POTENTIAL MALIGNANCIES IN THE ORAL CAVITY: WHAT YOU NEED TO KNOW

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Conflicts of interest & disclaimers

- This presentation is sponsored by Pierrel Pharma; they have generously covered my honorarium for this talk.
- The opinions expressed in this presentation are those of the speaker and not necessarily those of my company.
- The opinions expressed in this course should not be construed as advice to care for specific patients.

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Objectives

- Upon completion of this course, the participant should be able to:
  - Discuss potentially malignant disorders of the oral cavity, specifically leukoplakia
  - Determine an appropriate treatment plan for patients with leukoplakia
  - Discuss other ways in which oral potentially malignant disorders present

POTENTIALLY MALIGNANT DISORDERS

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Potentially malignant disorders

- The WHO adopted the phrase “potentially malignant disorders” to describe lesions with potential to progress to malignancy
- Terminology has changed; “premalignant” 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.

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.

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(12):1600-1609.

LEUKOPLAKIA

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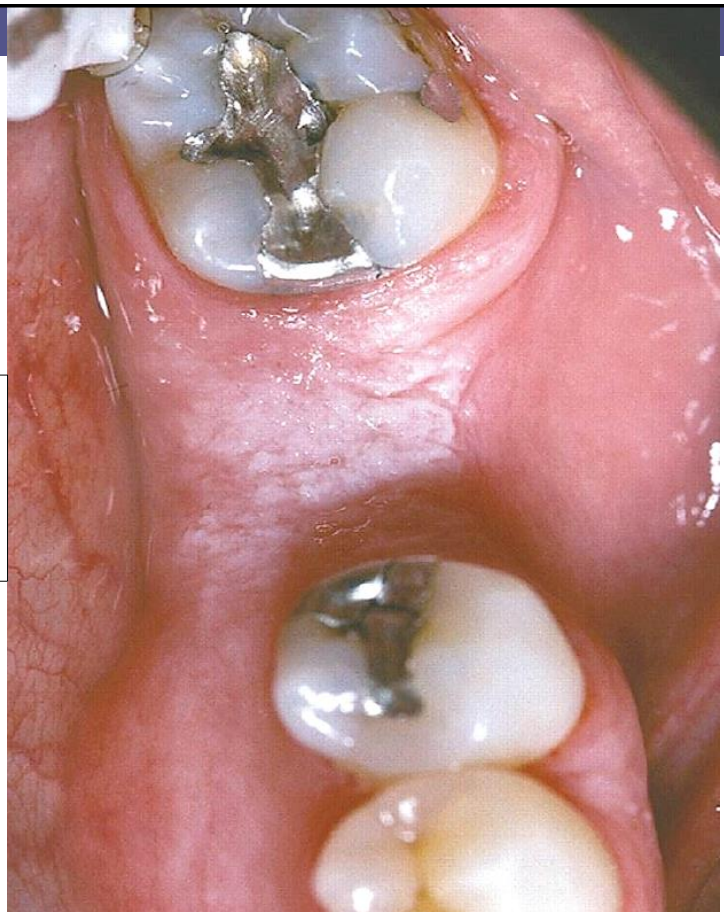
Leukoplakia

- 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

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

Frictional keratosis, not leukoplakia



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.

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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.

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 the lip vermilion, buccal mucosa, and gingiva
- 90% with dysplasia or carcinoma are found on the lip vermillion, lateral/ventral tongue, and floor of mouth

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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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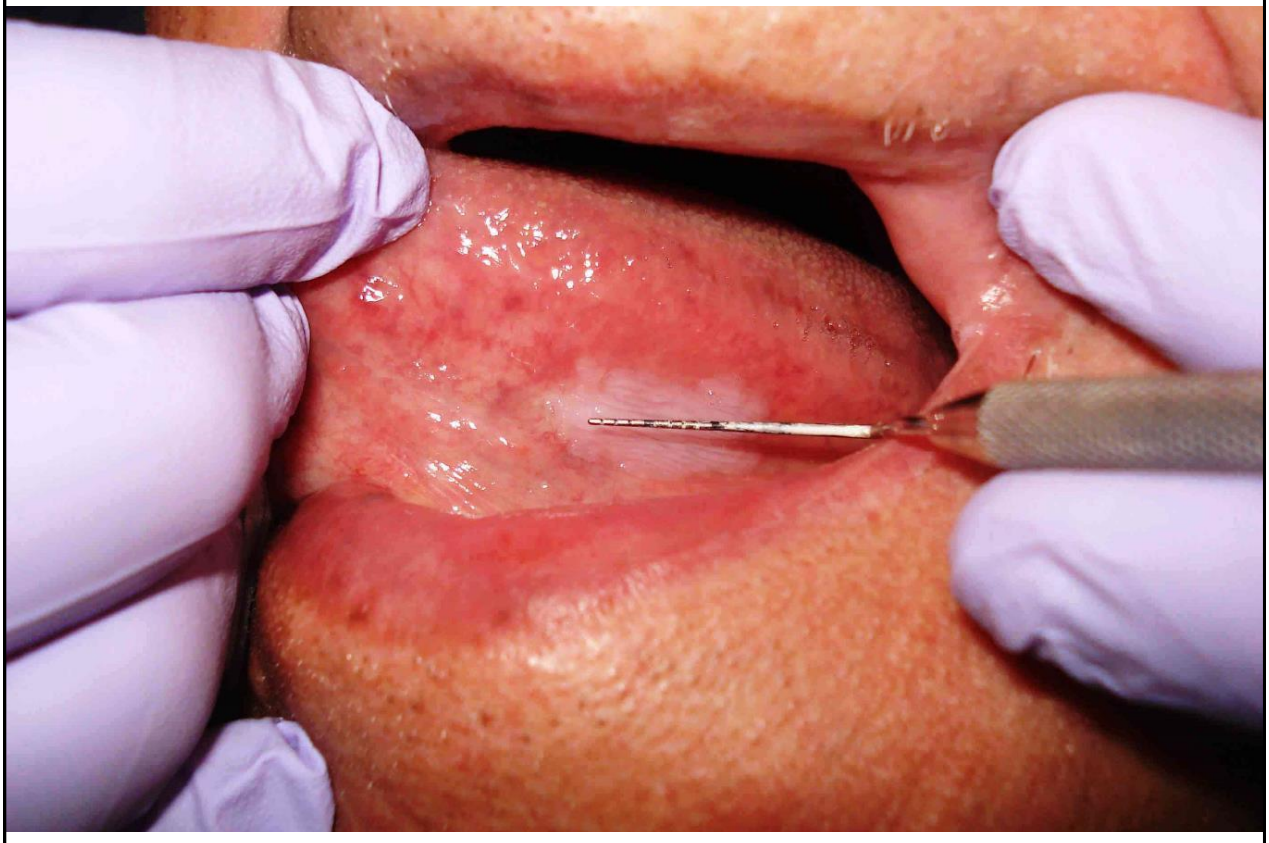
Thin leukoplakia; hyperkeratosis



