Stretching of the mucosa will reveal a pouch where the tobacco is commonly placed
- Mucosa also appears fissured or rippled
- Similar alterations can occur with anything chronically held in the vestibule (like sunflower seeds)

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62

Smokeless tobacco keratosis

- There is no associated induration, ulceration, or pain
- Once developed, most lesions do not advance if there is no change in tobacco use
 - Occasionally, the lesion may gradually thicken and look leathery or even nodular
- Chronic use of smokeless tobacco is considered carcinogenic
- Biopsy is needed only for more severe lesions because the risk for malignant transformation is low
 - ("Severe lesions" = those that are thick, granular, verruciform, indurated, ulcerated, etc.)

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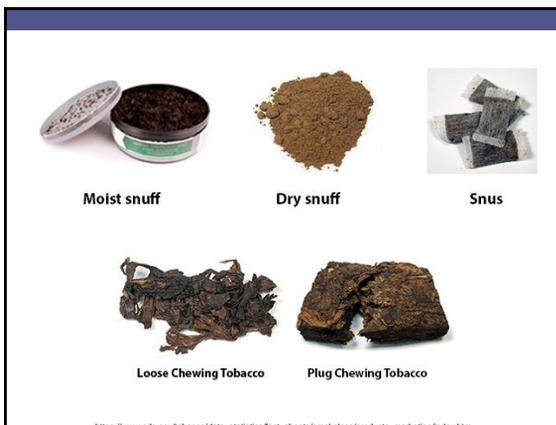
63

Smokeless tobacco keratosis

- Epithelial dysplasia is uncommon and if present, is almost always mild
- If it does undergo malignant transformation into squamous cell carcinoma or verrucous carcinoma, it does so after several decades
 - Exception: dry snuff tends to be much more carcinogenic, with a relative risk of malignancy at 26 and a faster rate of transformation
- Recent studies from Sweden have failed to show any increase in risk for malignancy in those who use Swedish moist snuff (*snus*)
- Habit cessation leads to lesion resolution; those that remain after 6 weeks should be biopsied

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64



65



66



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67



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68



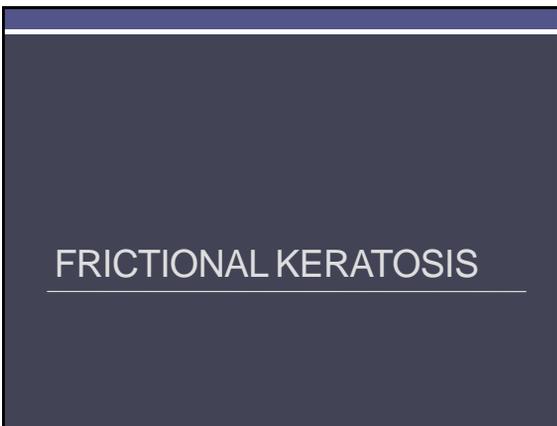
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70



71

Frictional keratosis

- Chronic mechanical irritation can produce a white lesion with a roughened surface called frictional keratosis
- Looks similar to true leukoplakia but should be distinguished from it because it does not have malignant potential
- Most commonly occurs on the retromolar pad or edentulous alveolar ridge
 - Some refer to this as benign alveolar ridge keratosis (BARK)

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72



73



74

Actinic cheilitis

- Common premalignant alteration of the lower lip vermilion
- Results from long-term exposure to UV light
- Outdoor occupation is associated; it is sometimes called farmer's lip or sailor's lip
- Similar to actinic keratosis in behavior
- Rare in persons younger than 45
- Strong male predilection (M:F is 10:1)
 - May reflect degree of outdoor activity or use of lip protecting agents

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75

Actinic cheilitis

- The lesion is slowly developing and the patient is usually not aware of the lesion
- Earliest clinical changes:
 - Atrophy of the lower lip vermilion border, characterized by a smooth surface and blotchy pale areas
 - Dryness and fissures
 - Blurring of the margin between the vermilion zone and cutaneous portion of the lip
- As the lesion progresses, rough and scaly areas develop on the drier portions of the vermilion

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76

Actinic cheilitis

- Lesions can then thicken to form leukoplakic lesions
 - The patient may be able to "peel away" the scaling with some effort, but it will come back within a few days
- Further progression leads to ulceration and suggests transformation into SCCa

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77

Actinic cheilitis

- Changes are irreversible, but patients should be instructed to use lip balms with sunscreens to prevent further damage
- Any area with induration, thickening, ulceration, or leukoplakia should be biopsied
- Patients require long-term follow-up
- Presence of actinic cheilitis more than doubles the risk for SCCa development of the lip
- The good news: it typically takes several decades for actinic cheilitis to undergo malignant transformation and it rarely metastasizes

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78



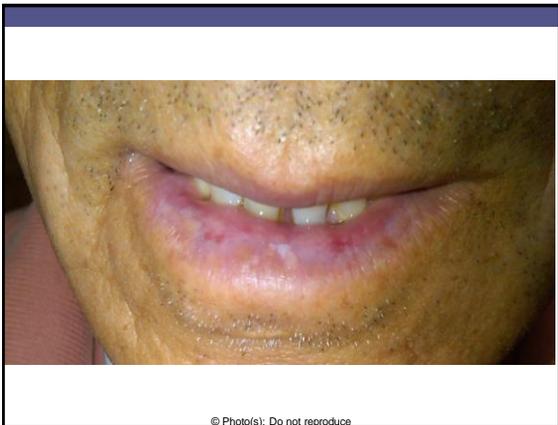
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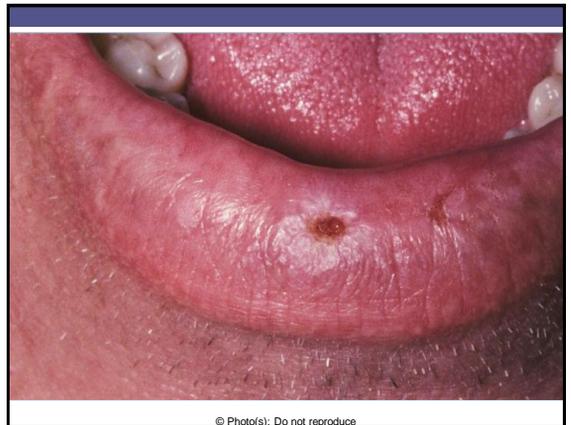
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84

Oral submucous fibrosis

- The areca nut is the seed of the areca palm, which grows in parts of the Indian subcontinent and Southeast Asia
- The nuts grow within a fibrous husk at the top of the trunks
 - Side note: areca nut husk is used as a traditional method of cleaning teeth
- The areca nut may be chewed on its own or combined with one or more ingredients
- In some cultures, users start the habit in childhood or adolescence; it marks transition to adulthood

Williams S, Malik A, Chowdhury S, et al. Areca Nut Symposium: Sociocultural aspects of areca nut use. *Addiction Biology*. 2002;7:147-154

85

Oral submucous fibrosis

- Some information from Dr. Indraneel Bhattacharyya, board-certified oral pathologist at University of Florida, regarding the terminology around areca nut:
 - Gutka is most carcinogenic; contains tobacco, spices, areca nut (areca nuts are sometimes called betel nuts)
 - Pan masala is a generic term for gutka, but usually does not have tobacco unless asked (may also be called paan)
 - Some pre-packaged forms will have tobacco; not all pre-packaged forms will have the ingredients listed
 - Betel quid is a packet of betel leaf wrapping the areca nut, spices, slaked lime (aka calcium hydroxide), tobacco, and other ingredients
 - Areca nut by itself is addictive and carcinogenic, but not nearly as carcinogenic compared to when it is mixed with tobacco

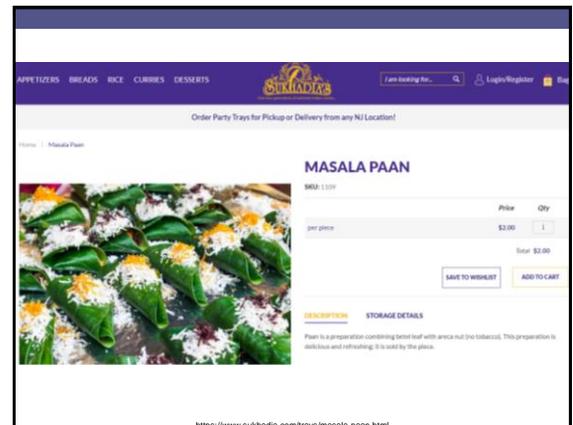
86

Oral submucous fibrosis

- Slaked lime releases alkaloids from the areca nut which results in euphoria
- It may be used for 16-24h/day
- One can purchase the ingredients legally in the US
 - The ingredients have a higher concentration of areca nut and cause lesions more rapidly

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87



88



"Paan is a preparation combining betel leaf widely consumed throughout Southeast Asia, East Asia, and the Indian and Pakistan Subcontinent. It is chewed as mouth freshener. After chewing, it is either spat out or swallowed. Paan has many variations. Slaked lime (chuna) and Katha paste is commonly added to freshen the breath."

<https://www.moonlightpaan.com/>

89

Oral submucous fibrosis

- Oral effects of areca nut/betel quid chewing are seen primarily in the Indian subcontinent
- 600 million people worldwide chew areca nut regularly, so you may encounter it in your dental practice
 - It is the world's fourth most-used stimulant after caffeine, alcohol, and tobacco
- Chronic use of areca nut, with or without the other ingredients, can cause alterations in the oral mucosa
 - The formulations with tobacco are the most carcinogenic
 - Oral submucous fibrosis is the potentially malignant condition on which we will focus

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90

Oral submucous fibrosis

- Oral manifestations:
 - Brown-red discoloration of the teeth and attrition
 - Brown-red discoloration of the mucosa termed betel chewer's mucosa; not precancerous (that we know of)
 - Lichenoid-like reactions
 - Periodontal disease
 - Oral submucous fibrosis – see next slide

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 355-390.

91

Oral submucous fibrosis

- Oral submucous fibrosis often manifests in young adult betel quid users
- It is a chronic, progressive, scarring, high-risk precancerous condition of the oral mucosa
- The most commonly affected site is the buccal mucosa, followed by the retromolar areas and the soft palate
- A few patients developed disease after only a few contacts with areca nut

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 355-390.

92

Oral submucous fibrosis

- The first symptoms include a burning sensation of the oral cavity and xerostomia
- Intraoral examination reveals vesicles, petechiae, and melanosis
- Lesions progress to develop a blotchy, pale appearance with progressive stiffness
- The tongue may shrink, become difficult to move, and the papillae may be gone
- Banding can be palpated on the buccal mucosa, soft palate, and labial mucosa in advanced cases
- **Leukoplakia** of the surface mucosa often is discovered

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93

Oral submucous fibrosis

- Patients who report to your office with oral submucous fibrosis will typically have chief complaints of trismus and oral burning with spicy foods
- In severe cases, the interincisal distance is less than 20 mm; in the most advanced cases, the jaws can become inseparable
- Unfortunately, the lesions do not regress with habit cessation (unlike with tobacco cessation)

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94

Oral submucous fibrosis

- Mild cases are treated with intralesional steroids to reduce symptoms and limit progression
- Moderate to severe cases may require surgical splitting or excision of the fibrous bands followed by lifelong physiotherapy; relapse is common
- Frequent follow-up is mandatory due to the risk of malignant transformation

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 355-390.

95

Oral submucous fibrosis

- The malignant transformation rate is around 5-10%
 - One factor that increases risk for malignant transformation is the presence of epithelial dysplasia upon biopsy
- The average duration for malignant transformation varies between 2.5 and 5 years
- Studies have shown patients are usually male, present at a younger age, and present at a lower stage
- Lesions tend to be thinner and less invasive; the patients have an overall better survival rate

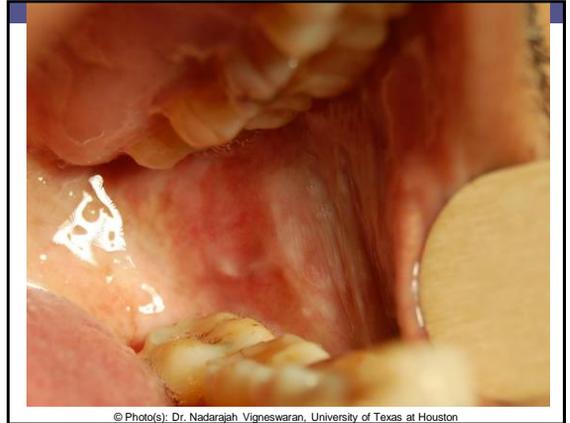
Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;125:612-627.

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Current surgical protocols

- "Surgical intervention is indicated in patients who have established trismus with interincisal mouth opening of less than 25 mm.
- The primary aim of surgery is to improve mouth opening in an attempt to restore articulation, mastication, and oral hygiene."

Arakeri G, Kumar K, Boraks G, et. al. Current protocols in the management of oral submucous fibrosis: An update. *J Oral Pathol Med.* 2017;46:418-423. m

106

Current surgical protocols

- Regardless of severity, all surgical interventions follow a standard protocol:
- 1. Preoperative clinical, radiological, and histopathological screening for malignancy
- 2. Incision of fibrous bands followed by adequate muscular release
- 3. Masticatory muscle myotomy and coronoidectomy if mouth opening is less than 35 mm after surgical release
- 4. Resurfacing of the surgical defect
- 5. Postoperative vigorous physiotherapy

Arakeri G, Kumar K, Boraks G, et. al. Current protocols in the management of oral submucous fibrosis: An update. *J Oral Pathol Med.* 2017;46:418-423.