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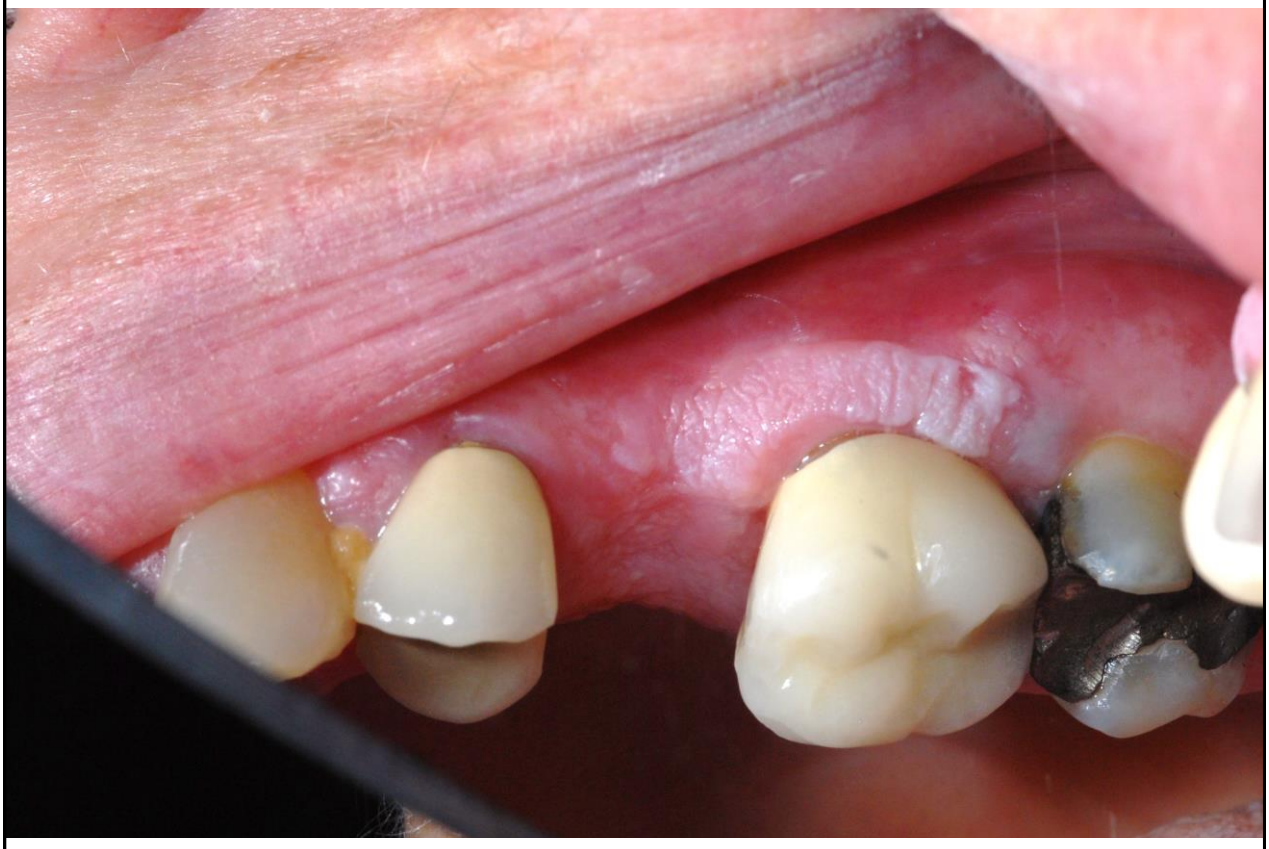
Thin leukoplakia; hyperkeratosis



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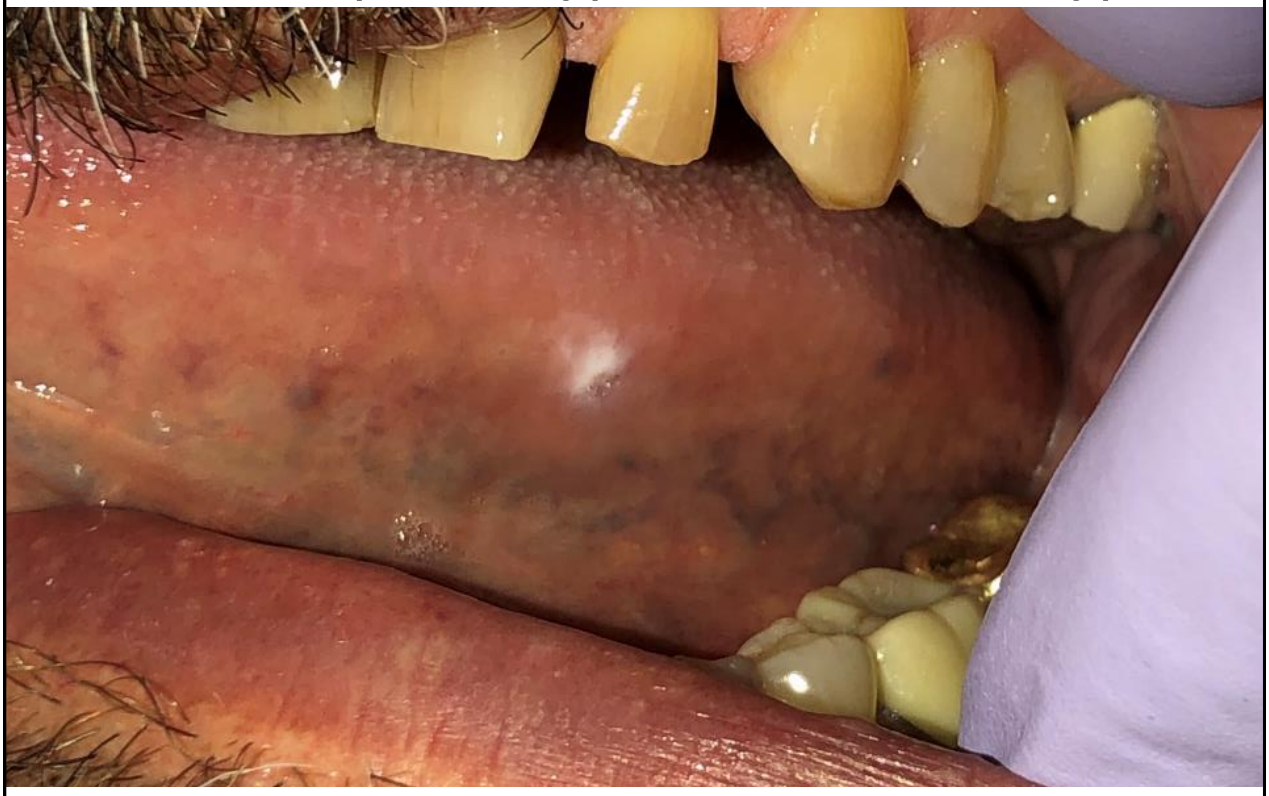
Thin leukoplakia; hyperkeratosis with atypia



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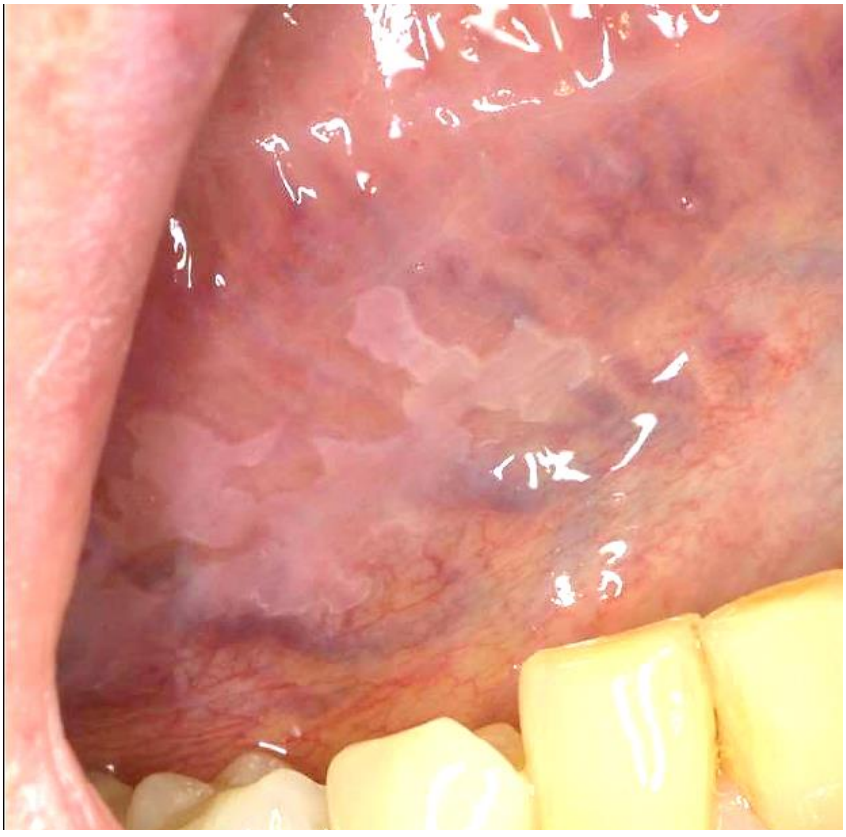
Thin leukoplakia; mild dysplasia