107

ERYTHROPLAKIA

108

Erythroplakia

- Defined as a red patch that cannot be diagnosed as any other condition
- Causes are unknown, but they are assumed to be the same as leukoplakia/SCCa
 - Tobacco and alcohol; high-risk HPV
- The good news: erythroplakia is not as common as leukoplakia (probably around 0.1% of Americans)
- The bad news: True erythroplakias are never completely benign and 90% show severe dysplasia or worse on biopsy (!!)
- Therefore, even though these lesions are not common, we MUST recognize them clinically

Reichart PA, Philipsen HP. Oral erythroplakia – A review. *Oral Oncology*. 2005;41:551-561.
Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

109

Erythroplakia

- Erythroplakia predominantly occurs in middle-aged to older adults (the average age is 70) with no gender predilection
- Most common locations:
 - Floor of mouth
 - Soft palate
 - Ventral tongue* - older studies suggest the tongue is an uncommon location
- Some studies suggest that the most common place for erythroplakia to occur in females is the gingiva
 - Ashley Clark Remark: these lesions can mimic many other forms of pathology so please do not ignore them!

Reichart PA, Philipsen HP. Oral erythroplakia – A review. *Oral Oncology*. 2005;41:551-561.
Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

110

Erythroplakia

- The altered mucosa is usually a well-demarcated, less than 1.5 cm macule or plaque with a velvety texture
 - The mucosa may also have a granular surface
- The lesion is soft in the dysplastic phases and becomes indurated when it progresses to squamous cell carcinoma
- Lesions are red in color due to epithelial thinness and the lack of keratin
 - This lets underlying vasculature show
- Patients are typically asymptomatic and have been aware of an alteration for over 2.5 years before biopsy (!)

Reichart PA, Philipsen HP. Oral erythroplakia – A review. *Oral Oncology*. 2005;41:551-561.
Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

111

Erythroplakia

- Biopsy is mandatory for erythroplakia
- Treatment is guided by definitive diagnosis
- Recurrence and multifocal oral involvement is common; therefore, long-term follow up at least every 6 months is required
 - I typically recall patients every 3 months for at least the first year

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112

Leukoplakia vs erythroplakia

- Leukoplakia is much more common than erythroplakia
- Leukoplakia can evolve, become more dysplastic, and show areas of redness (speckled leukoplakia or erythroleukoplakia)
- 90% of erythroplakias show severe dysplasia or worse on biopsy compared to 20% of leukoplakias
 - While both require biopsy, erythroplakia should be considered carcinoma *in situ* or squamous cell carcinoma until proven otherwise
- Recurrence is common for both and long-term follow-up is required for both

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113

Erythroplakia – squamous cell carcinoma



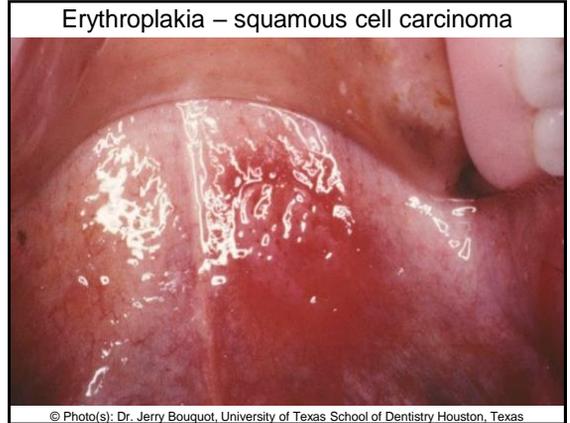
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114



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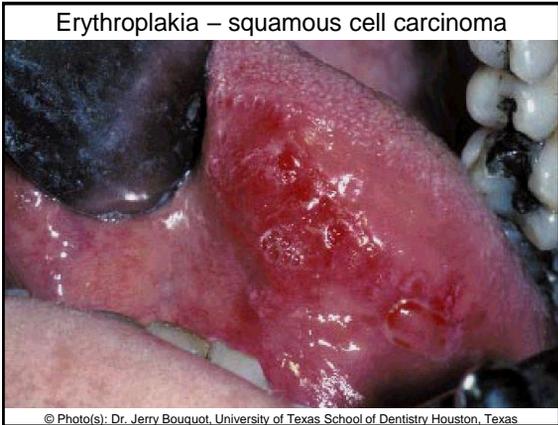
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Erythroplakia – squamous cell carcinoma

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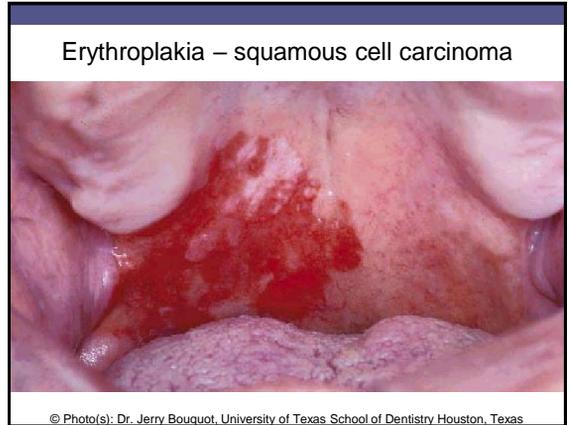
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Erythroplakia – squamous cell carcinoma

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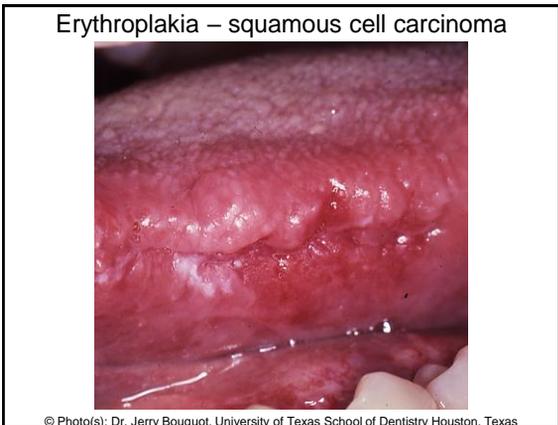
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Erythroplakia – squamous cell carcinoma

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Erythroplakia – squamous cell carcinoma

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Erythroplakia – squamous cell carcinoma



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121

TREATMENT

122

Treatment

- When to refer?
 - Old thought: wait two weeks to see if the lesion clears up
 - New thought: if you think the lesion may be a potentially malignant disorder, biopsy or refer for biopsy immediately
- Where to refer?
 - I typically refer oral potentially malignant lesions to an oral surgeon or periodontist if I do not feel comfortable performing the biopsy myself
 - One can refer to an oral pathologist, but ensure that person does their own biopsies before referral (also insurance considerations)
- With few exceptions, oral pathology labs will ship biopsy kits including formalin, paperwork, return mailing, etc. for free almost anywhere in the country

Lingen MW, Abi E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. *JADA*. 2017;148(10):712-727.

123

Ashley Clark Exceptions



124

Treatment

- The first step in the treatment of potentially malignant disorders is arriving at a definitive diagnosis
- Therefore, biopsy is mandatory and should be taken from most severe looking areas of involvement
- This is sometimes difficult to determine

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125

Treatment

- The biopsy will be evaluated by an oral pathologist
- What does your report mean?
- The differential diagnosis is:
 - Hyperkeratosis and/or acanthosis
 - Mild dysplasia
 - Moderate dysplasia
 - Severe dysplasia
 - Carcinoma-in-situ
 - Verrucous carcinoma
 - SCCa

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126

Treatment

- The benign entities:
 - Hyperkeratosis: Thickened keratin layer
 - Acanthosis: Thickened spinous layer
- ****Though neither hyperkeratosis nor acanthosis has dysplasia, follow-up is important****

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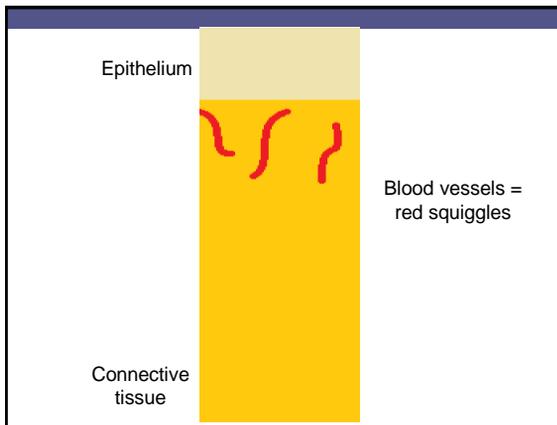
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Treatment

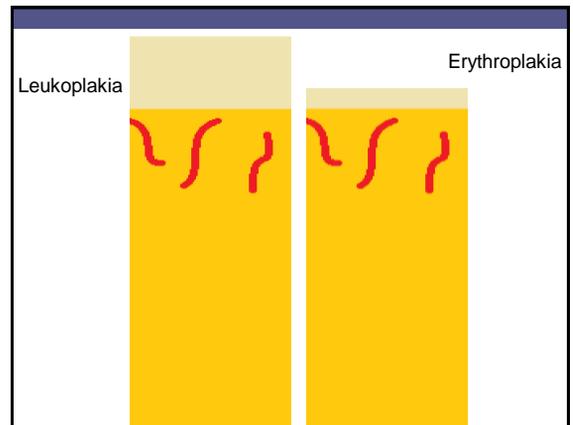
- The "precancers":
 - Mild dysplasia – the dysplastic alterations are 1/3 of the epithelium
 - Moderate dysplasia – the dysplastic alterations are ½ of the epithelium
 - Severe dysplasia – the dysplastic alterations are above ½ of the epithelium
 - Carcinoma *in situ* – the dysplastic alterations are seen through the entire thickness of the epithelium, but no invasion has occurred

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 355-390.

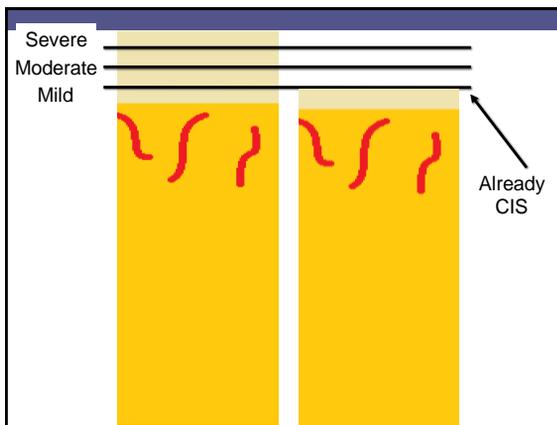
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129



130



131

Treatment

- After the biopsy report comes back, you will have a diagnosis...now what?
- Hyperkeratosis/acanthosis: follow-up every 6 months and re-biopsy if the lesion changes
- Mild dysplasia: it depends on the patient and their habits, lesion size, and clinician preferences
 - **I recommend tissue destruction**
 - If the lesion is small and the patient smokes, it may also be appropriate to re-evaluate mild dysplasia in 3 months after habit cessation to see if it regresses on its own
- Leukoplakia with moderate epithelial dysplasia or worse warrants complete destruction of tissue

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 355-390.

132

Treatment

- Long-term follow-up at least every 6 months is important because recurrences are frequent and additional leukoplakias or erythroplakias may develop
- The overall recurrence rate ranges from 10-35%, though verruciform or granular leukoplakias recur 85% of the time
- Some studies show a recurrence rate of over 70% for erythroplakia
- Recurrences should be re-biopsied to establish diagnosis
- It is important to encourage the patient to discontinue risky behaviors such as smoking cigarettes and drinking alcohol

Reichert PA, Phillips NP. Oral erythroplakia – A review. *Oral Oncology*. 2005;41:551-561.
Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*, Fourth edition, Elsevier, Inc.: St. Louis, Missouri; Pg 355-390.

133

Treatment

- 12% of leukoplakias become SCCa, usually within 2-4 years
- Thin leukoplakia seldom becomes malignant without clinical change
- Thick leukoplakia transforms up to 7% of the time
- Verruciform leukoplakia transforms up to 15%
- Erythroleukoplakia transforms up to 50%
- Most cases of erythroplakia are already carcinoma *in situ* or SCCa
- Some authors have reported PVL progressed in 100% of cases

Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*: Fourth edition, Elsevier, Inc.: St. Louis, Missouri; Pg 355-390.
Mehanna HM, Rattay T, Smith J, et al. Treatment and Follow-Up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck*. 2009;31(12):1600-1609.
Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125:612-627.

134

Treatment

- The transformation potential of the different phases of leukoplakia is closely related to the degree of dysplasia present:
 - Lesions with moderate dysplasia transform up to 20% of the time
 - Lesions with severe dysplasia transform up to 45% of the time

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135

Treatment

- Malignant transformation potential, in descending order:
 - Proliferative verrucous leukoplakia
 - Nicotine stomatitis in people who reverse smoke
 - Erythroplakia
 - Oral submucous fibrosis
 - Erythroleukoplakia
 - Verruciform (granular) leukoplakia
 - Actinic cheilosis
 - Smooth, thick leukoplakia
 - Smokeless tobacco keratosis
 - Lichen planus
 - Smooth, thin leukoplakia

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136

Treatment

- Features **strongly** associated with an increased risk for malignant transformation (leukoplakia):
 - Size of lesion is greater than 2 cm
 - Texture is nonhomogenous
 - Color is red or speckled
 - Location is tongue or floor of mouth
 - Microscopy shows severe dysplasia
- Features **moderately** associated with risk of progression:
 - Female sex
 - Patient is older than 50
 - Patient has high-risk HPV (note, this is for a leukoplakic lesion)
- Features **weakly** associated with risk of progression
 - Patient does **not** smoke*

Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125:612-627.

137

Treatment

- Factors that **decrease** the risk for malignant transformation:
 - Surgical excision (decreases risk by half)

Mehanna HM, Rattay T, Smith J, et al. Treatment and Follow-Up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck*. 2009;31(12):1600-1609.

138

Treatment

- Things to ponder: in a study of about 5,000 in California spanning 8 years:
 - Leukoplakia was associated with a 40.8-fold increased risk of oral cancer and a 5-year absolute risk of 3.3% (1 in 30 individuals progressing to cancer over 5 years)
 - Only a minority of oral cancers (<5%) were preceded by a documented clinical diagnosis of leukoplakia
 - We aren't doing a good job screening!
 - The American Dental Association recommends a visual and tactile examination of the oral mucosa on **all** dental visits
 - The authors concluded that, as previously mentioned, **all** leukoplakias require biopsy upon discovery

Chaturvedi AK, Udaltsova N, Engel EA, et al. Oral Leukoplakia and Risk of Progression to Oral Cancer: A Population-Based Cohort Study. *JNCI J Natl Cancer Inst*. 2020;112(10):662-670.

139

Potentially malignant disorders

- Takeaways:
 - Up to 1 in 200 patients have oral dysplasia
 - Dysplasia carries a significant risk for malignant transformation
 - This risk increases for severe dysplasia or worse
 - Surgical excision decreases the risk of malignant transformation but does not eliminate it
 - Therefore, long-term follow-up is required; the literature suggests a minimum of 20 years

Woo S-B, Cashman EC, and Lerman MA. Human papillomavirus-associated oral intraepithelial neoplasia. *Modern Pathology*. 2013;26:1288-1297.
Mehanna HM, Rattay T, Smith J, et al. Treatment and Follow-Up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck*. 2005;31(12):1600-1608.

140

Introduction to oral cancer

- Around ~53K people in the United States will be diagnosed with oral or oropharyngeal cancer this year
 - Around 10K patients will succumb to disease this year
- Men are twice as likely as women to be diagnosed with oral or oropharyngeal cancer
- 62 is the average age of all patients, though 25% occur in people younger than 55 years old
- Squamous cell carcinoma (SCCa) is the most common type of oral cancer by far (~85%)
 - The second most common are malignant salivary gland tumors (~6.5%)
 - The third most common are lymphomas (~4.5%)

<https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/about/key-statistics.html>
Dhanraj K, Rojanawattirak S, Thosorn W, et al. Oral cancer: A multicenter study. *Med Oral Patol Oral Cir Bucal*. 2018;23(1):e23-e29.

141

Introduction

- Though HPV-negative oral cancer is most common in older males, there is a rising incidence of SCCa affecting the tongue in young white women (ages 18-44)
 - From 1973-2012, there was a 0.6% annual increase
 - These tongue SCCas are HPV-negative and the etiology is not known (tobacco and alcohol are not considered etiologic factors in this increase)
 - Even in patients under 30 who smoke or drink, the duration of exposure is insufficient to account for SCCa development
 - It has been suggested in the literature that the risk for oral cancer increases after 21 years of smoking
 - Diets high in fruits and vegetables appear to be protective

Uwellyn CD, Linklater K, Bell J, et al. An analysis of risk factors for oral cancer in young people: a case-control study. *Oral Oncol*. 2004;40:304-313.
Tota JE, Anderson WF, Coffey C, et al. Rising incidence of oral tongue cancer among white men and women in the United States, 1973-2012. *Oral Oncology*. 2017;67:146-152.

142

Introduction

- There are two molecularly and epidemiologically distinct types of oral and oropharyngeal squamous cell carcinoma:
 - 1. Those that are positive for high-risk human papillomavirus (HPV)
 - 2. Those that are negative for high-risk HPV
- Each warrants their own discussion, as they have different etiologic factors, tend to occur in different locations, affect different demographics, and have different survival rates

Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol*. 2014;50:380-386.

143

Etiology

- The etiology of HPV-negative oral squamous cell carcinoma is multifactorial; extrinsic and intrinsic factors are involved
- Extrinsic factors include tobacco smoke, alcohol, and sunlight (sunlight only for lower lip vermilion)
- Intrinsic factors include systemic conditions or generalized states; for example:
 - Malnutrition
 - Iron-deficiency anemia
- Aside from a handful of rare, heritable conditions such as dyskeratosis congenita or Fanconi anemia, heredity does not appear to play a major causative role

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144

Etiology – human papillomavirus

- Human papillomavirus (HPV)
 - Common, highly transmissible virus with over 200 types that exclusively affect epithelial cells
 - 40 affect oral mucosa; 15 can lead to cancer

No risk	High risk
2 – verruca vulgaris	16
4 – verruca vulgaris	18
6 – condyloma	31
11 – condyloma	33
13 – Heck disease	45
32 – Heck disease	35, 51, 52, 56, 58, 59

Centers for Disease Control and Prevention (CDC). CDC Grand Rounds: Reducing the Burden of HPV-Associated Cancer and Disease. *MMWR Morb Mortal Wkly Rep.* 2014;63(04):69-72.
Centers for Disease Control and Prevention (CDC). Human papillomavirus associated cancers - United States, 2004-2008. *MMWR Morb Mortal Wkly Rep.* 2012 Apr 20;61:258-61.

145

Clinical features

- HPV-negative SCCa starts as a PMD
- Early lesions of HPV-negative oral cancer cause minimal pain, which may delay the patient in seeking treatment
 - The average time the patient is aware of the lesion is 4-8 months
 - In lower socioeconomic groups, this increases to 8-24 months
- The clinical presentation varies for the intraoral lesions; the lesion may be exophytic or endophytic, leukoplakic or erythroplakic, or a combination
- Those presenting as red/white lesions are likely early lesions that have not been around long enough to form a mass or ulcerate
- Lesions are typically indurated (feels hard)

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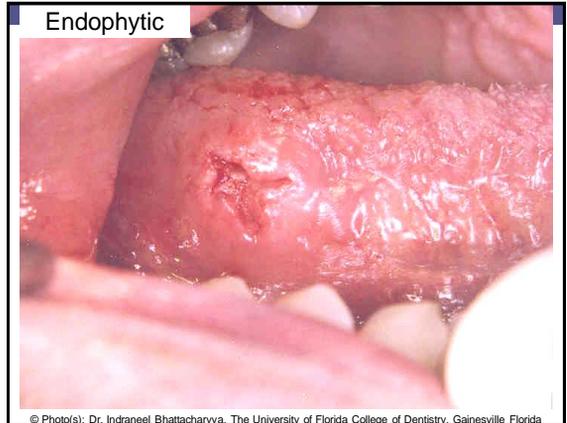
Exophytic



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Endophytic



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Erythroplakia



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Ulcerated erythroplakia



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150

Clinical features

- The most common sites are:
 - Posterior lateral tongue
 - Ventral tongue
 - Floor of mouth
 - Gingiva
- Other sites of involvement, in decreasing order:
 - Buccal mucosa
 - Labial mucosa
 - Hard palate

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

151

Clinical features

- Gingival carcinomas are unique:
 - Painless
 - Frequently arise from keratinized, posterior mandibular mucosa
 - Least associated with tobacco smoking
 - More common in females
 - Mimic benign and reactive lesions!
 - Can cause tooth mobility
 - May go unnoticed until the tooth is extracted and the lesion proliferates out of the socket, where it looks clinically similar to granulation tissue
 - 30% of maxillary gingival SCCAs are associated with lymph node metastasis

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.
Fitzpatrick SG, Neuman AN, Bhattacharyya I, Cohen DC. The Clinical and Histologic Presentation of Gingival Squamous Cell Carcinoma: A Study of 519 Cases. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012; 114(4):509-15.

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To compare, this is pemphigus vulgaris



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158

Clinical features

- Sites included in "oropharyngeal carcinoma" include:
 - Soft palate
 - Base of tongue
 - Tonsillar region (tonsil/fossa/pillars) – up to 80% of cases
 - Posterior pharyngeal wall
- Most of these SCCas will test positively for HPV

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

159

Clinical features

- SCCas affecting the oropharyngeal area have the same basic look as those affecting the oral cavity
 - Important note: there is no known dysplastic phase for HPV-positive lesions, but when the cancer develops, it looks the same as HPV-negative SCCas if large enough to be noted
- Due to the location, they are more difficult to visualize and may go unnoticed
- **About 80% of HPV-driven lesions in these areas have metastasized at the time of diagnosis**
- Presenting symptoms include sore throat and pain or difficulty swallowing

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

160

HPV-positive vs HPV-negative SCCa

HPV-negative tumors

- 95% of patients have a history of long-term exposure to tobacco and alcohol
- Have mutations in tumor suppressor p53
- Negative p16 immunohistochemical staining
- Almost always evidence of pre-malignancy (leukoplakia/erythroplakia)

HPV-positive tumors

- Develops independently of tobacco or alcohol exposure
- Wild-type p53
- Positive p16 staining
- No pre-malignant phase has been demonstrated

Pytnia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. Oral Oncol. 2014;50:380-386.

161

HPV-positive vs HPV-negative SCCa

- The overall incidence of HPV-negative oropharyngeal cancer decreased by 50% from 1988-2004, correlating with a decline in smoking
- HPV-positive oropharyngeal cancer increased 225% during the same period
- HPV-driven oropharyngeal cancer is more prevalent than cervical cancer

<https://www.cdc.gov/cancer/hpv/statistics/headneck.htm> <https://www.cdc.gov/cancer/hpv/statistics/cervical.htm>
Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. J Clin Oncol. 2011;29(32):4294-4301.

162

HPV-positive SCCa

- Remember, there are 100s of types of HPV; only about 15 drive malignancy in the oral cavity

	No Risk	High Risk
2 – verruca vulgaris		16
4 – verruca vulgaris		18
6 – condyloma		31
11 – condyloma		33
13 – Heck disease		45
32 – Heck disease	35, 51, 52, 56, 58, 59	

Centers for Disease Control and Prevention (CDC). CDC Grand Rounds: Reducing the Burden of HPV-Associated Cancer and Disease. *MMWR Morb Mortal Wkly Rep.* 2014;63(04):69-72.
Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers - United States, 2004-2008. *MMWR Morb Mortal Wkly Rep.* 2012 Apr 20;61:258-61.

163

HPV-positive SCCa

- HPV is the most common sexually transmitted disease
 - Point prevalence = **43-62%** in genital samples
 - Approximately **100%** of sexually active people will have HPV at some point in their life; there is a **60%** chance of infection after each sexual encounter with an HPV-positive partner
 - However, approximately **98%** of those HPV infections undergo spontaneous resolution in 2 years
- Changes in human sexual behavior are likely the driving force behind the HPV-positive oropharyngeal cancer epidemic

Centers for Disease Control. Ready-to-Use STD Curriculum for Clinical Educators: Genital Human Papillomavirus (HPV) Module. 2013.
Petryia KB, Dahlstrom KB, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Otol Otol.* 2014;50:380-386.
Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers - United States, 2004-2008. *MMWR Morb Mortal Wkly Rep.* 2012 Apr 20;61:258-61.

164

HPV-positive SCCa

- In 1950s, of approximately 6000 surveyed, less than 40% of women and 50% of men engaged in some form of oral sex
- As of 2010, that number is 89% for women and 91% for men for approximately 6000 surveyed
- Only 1 in 3 single, sexually active people use condoms regularly during any sex act
- About 6% of sexually active people routinely use condoms when engaging in oral sex

Kinsey AC, Pomeroy WB, Martin CE. *Sexual Behavior in the Human Male*. Philadelphia Pa: W.B. Saunders: 1948.
Kinsey AC, Pomeroy WB, Martin CE, et al. *Sexual Behavior in the Human Female*. Philadelphia Pa: W.B. Saunders: 1953.
Leichter JS, Chandra A, Liddon N, et al. Prevalence and Correlates of Heterosexual Anal and Oral Sex in Adolescents and Adults in the United States. *J Infect Dis.* 2007;196(12):1852-1859.
Herbenick D, Reece M, Schick V, et al. Sexual Behavior in the United States: Results from a National Probability Sample of Men and Women Ages 14-94. *J Sex Med. Special Issue: Findings from the National Survey of Sexual Health and Behavior (NSSHB) Center for Sexual Health Promotion, Indiana University.* 2012;9:265-266.

165

HPV-positive SCCa

- HPV prevalence in oropharyngeal tumors was 16.3% from 1984-1989 and **72.7%** from 2000-2004
- HPV-positive patients are more likely to be younger, male, and white
- The most commonly affected group are white males between the ages of 40-59**
 - Compared to HPV-negative, which tend to be diagnosed in older men (60s+)
 - No other group saw an increased incidence; however, this group saw an annual 10% increase in incidence from 2000-2004

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol.* 2011;29(23):4294-4301.
Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol.* 2008;26:612-9.

166

HPV-positive SCCa

- A 2011 article that accurately predicted HPV-positive oropharyngeal SCCa would outpace cervical cancer estimated oropharyngeal carcinomas would constitute approximately half of all head and neck cancers by 2030

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol.* 2011;29(23):4294-4301.

167

Oropharyngeal SCCa

- Currently: Around 19,700 people are diagnosed with HPV-driven oropharyngeal cancers each year, according to information published by the CDC

National Program of Cancer Registries SEER*Stat Database: U.S. Cancer Statistics Incidence Analytic file 1998-2017. United States Department of Health and Human Services, Centers for Disease Control and Prevention. Released June 2020, based on the 2019 submission.

168

19,700 is somewhere in this area...

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.

169

Treatment

- Clinical stage guides treatment
- SCCa of the lower lip are treated by surgical excision
 - Advanced cases may be treated by radiation + chemotherapy
- SCCa of the upper lip are rare; these patients may also undergo neck dissection as these cancers are high risk for lymph node metastasis
- Early lesions of intraoral, HPV-negative SCCa are treated with surgery
- Moderately advanced SCCAs are treated with surgery and possibly radiation therapy and chemotherapy
- Advanced lesions where surgical excision is not possible are treated with radiation and/or chemotherapy

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

170

Treatment

- Other indications for post-surgical radiation ± chemotherapy:
 - Close or positive margins on the resected tumor
 - High-grade histopathologic features
 - Extracapsular spread
 - Perineural or lymphovascular invasion
- Patients with intraoral SCCa almost always undergo modified radical or selective neck dissection
 - Radical neck dissection used to be preferred; it involves removal of the lymphatics of the lateral triangle of the neck along with the internal jugular vein, submandibular gland, sternocleidomastoid muscle, and spinal accessory nerve
 - Modified = similar to radical but preserve the non-lymphatic structures
 - Selective = removal of only select cervical lymph node groups

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

171

Treatment

- For oropharyngeal squamous cell carcinoma:
 - Early-stage SCCa is treated by radiation therapy or surgery
 - Most cases are discovered at an advanced stage and require surgery, radiation therapy, and/or chemotherapy

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

172

Prognosis

- HPV-positive cancers have an improved response to chemotherapy and radiotherapy
- 3-year survival rates and 5-year survival rates:
 - HPV-positive: 5 year survival = 75-80%
 - HPV-negative: 5 year survival = 45-50%
- HPV-positive have reduced risk of recurrence
 - Lack of field cancerization
 - Fewer chromosomal mutations
- Overall, HPV-positive patients have a 69% reduction in risk of death compared with HPV-negative patients

Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. *N Engl J Med*. 2010; 363:24-35.
Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.
Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol*. 2008;26:612-9.