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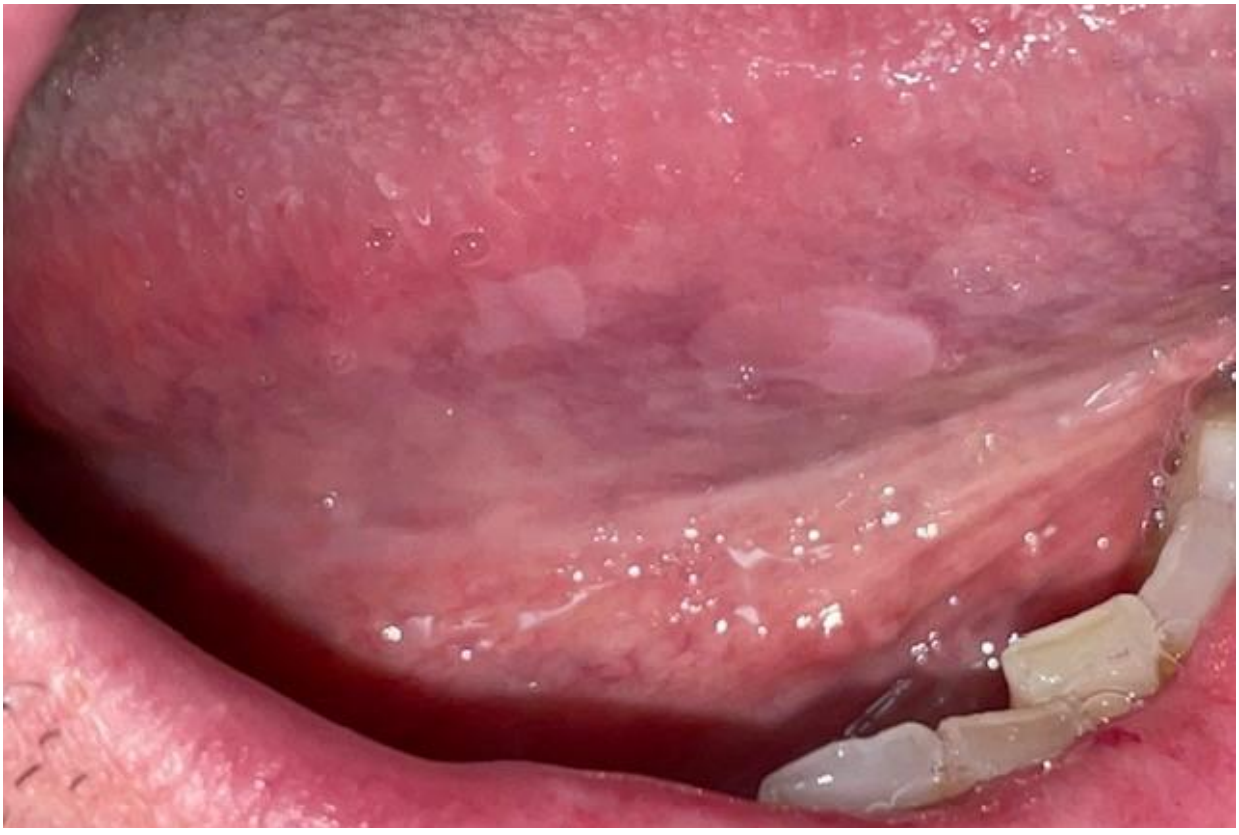
Thin leukoplakia; carcinoma-in-situ (HPV-16)



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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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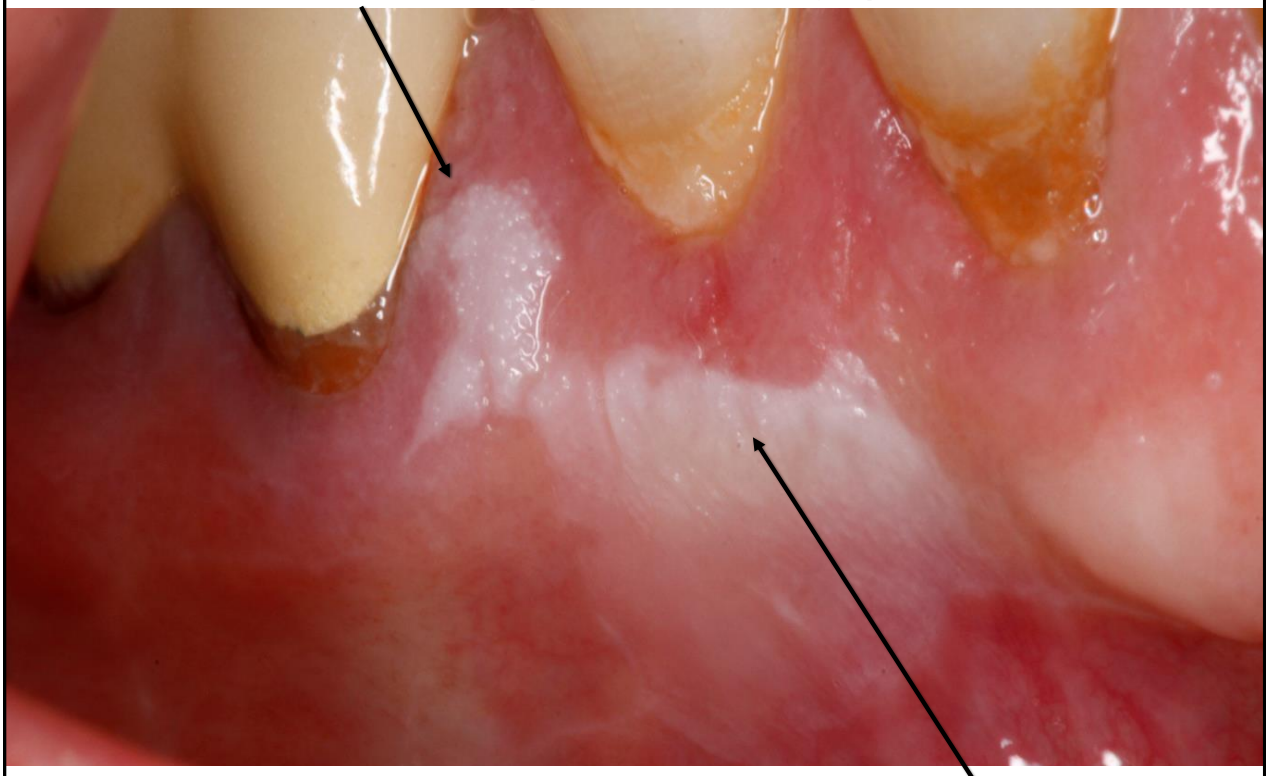
Thick leukoplakia; mild dysplasia



Thin leukoplakia; hyperkeratosis

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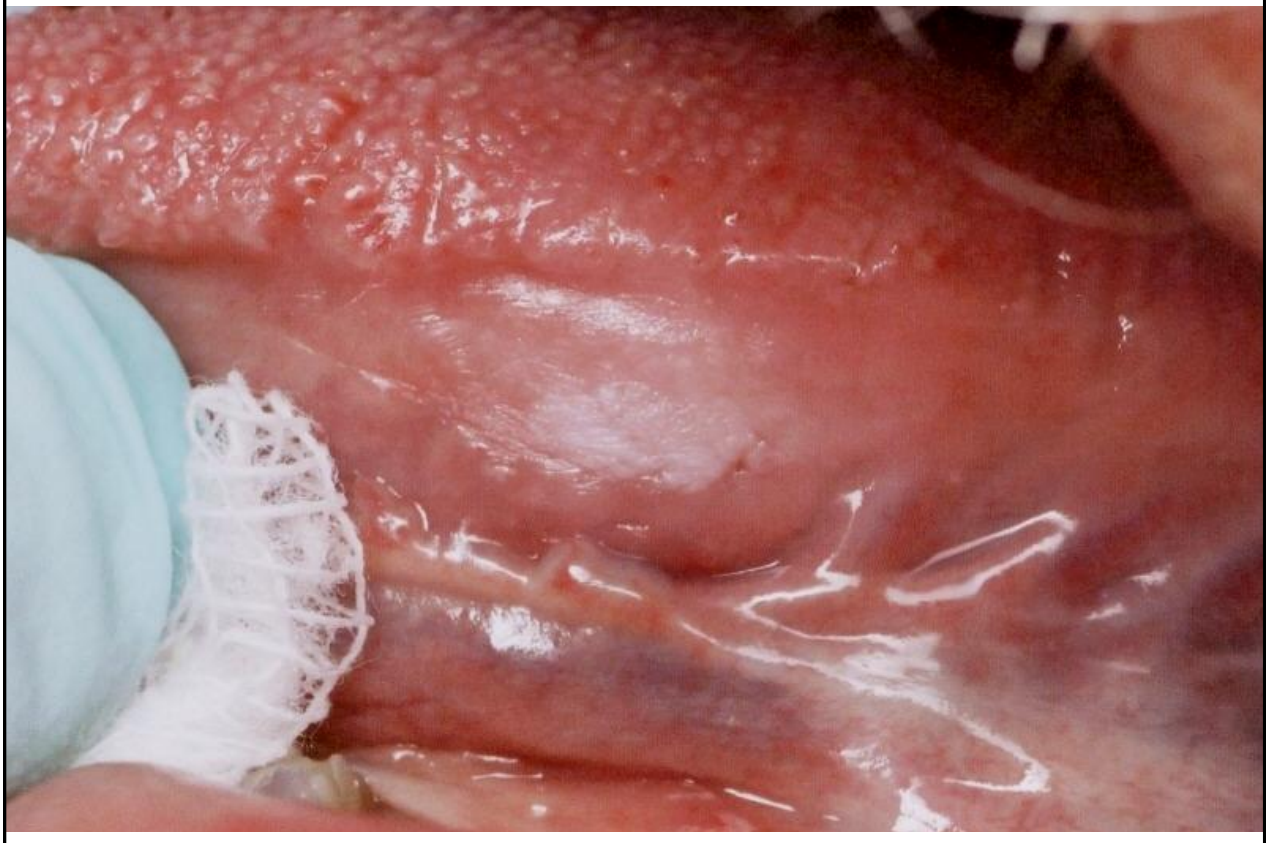
Thick leukoplakia; mild dysplasia



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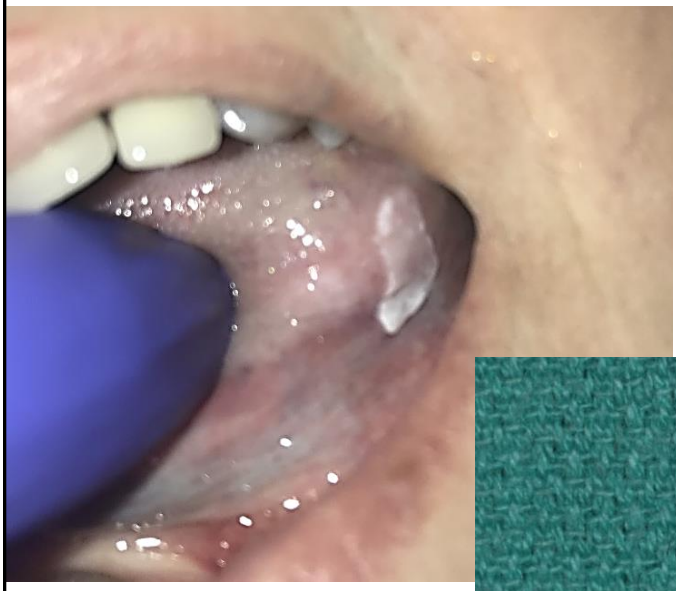
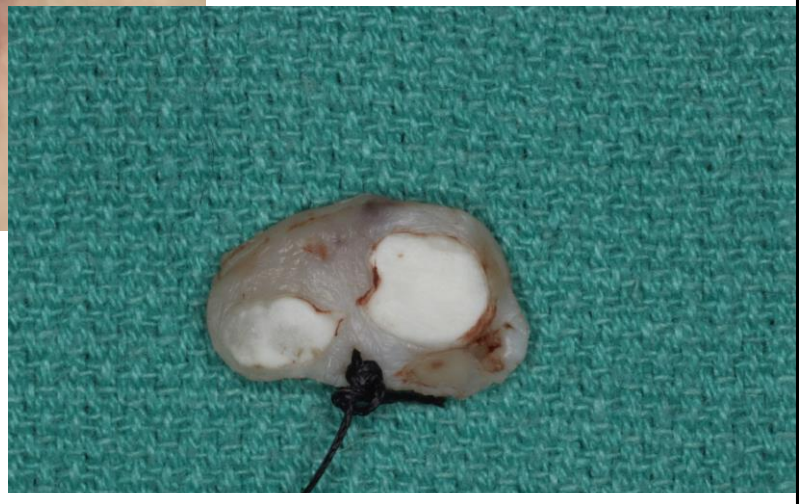
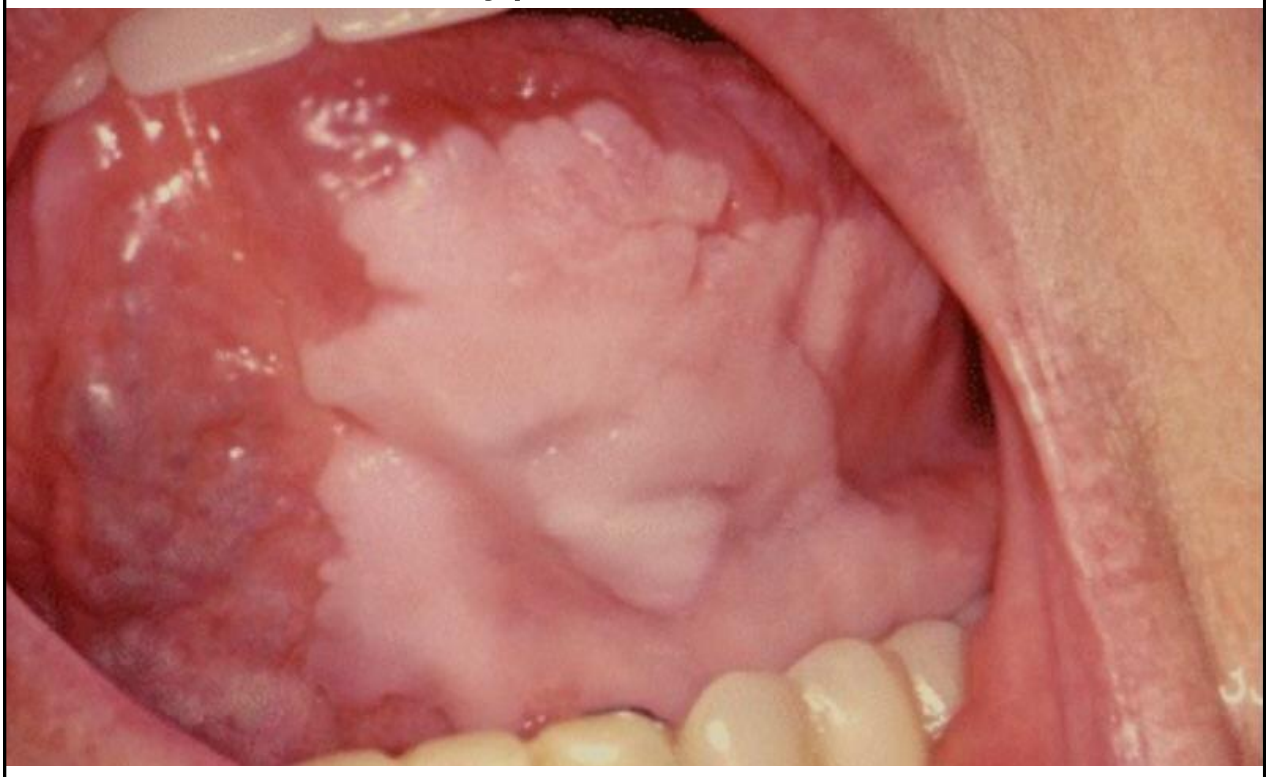
Thick leukoplakia; mild to focally moderate dysplasia