173

How can we decrease risk?

- Smoking cessation and vaccination!
- The role of the dentist in tobacco cessation:
 - 1. Screen every patient for use
 - 2. Document tobacco status
 - 3. Advise users to quit
 - Cessation medication, counseling, assistance, follow-up, referral
- The 5 As:
 - 1. Ask about tobacco use
 - 2. Advise to quit
 - 3. Assess willingness to quit
 - 4. Assist in quitting
 - 5. Arrange follow-up

Flore MC, Bailey WC, Cohen SI et al [The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives]. A Clinical Practice Guideline for Treating Tobacco Use and Dependence: A US Public Health Service Report. *JAMA*. 2000; 283(24):3244-3254.

174

Smoking cessation

- Possible pharmacological cessation tools:
 - Nicotine replacement therapy (NRT) – works for 17.6%
 - Bupropion (Wellbutrin® or Zyban®) – works for 19.1%
 - Varenicline (Chantix®) – works for 27.6%
 - **Varenicline with NRT works for 31.5%**
 - Placebo worked for 10.6%

Cahill K, Stevens S, and Lancaster T. Pharmacological Treatments for Smoking Cessation. JAMA. 2014. 311(2):193-194.

175

Smoking cessation

- How to prescribe varenicline:
 1. Set a date to stop smoking; start medication 1 week prior
 2. Instruct patient to take the medication with food and 8 oz of water
 3. Prescribe 1 mg pills; #160 (12 week supply)
 - Take 0.5 mg (half pill) once a day for three days
 - Take 0.5 mg (half pill) twice a day for four days (the rest of the first week)
 - Take 1 pill two times a day until medication is finished (there will be 0.5 mg pill leftover)
- If patients have stopped smoking at the end of 12 weeks, 12 more weeks of the drug can be prescribed
- If patients have not stopped smoking after 12 weeks, address the reasons why and try again the drug again (try again once)

<http://labeling.pfizer.com/ShowLabeling.aspx?id=557952.1>

176

Smoking cessation

- Warning: some patients taking varenicline have “serious neuropsychiatric events” which include depression and suicide
- Varenicline can interact with alcohol; patients should be encouraged to reduce or eliminate alcohol consumption
- Some patients have experienced adverse cardiovascular events
- Patients with renal impairment need a medical consult
- Nearly 30% experience nausea, trouble sleeping, or headache

<http://labeling.pfizer.com/ShowLabeling.aspx?id=557952.3>

Jorenby DE, Hays T, Rigotti NA, et al. Efficacy of Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomized Controlled Trial. JAMA. 2006. 296(1):56-63.

177

Smoking cessation

- People who quit smoking by ages 35-44 avoid most risks of dying from a smoking-related disease (n=202,248)
- Quitting by age 40 reduces death risk due to smoking-related disease by 90%
- On average, people who smoke lose approximately 10 years of life compared to people who do not smoke

Jha P, Ramasundaramhettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. New England Journal of Medicine. 2013. 368(4):341-50.

178

How can we decrease risk?

- Smoking cessation and vaccination!
- Three vaccines are (or have been) available for the prevention of high-risk HPV
 - Gardasil for women and men (quadrivalent originally) - 2006
 - Gardasil-9 for women and men (9-valent; **recommended**) - 2014
 - Cervarix for women (bivalent) – 2009
- To be used before patient is sexually active; recommended age is to start the 2 or 3 shot series between ages 11-12

Petrosky E, Bocchini Jr JA, Hariri S, et al. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2015;64(11):300-304.

179

Virus Like Particles (VLPs) are artificial nanostructures that resemble a virus
They do not contain genetic material
They cannot cause HPV infection

<https://www.creative-diagnostics.com/news-recombinant-bov1-vlc-f8.htm>

180

HPV-positive SCCa

- A salivary diagnostic test became available for office use in Feb 2010
 - Rinse with sterile saline for 30 seconds
 - Expectorate into collection tube
 - PCR analysis & report generated by company
- Pros: Non-invasive and user-friendly
- Cons: ADA Center for EBD does not recommend, not FDA approved, most people who test positively for the virus will never have disease, unclear treatment plan if patient does not have a visible lesion

<https://www.oraldna.com/oral-hpv-testing.html>

<https://www.cdc.gov/std/hpv/stdfact-hpvandoropharyngealcancer.htm>

Lingen MW, Abt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. *JADA*. 2017;148(10):713-727.

181

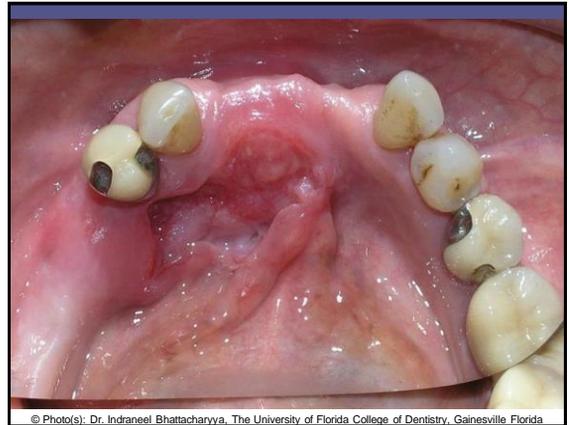
How can we decrease risk?

- Smoking cessation and vaccination!
- ...and surgical removal of any incisional-biopsy proven potentially malignant disorder (leukoplakia, erythroplakia, or a combination of the two)
 - Decreases the risk for malignant transformation rate by half

Mehanna HM, Rattay T, Smith J, et al. Treatment and Follow-Up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck*. 2009;31(12):1600-1609.

182

CLINICAL IMAGES



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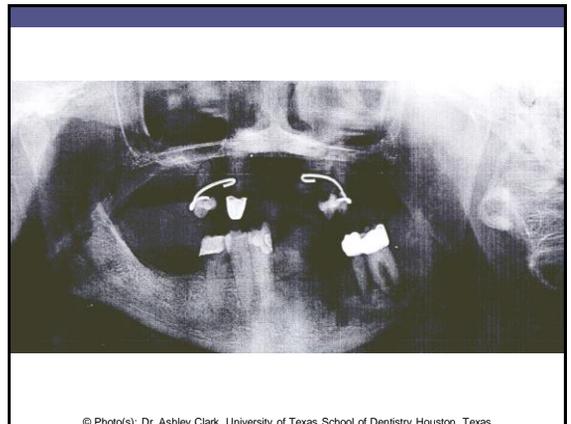
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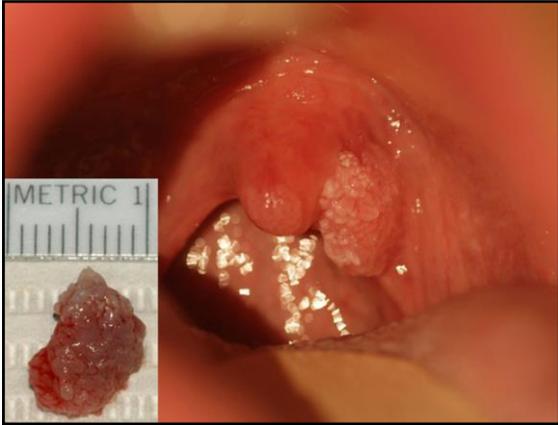
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211



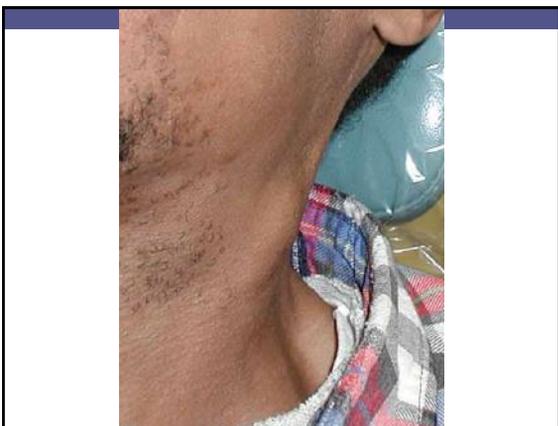
212



213



214



215



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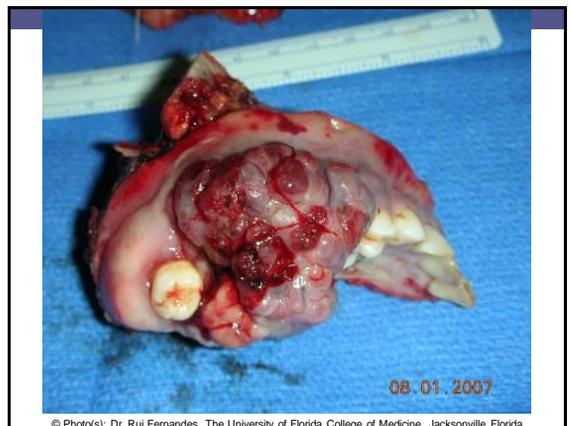
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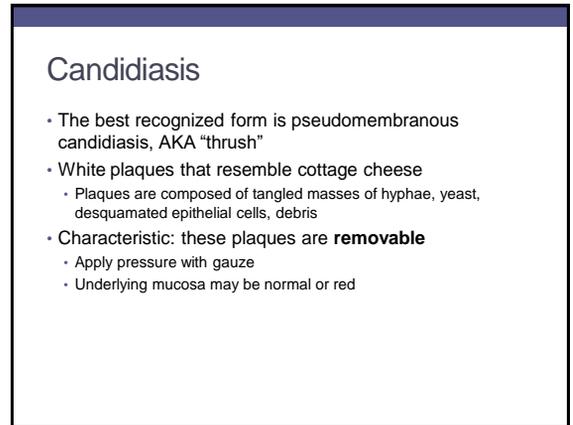
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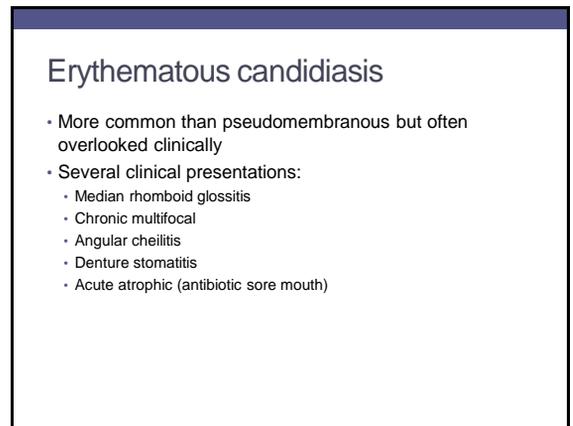


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227



228

Candidiasis - erythematous

- **Median rhomboid glossitis:**
 - Well-demarcated red zone affecting the midline, posterior dorsal tongue just anterior to the circumvallate papilla
 - Asymptomatic and symmetrical
- **Chronic multifocal candidiasis:**
 - Median rhomboid glossitis with signs of infection at other sites
 - Junction of hard and soft palate ("kissing lesion")
 - Angles of the mouth (angular cheilitis)
- **Angular cheilitis:**
 - Occurs most commonly in older edentulous patients
 - Characterized by erythema, fissuring, and scaling at the corners of the mouth
 - Etiology can be fungus, bacteria, or both

229

Candidiasis - erythematous

- **Denture stomatitis:**
 - Redness on denture-bearing areas of a removable denture
 - Denture harbors most of the organism
- **Acute atrophic candidiasis:**
 - "Antibiotic sore mouth" – follows a course of broad-spectrum ABX
 - Mouth feels as though a hot liquid scalded it
 - Diffuse loss of filiform papillae of dorsal tongue (appears bald)
 - Similar appearance & symptomology is noted in xerostomia patients

230

Angular cheilitis



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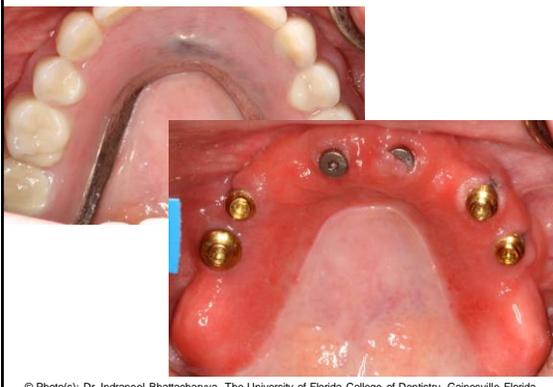
Angular cheilitis



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Denture stomatitis



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233

Candidiasis - treatments

- Clotrimazole 10 mg troche, #70, dissolve 1 on tongue 5x/d for 14 days. Finish all medication
- Fluconazole 100 mg tab, #15, take 2 tab on first day and 1 tab every day after. Finish all medication**
 - **Ensure patient can take this medication! Call pharmacy if you must. Examples of contraindications include cisapride, astemizole, erythromycin, pimozide, and quinidine.
- Clotrimazole 1% cream is over the counter
 - Best for angular cheilitis because it also has antibacterial properties
 - Have patient stop other soothing remedies
- Clean denture if the patient has chronic atrophic candidiasis (denture stomatitis)

234

EPITHELIAL LESIONS

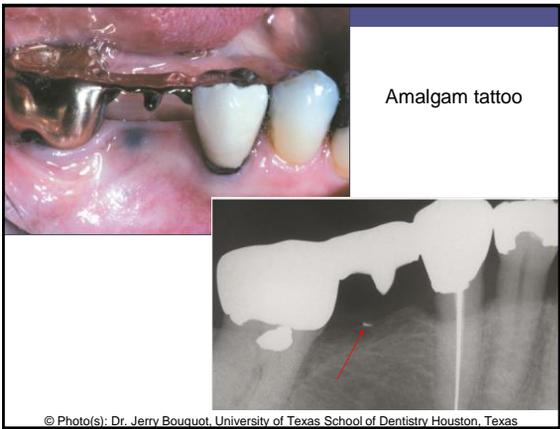
Pigmented lesions, papillary lesions

235

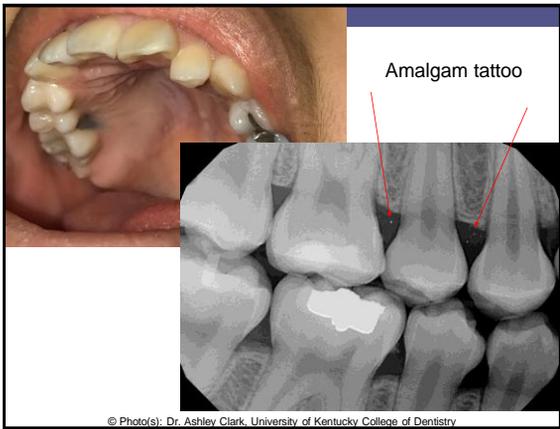
Pigmented lesions

- Differential diagnosis includes: amalgam tattoo, melanotic macule, melanocytic nevus, melanoma
- Anytime one encounters a solitary pigmented lesion in the oral cavity:
 - If appropriate, take a radiograph
 - If radiopacity is present: no further treatment
 - If no radiopacity present: biopsy is required
 - Exceptions: documented, unchanging, labial melanotic macule
 - If it is not melanoma, no further action required unless there is clinical change
- Mucosal melanomas tend to present in an advanced state and have a poor prognosis

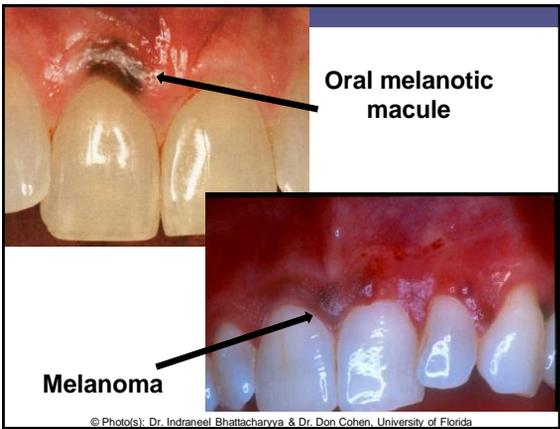
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237



238



239



240

Melanoma



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Melanoma



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242

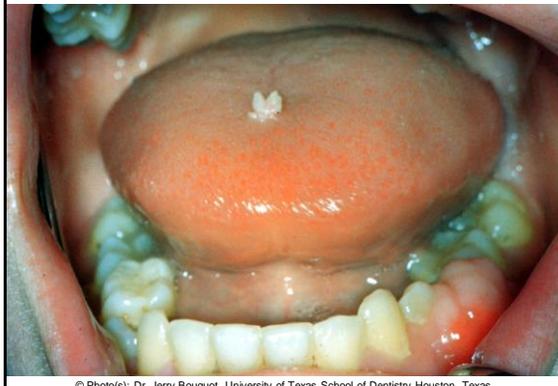
Papillary lesions

- All papillary lesions must be biopsied
- **Squamous papilloma:**
 - Common, solitary, not an STD, not very infectious (doesn't spread easily), no malignant potential, no further action after diagnosis
- **Verruca vulgaris:**
 - Not an STD, multiple lesions, infectious (spreads easily), no malignant potential, follow-up in case the patient has recurrences
- **Condyloma acuminatum:**
 - Is an STD, infectious, no malignant potential unless co-infected with high-risk strain (never been documented in oral cavity), follow-up in case the patient has recurrences

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri. Pp 331-340.

243

Squamous papilloma



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Squamous papilloma



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Squamous papilloma



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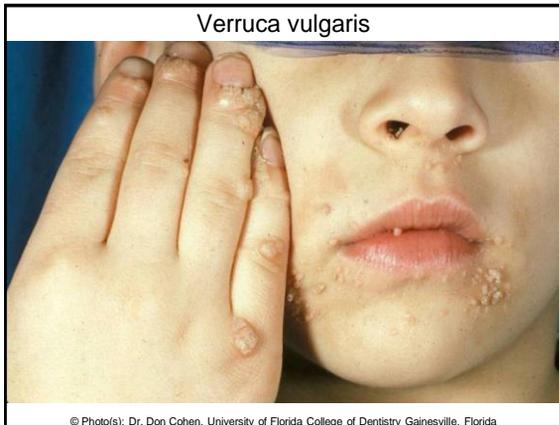
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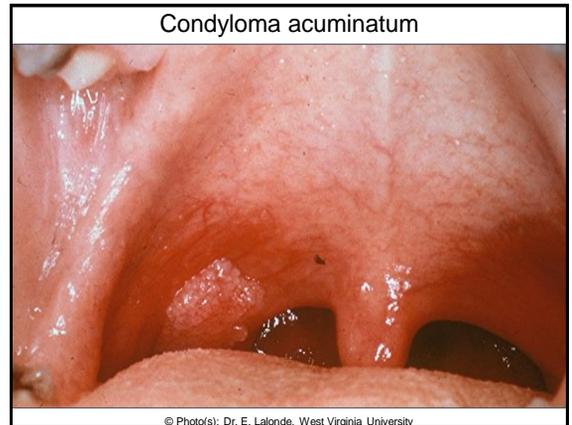
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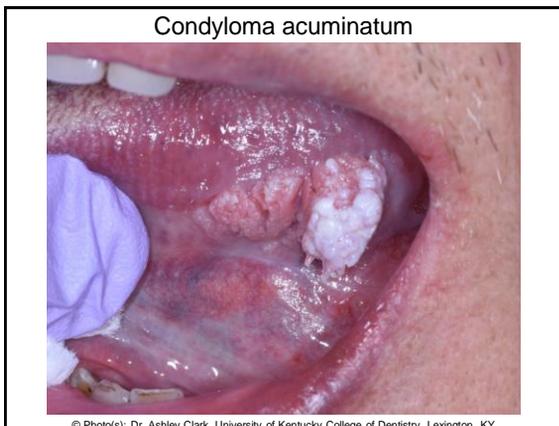
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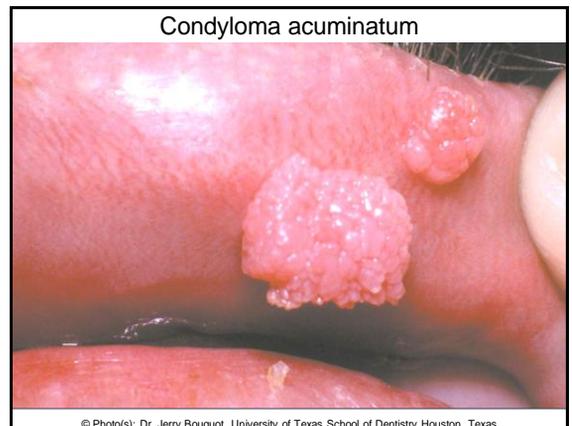
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250



251



252

Condyloma acuminatum



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Condyloma acuminatum



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254

MESENCHYMAL LESIONS

Fibroma
Bumps on the gum

255

Fibroma

- Most common mesenchymal lesion of the oral cavity
- Most common in middle-aged adults around the bite line on the buccal mucosa
- Appears as an asymptomatic, sessile, smooth-surface, mucosal-colored nodule
- Treatment is conservative surgical excision with submission for histopathologic diagnosis

256

Bumps on the gum

- Differential diagnosis includes the 3 Ps: pyogenic granuloma, peripheral ossifying fibroma, and peripheral giant cell granuloma
 - These are all reactive lesions
- Pyogenic granulomas are unique in that they can occur anywhere in the oral cavity (the other two are only found on the ridge) and they occur in pregnant patients with higher frequency
- All should be surgically excised to the periosteum (and scale adjacent teeth) with submission for histopathologic diagnosis
- All have about a 15% recurrence rate

257



258



259



260

DERMATOLOGIC LESIONS

Geographic tongue

261

Geographic tongue

- AKA erythema migrans or benign migratory glossitis
- Affects up to 3% of the population
- Unknown etiology, but an association with fissured tongue
- Lesions appear as red macules with slightly raised, yellowish borders concentrated on the tip and lateral borders of the tongue (Early lesions do not have this border)
- Lesions appear quickly, heal, then appear in a different area
- Most patients are asymptomatic but may experience burning when eating spicy foods
- Only treat symptomatic patients; use topical steroids

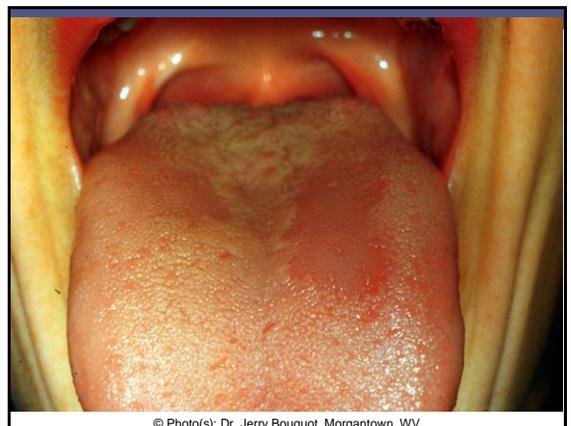
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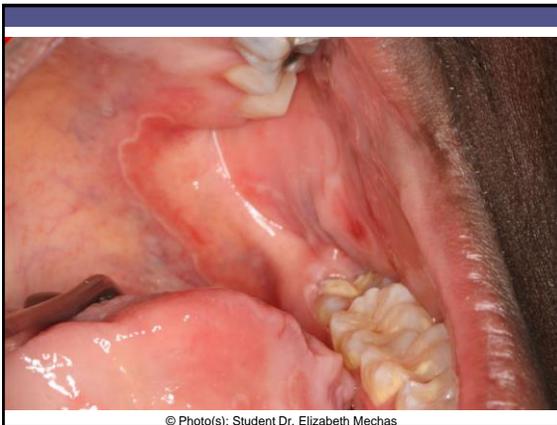
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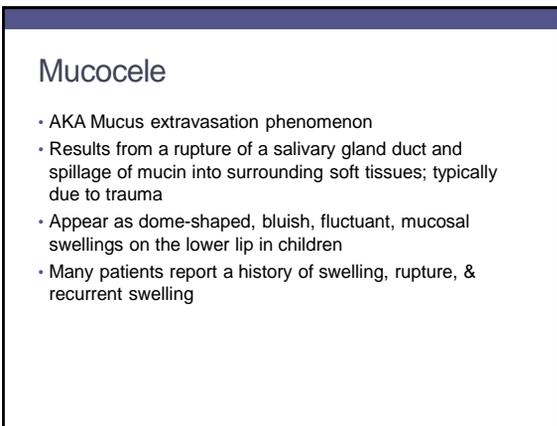


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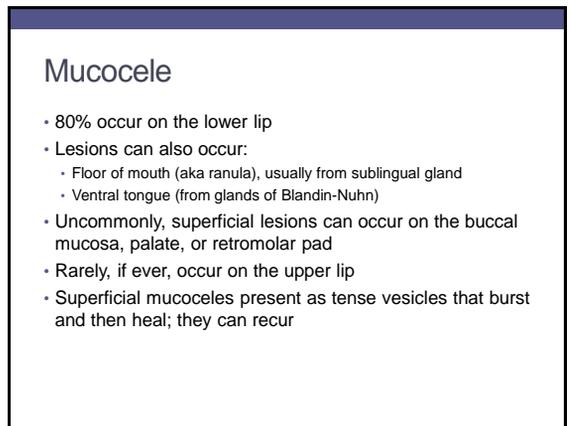
267



268



269



270

Mucocele

- AKA Mucus extravasation phenomenon
- Results from a rupture of a salivary gland duct and spillage of mucin into surrounding soft tissues; typically due to trauma
- Appear as dome-shaped, bluish, fluctuant, mucosal swellings on the lower lip in children
- Many patients report a history of swelling, rupture, & recurrent swelling

Mucocele

- 80% occur on the lower lip
- Lesions can also occur:
 - Floor of mouth (aka ranula), usually from sublingual gland
 - Ventral tongue (from glands of Blandin-Nuhn)
- Uncommonly, superficial lesions can occur on the buccal mucosa, palate, or retromolar pad
- Rarely, if ever, occur on the upper lip
- Superficial mucoceles present as tense vesicles that burst and then heal; they can recur

Mucocele

- Lesions are chronic and local surgical excision with submission for histopathologic diagnosis is necessary
 - Exception: superficial mucoceles
- A lesion which clinically appears to be a mucocele on the retromolar pad should be viewed with suspicion
 - Considered a mucoepidermoid carcinoma until proven otherwise
- To prevent recurrence, the surgeon should remove adjacent minor salivary glands that could be feeding into the lesion
- Prognosis is excellent

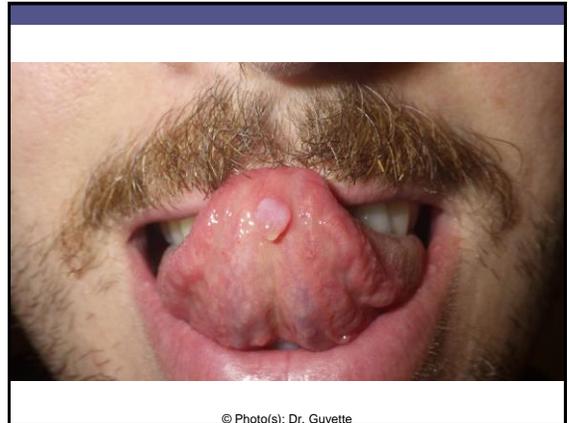
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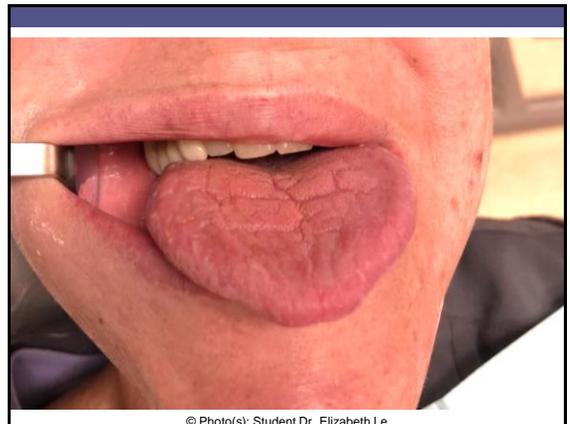