Thick leukoplakia; mild dysplasia with hyperkeratosis



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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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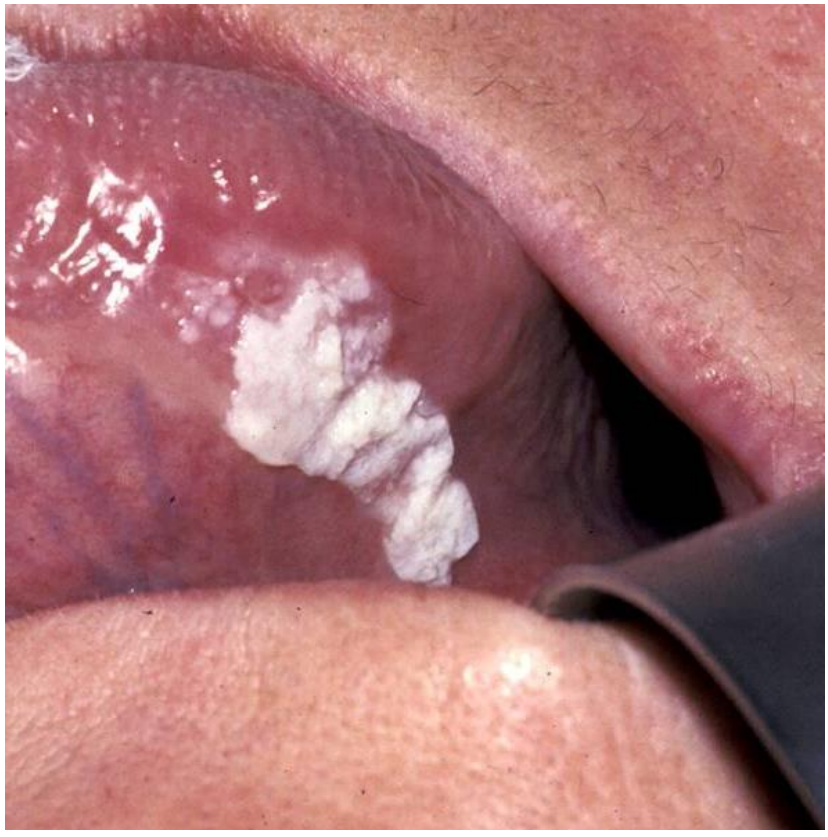
Verruciform leukoplakia; severe dysplasia



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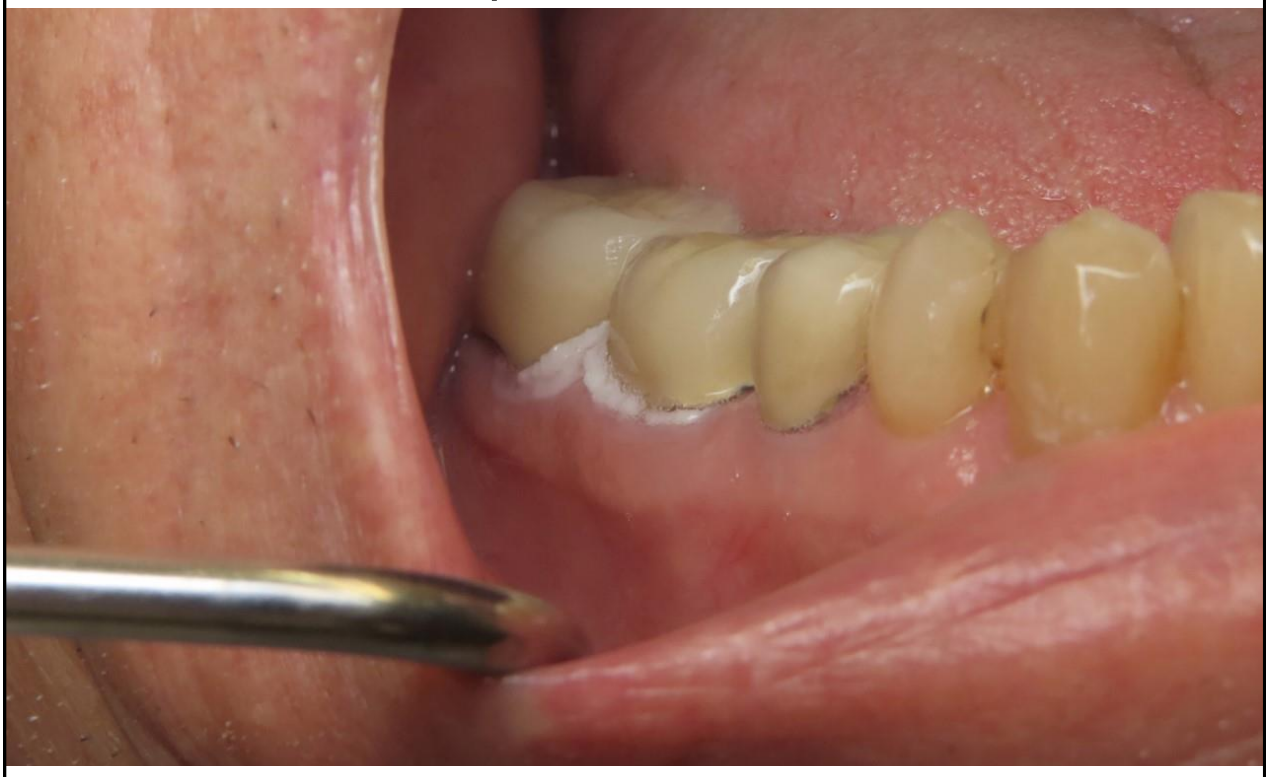
Verruciform leukoplakia; atypical epithelial proliferation



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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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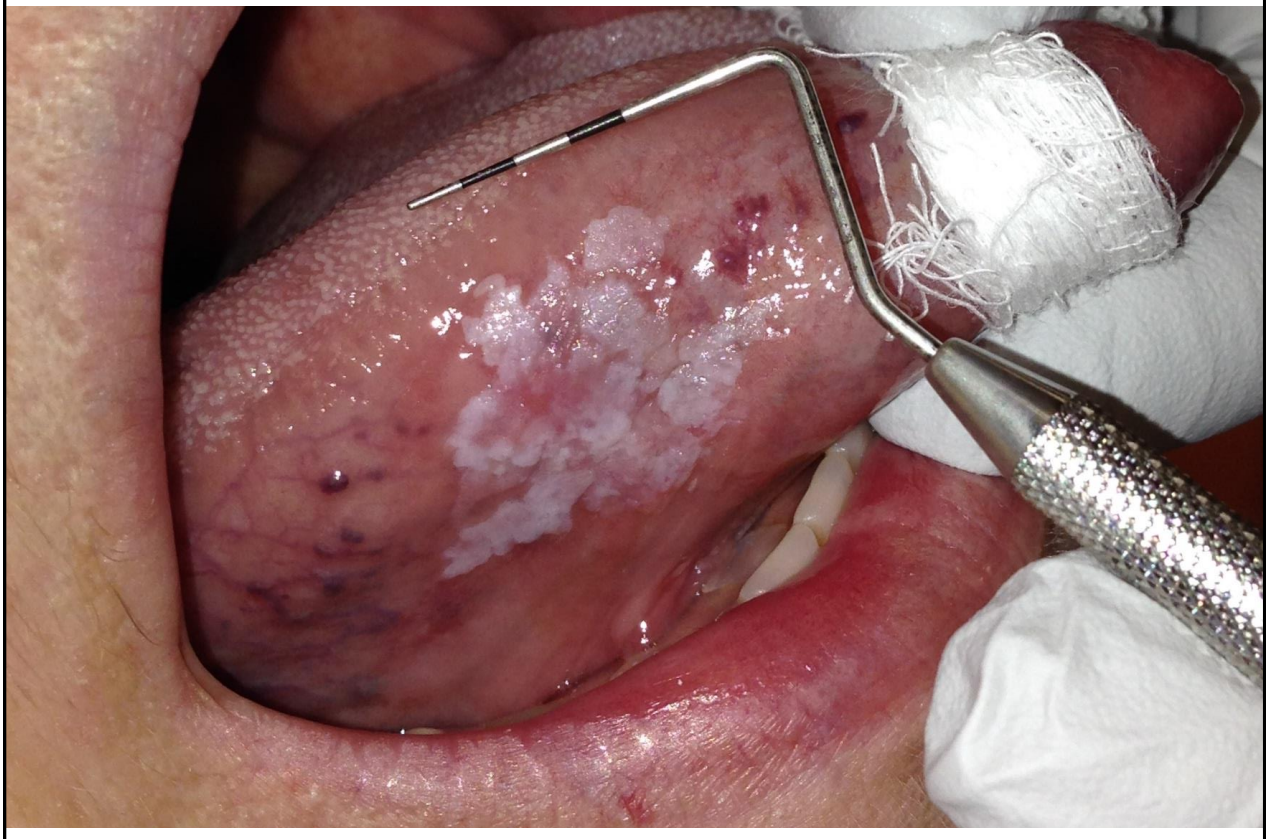
Erythroleukoplakia; moderate dysplasia