274

Xerostomia

- Very frustrating and treatment is often unsatisfactory
- Most likely due to medications
- Over the counter treatments: Xylimelts®, Salivea®, aloe water held in mouth
 - Note: Biotene® removed lactoperoxidase, lysozyme, and lactoferrin enzymes and is likely not as effective
- Prescription medications: such as NeutraSal®, SalivaMax®, Salivart® Synthetic Saliva, 3M™ Xerostomia Relief Spray
- If these do not work, pilocarpine or cevimeline can be prescribed if no contraindications (such as narrow-angle glaucoma)
 - Pilocarpine = 5 mg up to tid up to a maximum dose of 10 mg tid
 - Cevimeline = 30 mg tid

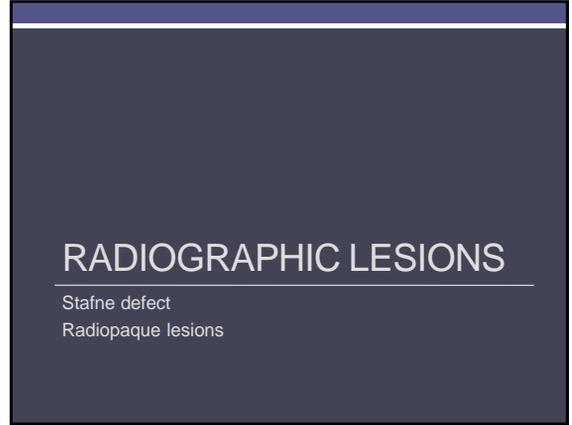
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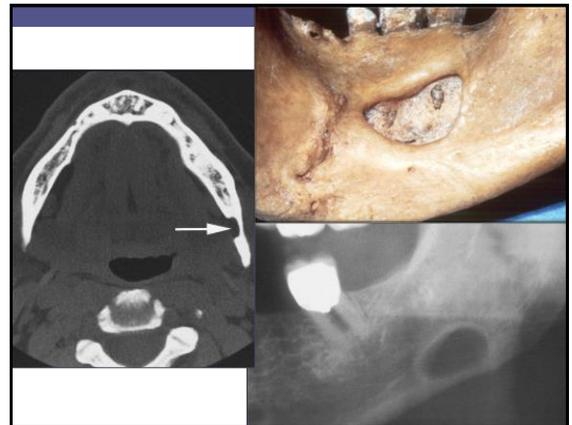


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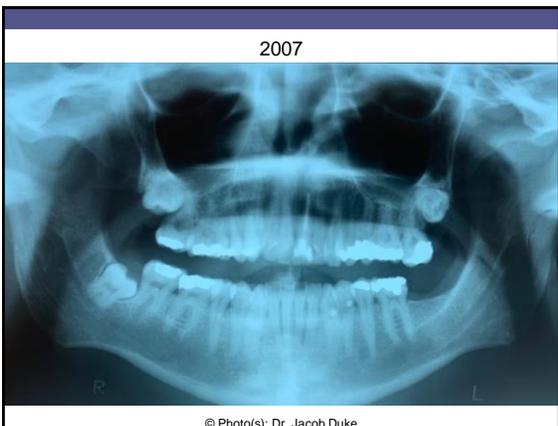
Stafne defect

- AKA submandibular salivary gland depression
- Focal concavity of the cortical bone in the lingual surface of the md
- Classically presents as an asymptomatic, well-circumscribed radiolucency below the mandibular canal in the posterior mandible
- Usually unilateral but can be bilateral
- Found in up to 0.5% of adults; 90% are in males
- No treatment except to radiograph periodically

279



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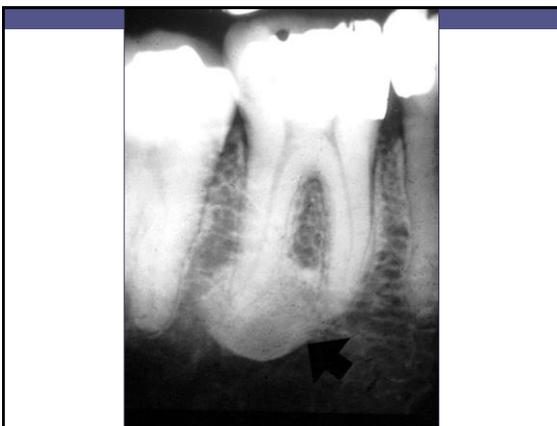


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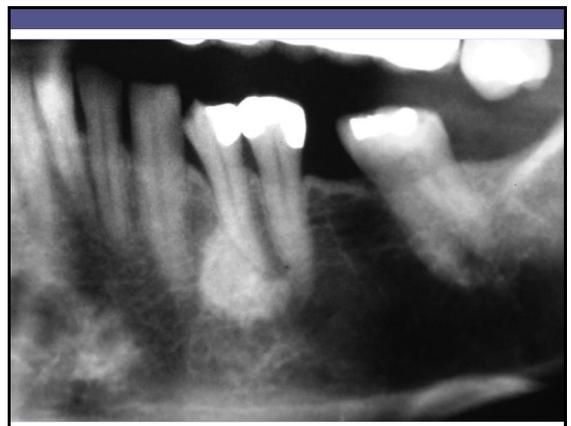
Condensing osteitis

- Localized area of bone sclerosis associated with apices of teeth with pulpitis
- Association with inflammation is necessary for diagnosis
- Radiographically, appears as an increased radiopacity adjacent to a tooth apex that has a thickened PDL or apical inflammatory lesion
- No clinical expansion of bone or radiolucent border
- 85% regress after odontogenic infection is eliminated
 - Residual areas are termed bone scars
- No other treatment is necessary

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287



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Idiopathic osteosclerosis

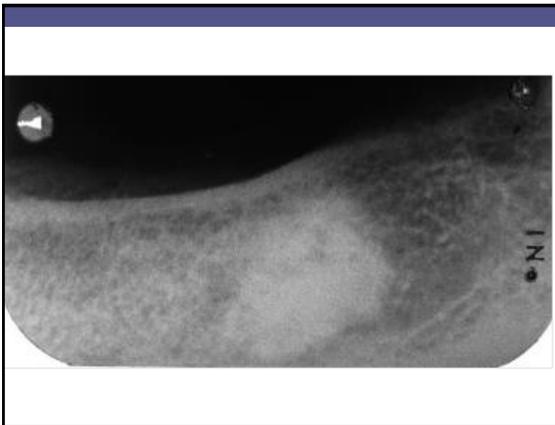
- AKA dense bone island, bone scar, or enostosis
- Focal area of increased radiodensity that is of unknown cause and cannot be attributed to anything else
- Affects approximately 5% of Americans
- Most cases arise in teenage years and remain static
- Invariably asymptomatic and nonexpansile
- 90% occur in the mandible; most often in the first molar area

289

Idiopathic osteosclerosis

- Radiographic features:
 - Well-defined, round or elliptical, radiopaque lesion
 - Most are associated with a root apex
 - Vary from 3mm to 2cm in greatest diameter
 - A radiolucent rim does NOT surround the lesion
- Diagnosis can be made based on history, clinical features, and radiographic findings
- Biopsy is considered only if there are symptoms, continued growth, or cortical expansion
- If lesion is discovered during adolescence, periodic XRAYs are prudent until the area stabilizes; after that, no treatment is necessary

290



291



292

Cemento-osseous dysplasia

- Occurs in tooth-bearing areas of the jaws
- Most common fibro-osseous lesion encountered in clinical practice
- Three variants:
 - Focal
 - Periapical
 - Florid

293

Focal cemento-osseous dysplasia

- Exhibits a single sight of involvement
- 90% occur in females
- Average age is 40
- Most common in Black people; however, this variant is seen in a greater proportion of white people when compared to the periapical and florid variants
- Most commonly present as asymptomatic lesions in the posterior mandible; less than 1.5 cm

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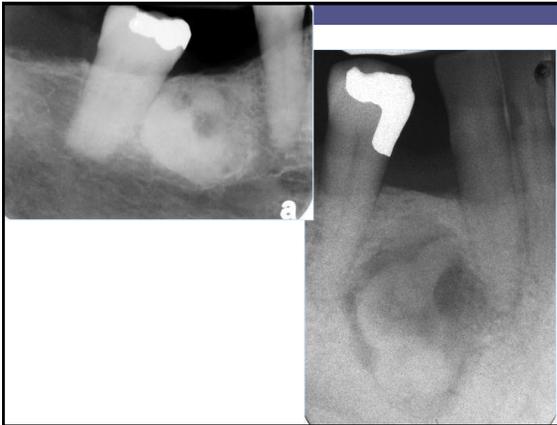
Focal cemento-osseous dysplasia

- Radiographic features:
 - Lesion is usually well-defined
 - Vary from completely radiolucent to densely radiopaque with a thin radiolucent rim
 - The radiolucent rim differentiates from idiopathic osteosclerosis & condensing osteitis
 - Most commonly, there is a mixed radiolucent-radiopaque pattern
 - The PDL is usually intact, though ankylosis can occur

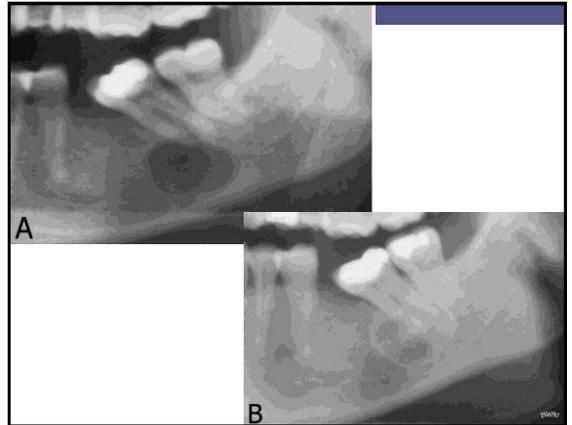
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Periapical cemento-osseous dysplasia

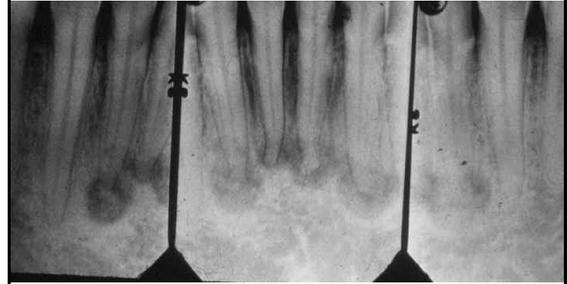
- Involves the periapical region of the anterior mandible
- Multiple foci are usually present
- 90% are female
- 70% are Black
- Average age = 40
- Teeth are vital
- Asymptomatic and discovered when XRAYs are taken for other reasons
- Early lesions are circumscribed areas of radiolucencies involving the apex of a tooth – this lesion looks identical to that of a periapical granuloma or cyst

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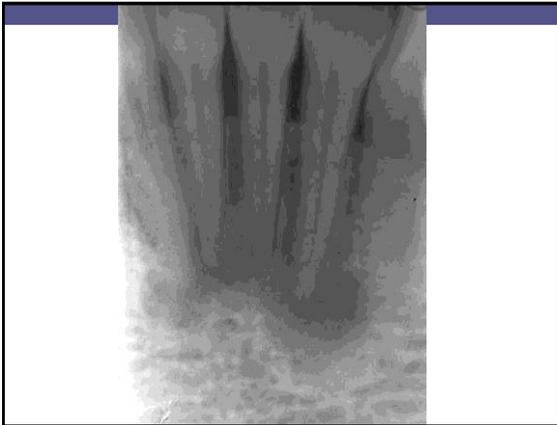
Periapical cemento-osseous dysplasia

- Over time, adjacent lesions fuse together to form a linear pattern of radiolucency that involves the apices of several teeth
- Lesions "mature" over time to have a mixed radiolucent-radiopaque appearance
- End-stage lesions are densely radiopaque with a radiolucent rim
- The PDL will be intact; the lesion will not fuse to the tooth
- Each lesion is self-limiting and progressive growth does not occur

301



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303

Florid cemento-osseous dysplasia

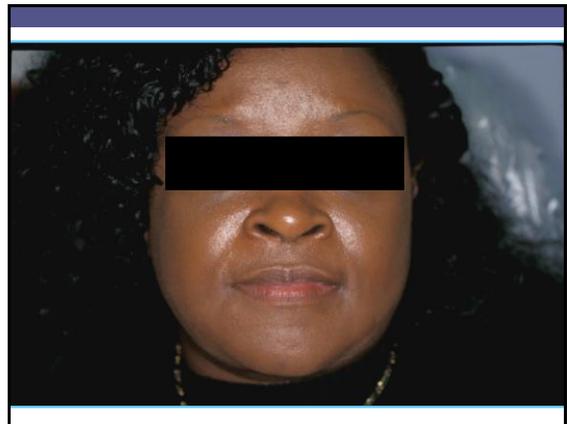
- Multiple focal involvement not limited to the anterior mandible
- Patients may just have lesions in the posterior jaws, but many patients have lesions throughout
- 90% are female
- 90% are Black
- Occurs in middle-aged or older adults
- Marked tendency to be bilateral and symmetrical
- May be completely asymptomatic
- Patients may complain of dull pain or have an alveolar sinus tract which exposes yellowish, avascular bone to the oral cavity
- Rarely, there may be jaw expansion