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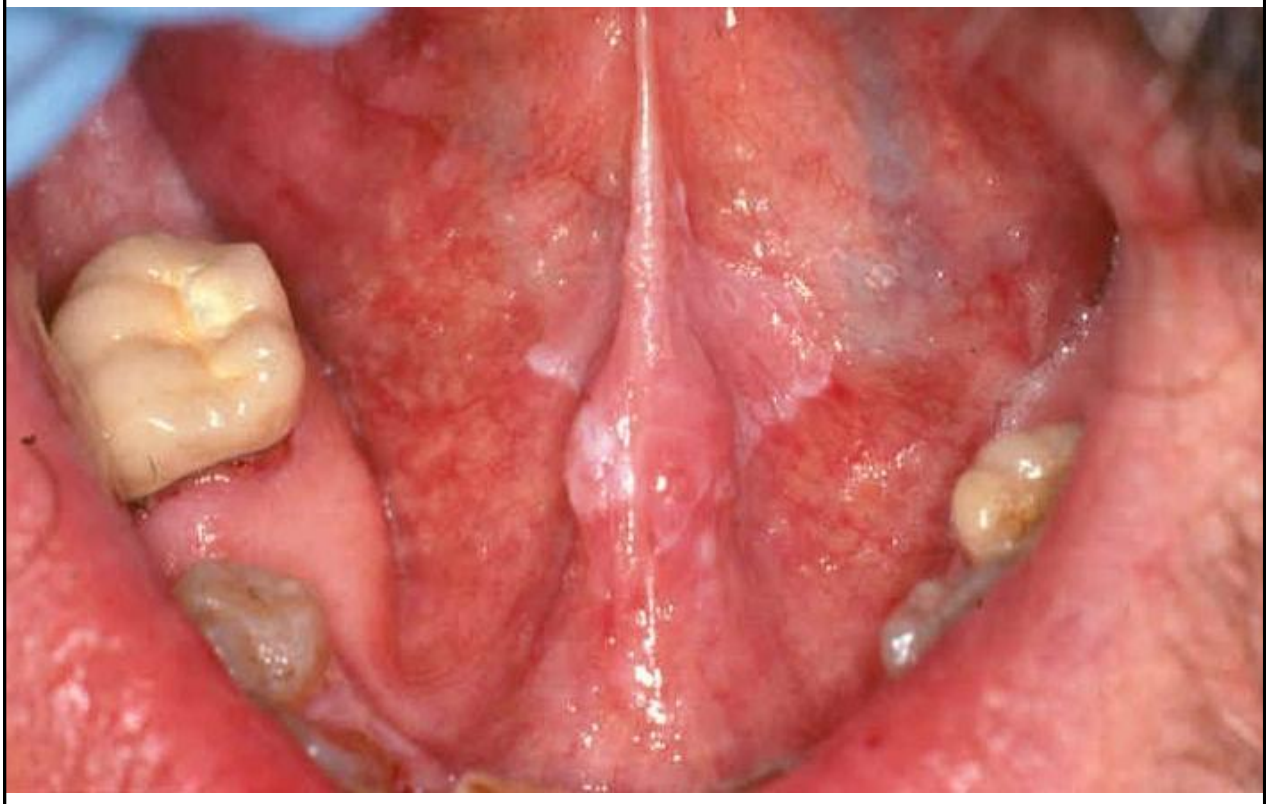
Erythroleukoplakia – severe dysplasia



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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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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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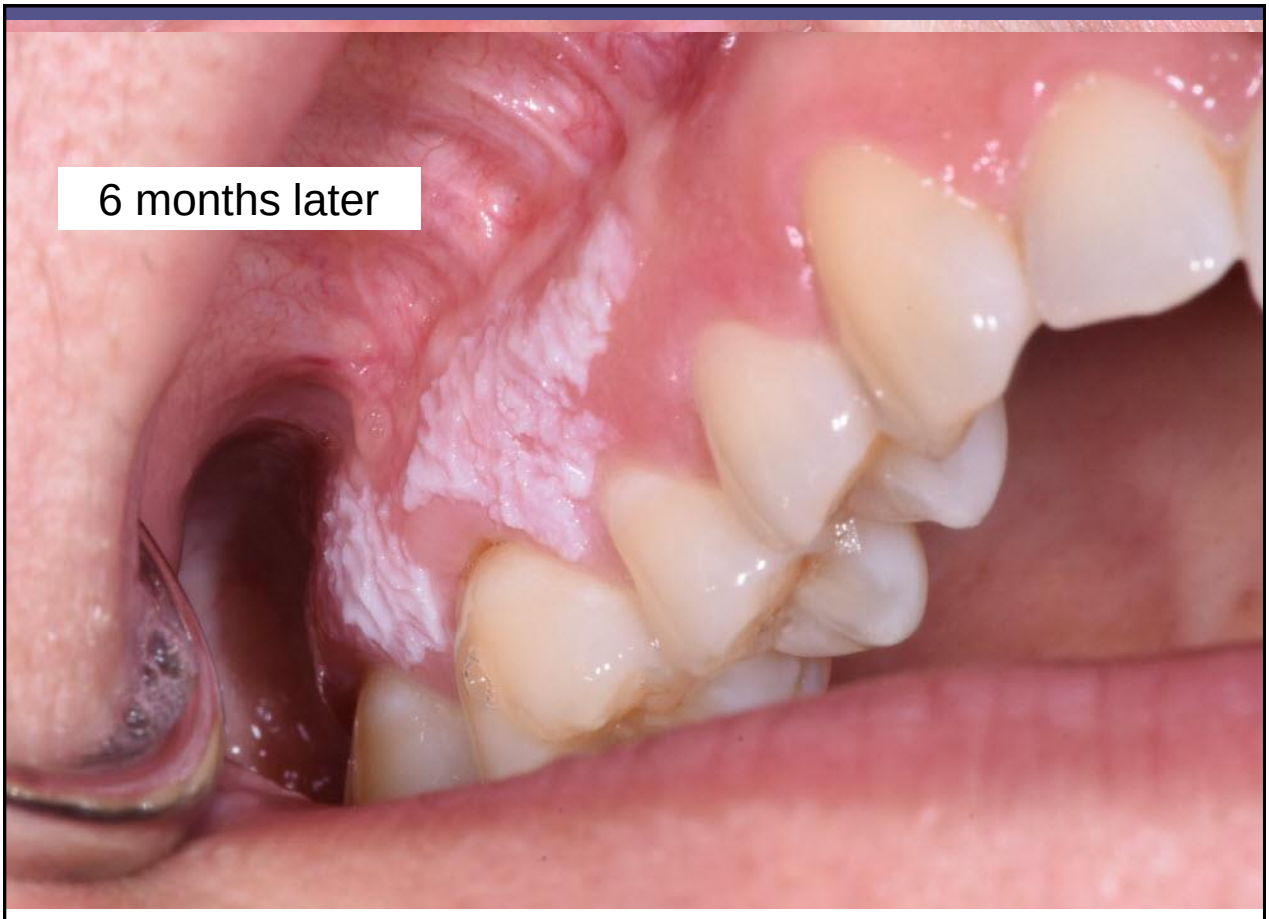

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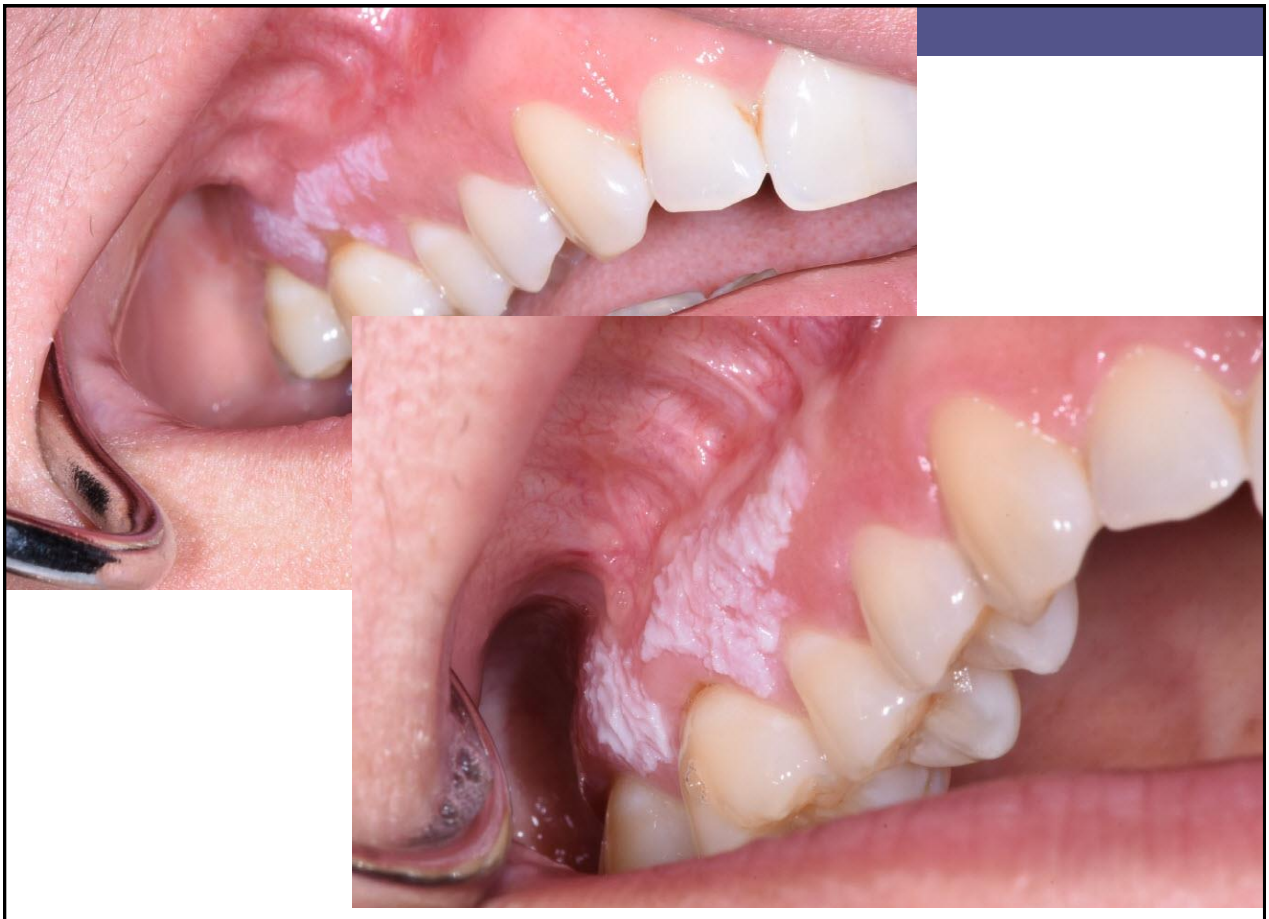

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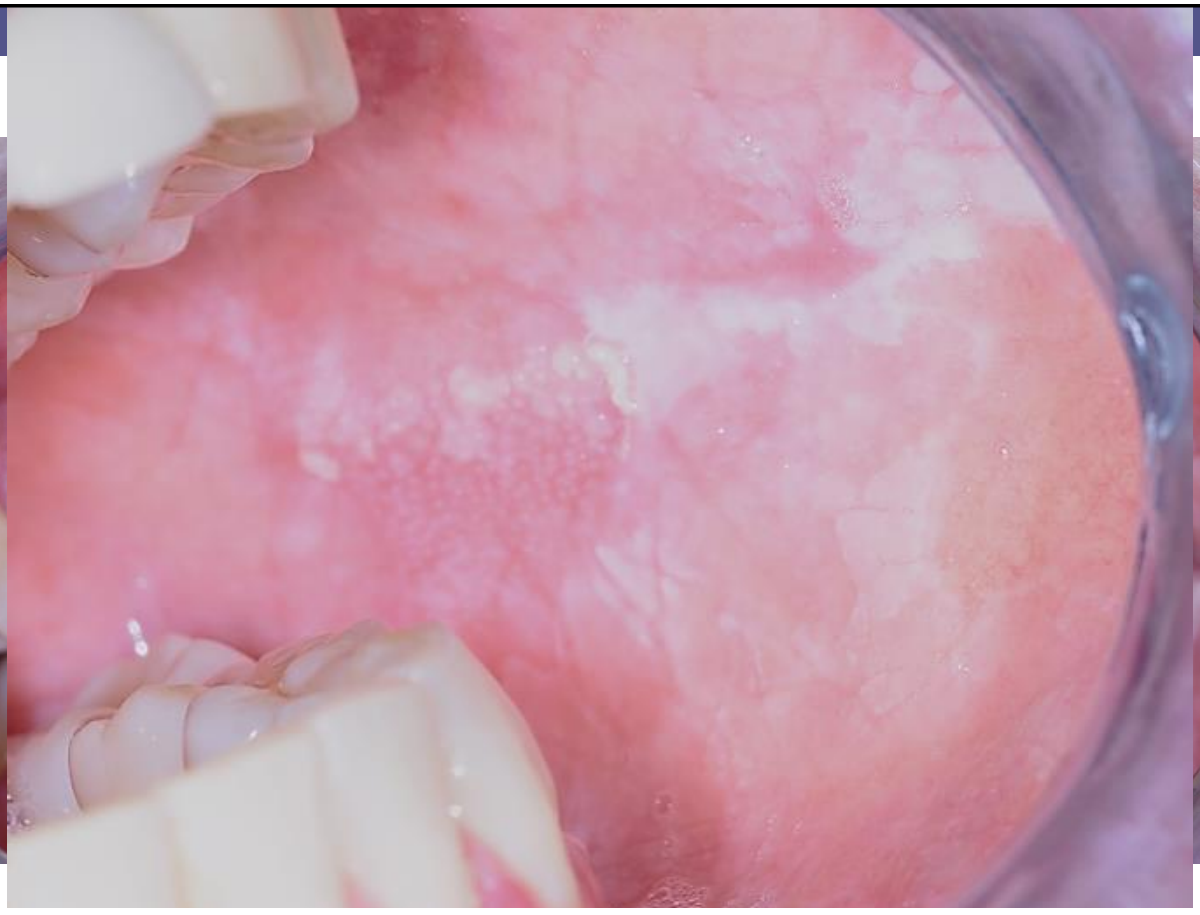

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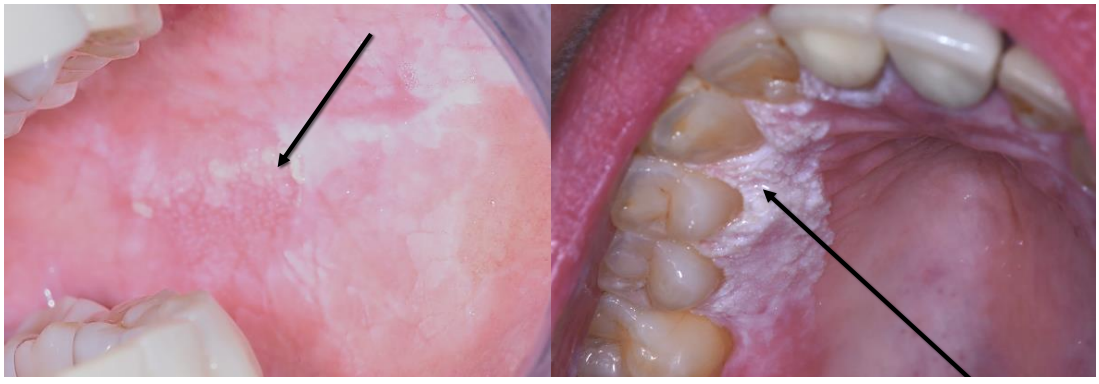
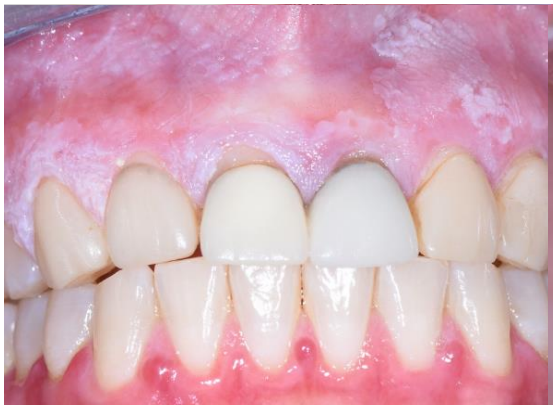
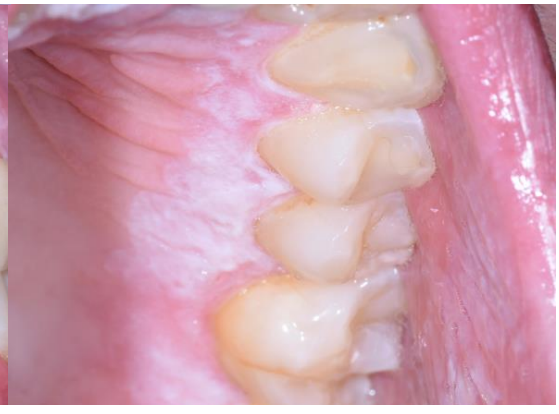


Severe dysplasia

Hyperkeratosis





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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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LICHEN PLANUS

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Lichen planus

- We will limit our discussion now to the malignant transformation potential of lichen planus
- Determining the malignant potential of lichen planus is challenging and 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.