304

Florid cemento-osseous dysplasia

- Radiographic examination demonstrates an identical pattern of maturation noted in the other two forms:
 - Initially, lesions are predominantly radiolucent
 - Over time become mixed radiolucent-radiopaque
 - End-stage lesions are predominantly radiopaque with a thin radiolucent rim
- Involvement is unrelated to presence or absence of teeth
- Traumatic bone cysts may be seen

305



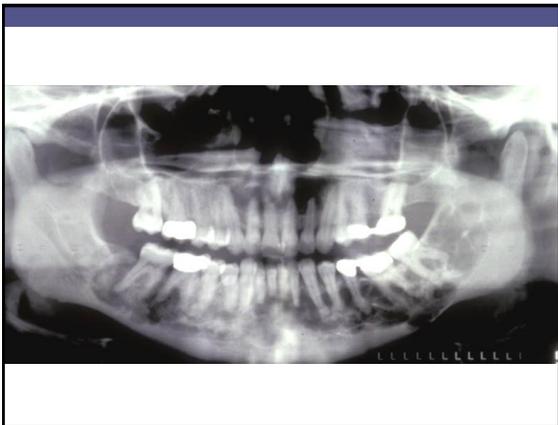
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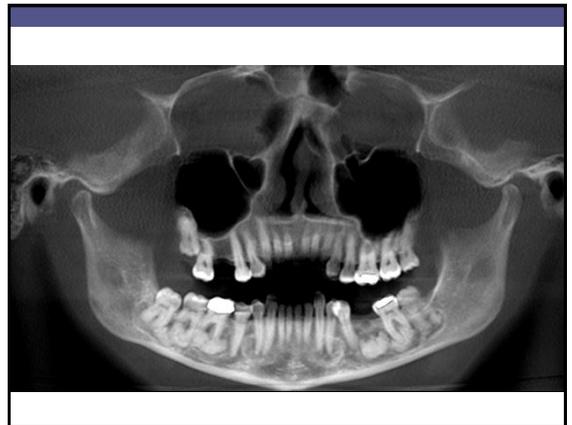
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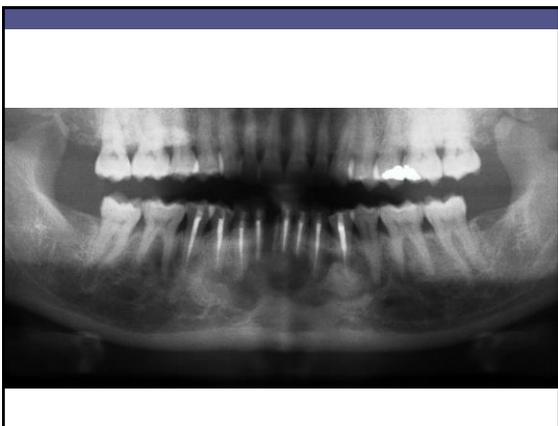
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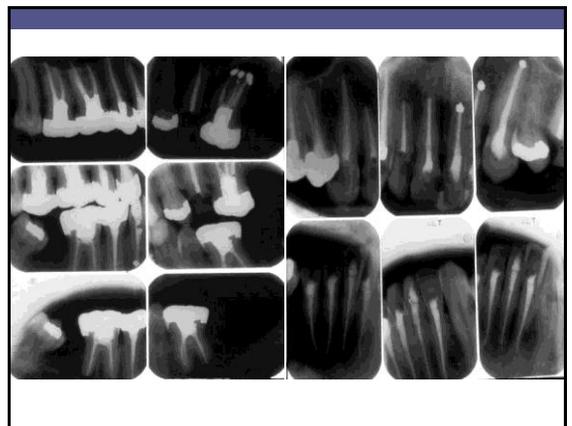
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312

Cemento-osseous dysplasia

- For periapical- or florid cemento-osseous dysplasia, diagnosis can be made from the distinctive clinical & radiographic findings – do not biopsy
 - In fact, biopsy of florid cemento-osseous dysplasia may lead to necrosis due to the hypovascularity
- FCOD (focal cemento-osseous dysplasia) may require biopsy because the features are less specific

313

Cemento-osseous dysplasia

- Encourage good oral hygiene to those with periapical or florid cemento-osseous dysplasia so they keep their teeth as extraction may lead to necrosis
- Management of symptomatic patients is difficult because of the inflammatory component – patients can develop osteomyelitis
 - Antibiotics are indicated but usually not effective
- Follow-up is required as a handful of cases will cause significant expansion

314

Cementoblastoma

- Odontogenic neoplasm of cementoblasts
- Closely related to osteoblastoma
 - The difference: cementoblastomas will be directly attached to the cementum of an adjacent tooth
- 80% arise in the mandible, almost always in the molar/premolar region
- Typically only affect permanent teeth
- There is no sex predilection
- 75% occur before age 30
- Pain and swelling are present in 2/3
- Slow, progressive growth is typical

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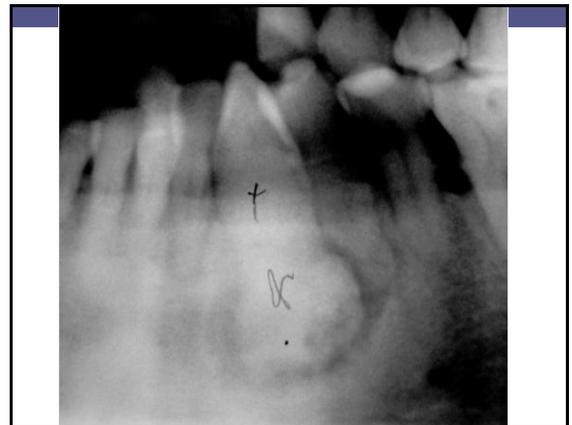
Cementoblastoma

- Radiographic examination:
 - Radiopaque mass that is fused to one or more tooth roots
 - Outline of the root or roots is usually obscured
 - Surrounded by a thin radiolucent rim
- Treatment is surgical extraction of the tooth with the calcified mass
- Excision of mass with root amputation and RTC can be considered
- Recurrence is about 20%; this is probably due to incomplete removal

316



317



318



319



320

MISCELLANEOUS

Burning mouth disorder

321

Burning mouth disorder

- Affects postmenopausal women
- Patients will have a severe burning sensation and 2/3 experience altered taste (metallic, etc.)
- Starts on the dorsal tongue and can spread
- Mild discomfort on waking; pain increases throughout the day but does not interfere with sleep
- May flare with stress or certain foods
- As with all chronic pain conditions, patients are at an increased risk for psychologic dysfunction
- There are no oral findings; this is a diagnosis of exclusion

322

Burning mouth disorder

- Rule out the following:
 - Hypothyroidism, diabetes mellitus, deficiencies in vitamin B, xerostomia, etc.
- Inform patients this is a chronic condition, but it is benign
- Medications:
 - Alpha lipoic acid (over the counter; may be a placebo?): 600 mg/d for 1 month, 200-300 mg per day thereafter
 - Oral disintegrating clonazepam, 0.5 mg. Dissolve on tongue, swish around, and spit. Start with once per day at night. Can increase to tid over the next few weeks.
- Taste distraction – sugarless candy

323

ULCERATIVE CONDITIONS

324

Differential diagnosis

- The differential diagnosis for chronic ulcerative conditions includes:
 - Erosive lichen planus
 - Mucous membrane pemphigoid
 - Pemphigus vulgaris

325

Lichen planus

- Lichen planus is a common, chronic dermatologic disease that can affect the oral mucosa
- Approximately 1% of the population is affected
- May be a reaction to medications, amalgam, etc. – this is better known as “lichenoid mucositis”
 - Patients with suspected lichen planus need a thorough drug history to exclude this as the real diagnosis

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 729-734.
Alrashdan MS, Cirillo N, and McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308:539-551

326

Lichen planus

- Patients are middle-aged adults
- Females are more commonly affected than males
- Cutaneous lesions classically present as purple, pruritic, polygonal papules that affect the extremities
- Skin lesions itch, but the patient will not usually scratch them because they will hurt
- The skin papules will also have a thin, lacelike network of white lines surfacing them – termed **Wickham striae**
- Other possible extraoral sites of involvement include glans penis, vulvar mucosa, and nails

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 729-734.
Alrashdan MS, Cirillo N, and McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308:539-551

327

Lichen planus

- Oral mucosal lesions are typically multiple and nearly always have a bilateral and symmetrical distribution
- The most common sites of involvement is the buccal mucosa
- If lesions are limited to the gingiva, it is termed “desquamative gingivitis” – this occurs in 10%

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pp 729-734.
Alrashdan MS, Cirillo N, and McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308:539-551

328

Lichen planus

- There are several different clinical presentations of oral lichen planus; patients may have more than one clinical form at the same time
- Subtypes and frequency:
 - Reticular - 92%
 - Atrophic - 44%
 - Plaque-like - 36%
 - Papular - 11%
 - Ulcerative - 9%
 - Bullous - 1%
- The plaque-like and papular forms are usually included under the umbrella of reticular oral lichen planus
- The atrophic and bullous forms are usually included in erosive lichen planus

Ion DJ and Setterfield JF. Oral lichen planus. Prim Dent J. 2016;5(1):40-44.

329

Lichen planus - reticular

- The reticular form is the most common
- It is usually asymptomatic
- Presents as white, linear, lace-like lines (Wickham striae)
 - Post-inflammatory melanosis is common, especially in patients of color
- This form is most commonly noted on the buccal mucosa bilaterally; lesions also occur on the lips, tongue, or gingiva
- Patients may complain of roughness or dryness

Ion DJ and Setterfield JF. Oral lichen planus. Prim Dent J. 2016;5(1):40-44.

330

Reticular



331

Lichen planus - papular

- The papular form presents as small, white, raised areas which are approximately 2 mm in greatest diameter
- They are most frequently noted on the dorsum of the tongue

Ion DI and Setterfield JF. Oral lichen planus. *Prim. Dent. J.* 2016;5(1):40-44.

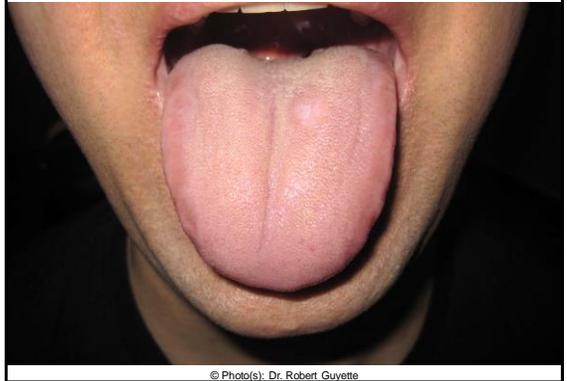
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Reticular & papular



333

Papular



334

Lichen planus – plaque-like

- Plaque-like oral lichen planus presents as thicker, more homogenous white lesions
- They are also present on the buccal mucosa and dorsal tongue
- Plaque-like lesions have been reported to occur more often in patients who smoke

Ion DI and Setterfield JF. Oral lichen planus. *Prim. Dent. J.* 2016;5(1):40-44.

Alrabthan MS, Cillo N, and McCullough M. Oral lichen planus: a literature review and update. *Arch Dermatol Res.* 2016;308:539-551

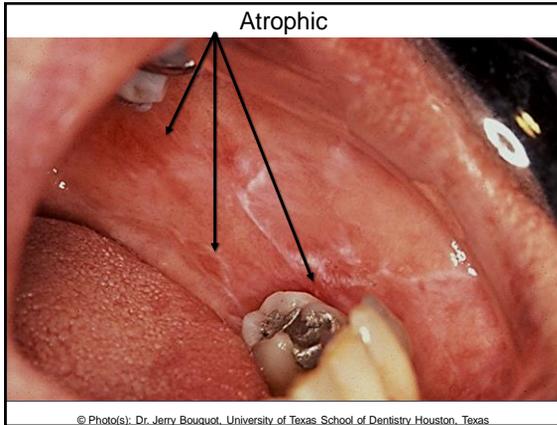
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Lichen planus - atrophic

- The atrophic form presents with white patches that have central areas of mucosa atrophy
- Clinically, these lesions present as erythroleukoplakia
- These patients are usually symptomatic

Ion DI and Setterfield JF. Oral lichen planus. *Prim. Dent. J.* 2016;5(1):40-44.

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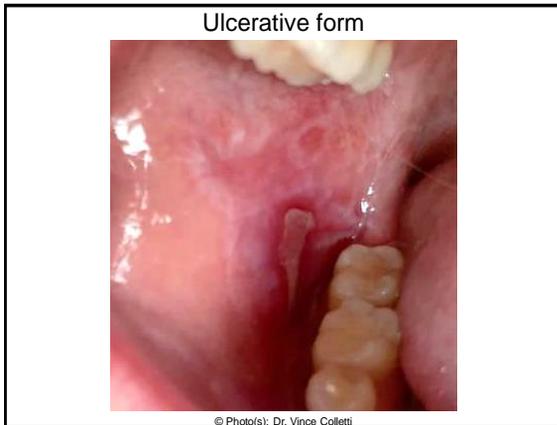
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Lichen planus – ulcerative

- The ulcerative form of lichen planus may develop in reticular regions, atrophic regions, or de novo
- Most commonly, the ulceration will be located centrally in erythematous, atrophic areas; the periphery is usually bordered by Wickham striae
 - Occasionally, only ulcerative lesions without any white areas are present
- Patients complain of soreness, especially when eating spicy or acidic foods

Iton DI and Setterfield JF. Oral lichen planus. *Prim. Dent. J.* 2016;5(1):40-44.
 Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri, Pp 729-734.

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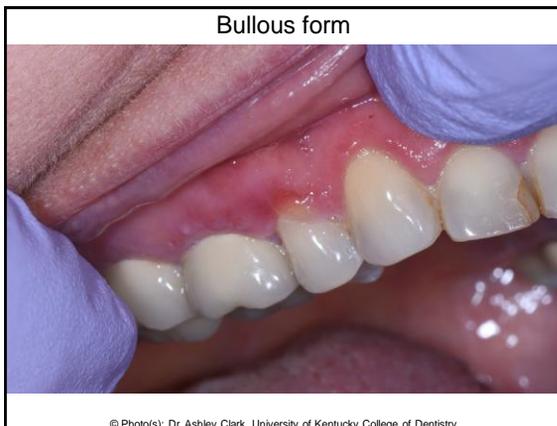
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Lichen planus - bullous

- Bullous oral lichen planus is rare
- It presents as small vesicles or blisters which may be indistinguishable from other vesiculobullous conditions

Iton DI and Setterfield JF. Oral lichen planus. *Prim. Dent. J.* 2016;5(1):40-44.

340



341

Lichen planus

- Reticular lichen planus can usually be diagnosed clinically
- If lesions are symptomatic or unilateral, biopsy is required for definitive diagnosis
- Take two separate biopsies of lesional, but not ulcerated, tissue
 - One specimen should be placed in formalin for routine light microscopy
 - The other specimen should be placed in a transport medium such as Michel solution for direct immunofluorescent (DIF) studies
 - The DIF is helpful for distinguishing lichen planus from other, more rare conditions such as chronic ulcerative stomatitis or lupus erythematosus, which will present with similar histopathologic findings under light microscopy

Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri, Pp 729-734.

342

Lichen planus

- Reticular lichen planus does not require treatment except yearly evaluations
- Topical corticosteroids are the mainstay of treatment for oral erosive lichen planus
- Options include:
 - Midpotency: triamcinolone
 - Potent: fluocinonide
 - Superpotent: clobetasol
 - I use clobetasol propionate 0.05% gel, 15g tube, apply sparingly up to three times per day as necessary for pain
- The lesions should resolve in 2 weeks
- The lesions will recur; the same treatment is used

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 729-734.
Alrashdan MS, Cirillo N, and McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308:539-551

343

Lichen planus

- For cases not responding to steroids, I prescribe a topical tacrolimus
 - Tacrolimus has been associated with increased incidence of lymphoma or other malignancies when used extraorally
- For cases that do not respond to corticosteroids or tacrolimus, referral to a dermatologist is suggested so he or she can prescribe different agents
 - These agents carry more serious side effects and require close monitoring
 - Examples: azathioprine, mycophenolate mofetil, and methotrexate

Ion DI and Setterfield JF. Oral lichen planus. Prim. Dent. J. 2016;5(1):40-44.
Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 729-734.
Alrashdan MS, Cirillo N, and McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308:539-551

344

Lichen planus

- Malignant potential
 - "The World Health Organization (WHO) classifies OLP as a potentially malignant condition, and patients who are diagnosed with OLP should be informed of the low risk of cancer development."
 - I recall my patients at least yearly for examination
 - Re-biopsies may be necessary

Ion DI and Setterfield JF. Oral lichen planus. Prim. Dent. J. 2016;5(1):40-44.
Alrashdan MS, Cirillo N, and McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308:539-551

345

Lichen planus

- In my patient population, I warn the patients that skin and/or genital lesions might occur
- I warn of the anecdotal triggers of stress, trauma, and yeast
- For patients with localized lesions, I will have the patient dip a Q-tip in chlorhexidine gluconate and clean the area before applying the topical steroid

346



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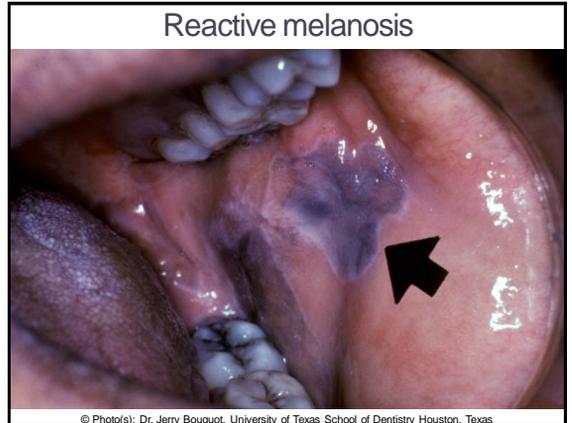
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Reactive melanosis

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Desquamative gingivitis

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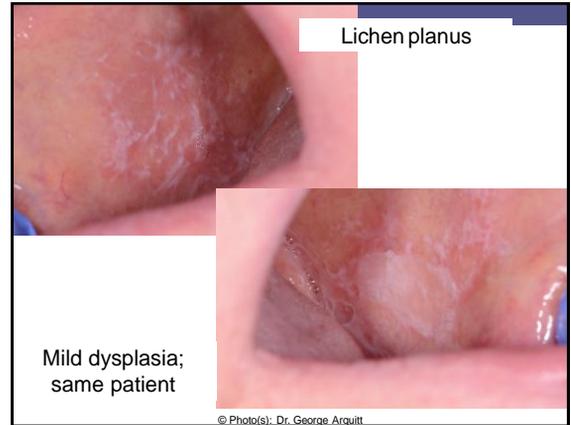
Desquamative gingivitis

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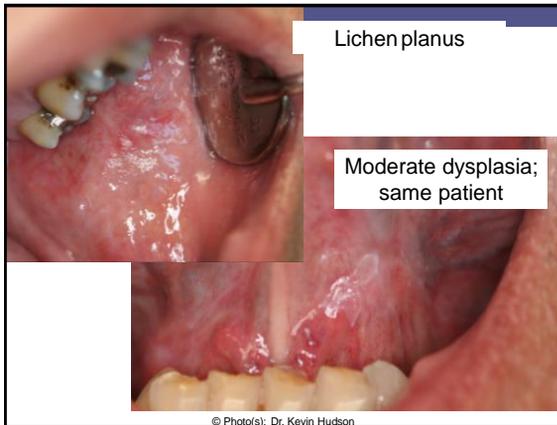
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357

Mucous membrane pemphigoid

- Mucous membrane pemphigoid (MMP) is a group of chronic, blistering, mucocutaneous conditions in which antibodies are directed against the basement membrane
- Termed pemphigoid due to its resemblance to pemphigus
- Another name for the condition is cicatricial pemphigoid
 - Cicatrix means scar
 - Lesions affecting the conjunctival mucosa will scar and lead to blindness, which is the most significant aspect of this disorder

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pg 718-723

358

Mucous membrane pemphigoid

- Disease of adults; average age of onset is around 60
- Incidence is unknown; estimated 1-2 per million
- Females are affected twice as often as males
- Oral mucosa is the most commonly involved site (85%)
 - Lesions begin as vesicles or bullae which may remain intact
 - Blood blisters of the oral mucosa are highly suggestive of MMP
 - The vesicles rupture and leave areas of ulcerated or denuded mucosa
 - These ulcerations are painful and can persist for months without treatment
 - Any oral mucosal surface can be affected, but the gingiva is the most common site of involvement

Hong-Hui X, Werth VP, Parisi E, et al. Mucous Membrane Pemphigoid. Dent Clin N Am. 2013;57:611-630.
Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pg 718-723

359

Mucous membrane pemphigoid

- The most serious aspect of this disease are the ocular lesions, which affect anywhere from 25%-65% of patients
- The first manifestation is subconjunctival fibrosis, which can be detected by an ophthalmologist using slit-lamp examination
- With more advanced lesions, the conjunctiva become inflamed and eroded
- Without treatment, scarring and adhesions (termed symblepharons) can cause the eyelids to turn inward, causing the eyelashes to rub against the cornea

Hong-Hui X, Werth VP, Parisi E, et al. Mucous Membrane Pemphigoid. Dent Clin N Am. 2013;57:611-630.
Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth edition, Elsevier, Inc.: St. Louis, Missouri, Pg 718-723

360

Mucous membrane pemphigoid

- Scarring closes the opening of the lacrimal glands, which causes extremely dry eyes
- In an attempt at protection, the cornea produces keratin (which is opaque and not removable); this is one way patients become blind
- In extreme cases, the eyelids scar together – this is another way patients become blind
- Females may experience pain due to vaginal lesions

Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc., St. Louis, Missouri. Pp 718-723.

361

Mucous membrane pemphigoid

- If pemphigoid is suspected, two biopsies should be obtained from perilesional tissue
 - One specimen should be placed in formalin for routine light microscopy
 - The other specimen should be placed in a transport medium such as Michel solution for direct immunofluorescent (DIF) studies
- In order to be diagnostic, the connective tissue must have overlying, intact epithelium (lesional, ulcerated tissue will not have epithelium)
 - This is challenging because the epithelium tends to separate easily from the underlying connective tissue
 - This is why taking two pieces rather than taking one large section and cutting it in half is the preferred technique

Hong-Hui X, Werth VP, Parisi E, et al. *Mucous Membrane Pemphigoid*. *Dent Clin N Am*. 2013;57:611-630.

362

Mucous membrane pemphigoid

- Once diagnosis is established, the patient should be referred to an ophthalmologist familiar with ocular lesions of MMP
 - This referral should be made regardless if the patient is having ocular complains
 - If the patient has lesions at other sites, the patient should be referred to the appropriate specialist
- The primary goal for treatment is to prevent blindness

Hong-Hui X, Werth VP, Parisi E, et al. *Mucous Membrane Pemphigoid*. *Dent Clin N Am*. 2013;57:611-630.
Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc., St. Louis, Missouri. Pp 718-723.

363

Mucous membrane pemphigoid

- Treatment varies with each patient
 - If only oral lesions are present, topical steroids can be used
 - I use clobetasol propionate (same as patients with lichen planus)
 - Tacrolimus can be used if the patient is not responsive to topical steroids
- If patients require systemic medications, I refer to a dermatologist (or ophthalmologist will prescribe them if the patient has ocular lesions)
 - Treatments include dapsone, systemic corticosteroids, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, and etcetera.

Hong-Hui X, Werth VP, Parisi E, et al. *Mucous Membrane Pemphigoid*. *Dent Clin N Am*. 2013;57:611-630.
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364



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373

Pemphigus vulgaris

- Seen in 1-5 per million people
- If untreated, patients will succumb to disease
- Average age of onset is 50 years old; no sex predilection
- The oral lesions are the "first to show, last to go"
 - Over 50% will have oral lesions for up to a year before cutaneous lesions (and close to 100% develop oral lesions eventually)
 - Oral lesions are very difficult to resolve
- Examination shows superficial erosions throughout the oral mucosa without intact vesicles

Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 712-716.

374

Pemphigus vulgaris

- The cutaneous lesions are flaccid vesicles or bullae which rupture quickly to leave a denuded surface
 - Patients will have a positive Nikolsky sign, which means a bullae can be induced on normal-appearing skin after applying lateral pressure
- Ocular lesions can occur, but scarring is uncommon
- Without proper treatment, the oral and cutaneous lesions are progressive
 - Before corticosteroid therapy was developed, patients succumbed to infections or electrolyte imbalances

Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 712-716.

375

Pemphigus vulgaris

- If pemphigus is suspected, two biopsies should be obtained from perilesional tissue
 - One specimen should be placed in formalin for routine light microscopy
 - The other specimen should be placed in a transport medium such as Michel solution for direct immunofluorescent (DIF) studies
- In order to be diagnostic, the connective tissue must have overlying, intact epithelium (lesional, ulcerated tissue will not have epithelium)
 - This is challenging because the epithelium tends to separate easily from the underlying connective tissue
 - This is why taking two pieces rather than taking one large section and cutting it in half is the preferred technique

376

Pemphigus vulgaris

- Treatment:
 - Refer to dermatologist – these patients require systemic corticosteroids in combination with other steroid-sparing agents
 - Patients will be placed on high doses of systemic corticosteroids when first diagnosed in an attempt to clear the lesions; then patients will be placed on as low of a dose as possible to control the disease
 - Up to 30% will experience disease remission after 10 years
 - Up to 10% of these patients succumb to complications of long-term systemic corticosteroid use

Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*. Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 712-716.

377



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380



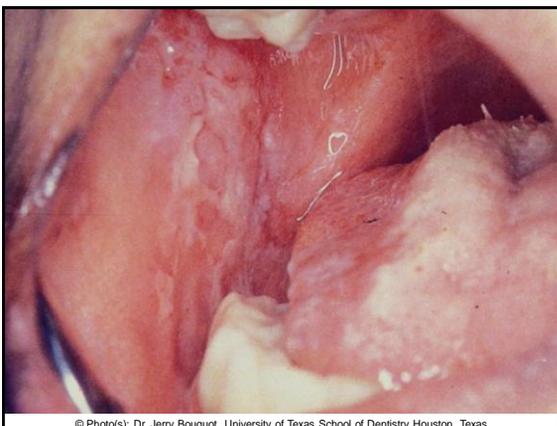
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384



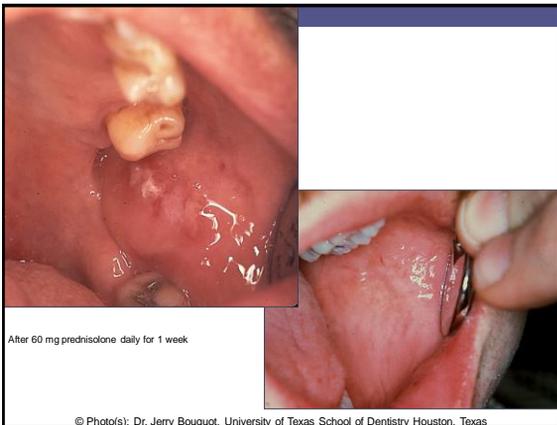
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385



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386



After 60 mg prednisolone daily for 1 week

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387

Takeaways

- If you suspect lichen planus, pemphigoid, or pemphigus – diagnose before treating!
 - Do not give steroids before biopsy (DIF will be false -)
 - Each condition has different systemic ramifications
- Once diagnosed, all are typically treated effectively with powerful topical steroids
- Patients with lichen planus may get genital lesions – may require referral to gynecologist
- Patients with pemphigoid MUST be seen by an ophthalmologist, regardless of clinically visible ocular lesions; they may also require referral to gynecologist
- Patients with pemphigus MUST be seen by a dermatologist

388

CONCLUSIONS & QUESTIONS

AshleyClarkDDS@gmail.com

389