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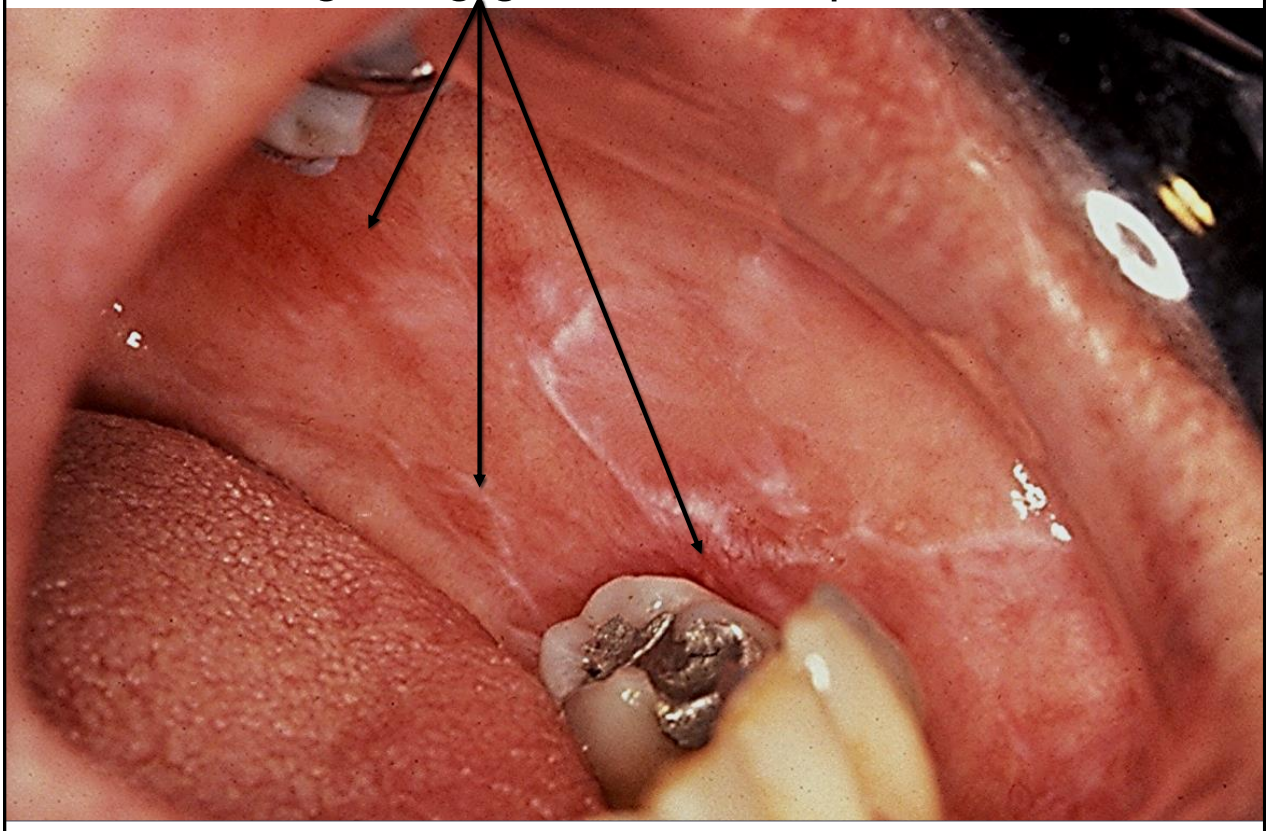
Lichen planus

- 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
- **Take away**: Biopsy anything suspicious; patients with lichen planus may require several in their lifetime

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.

Risk getting greater in atrophic areas



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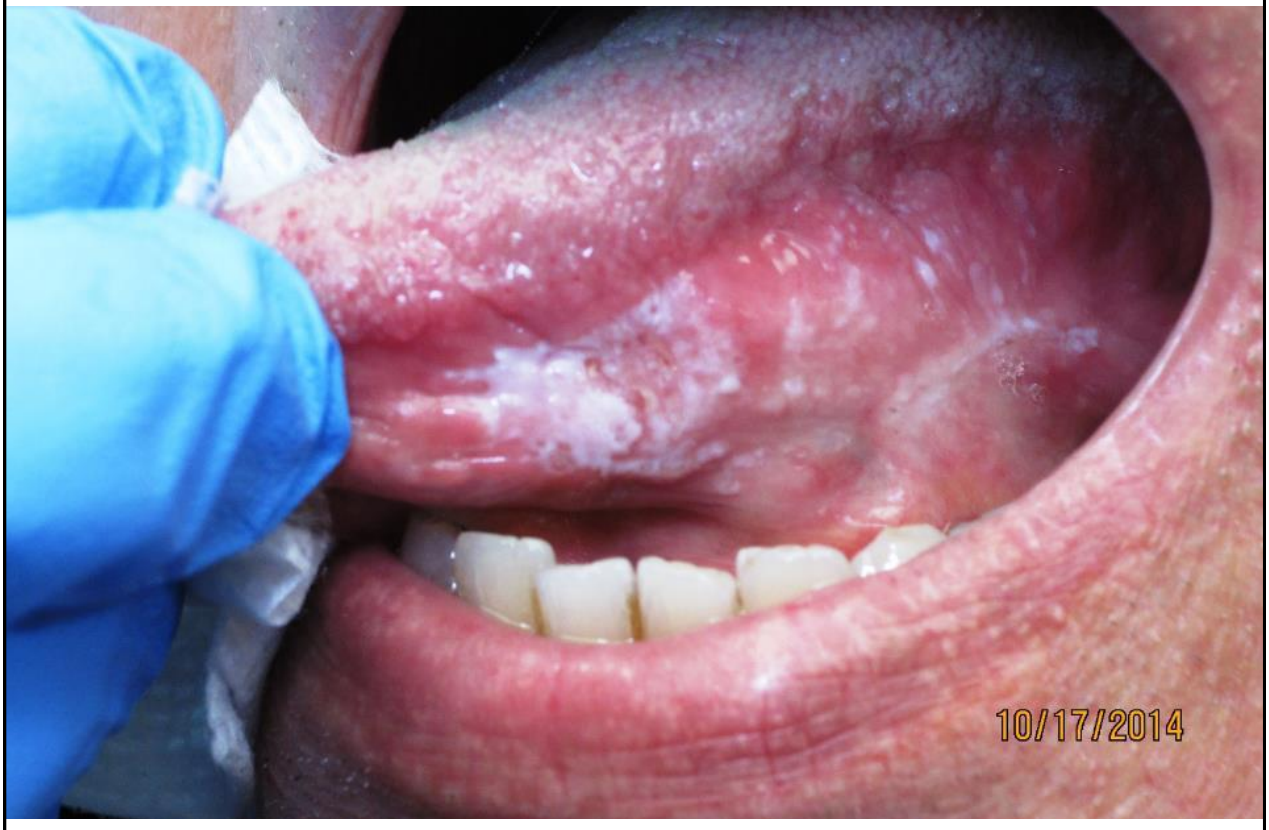
SCCa until proven otherwise



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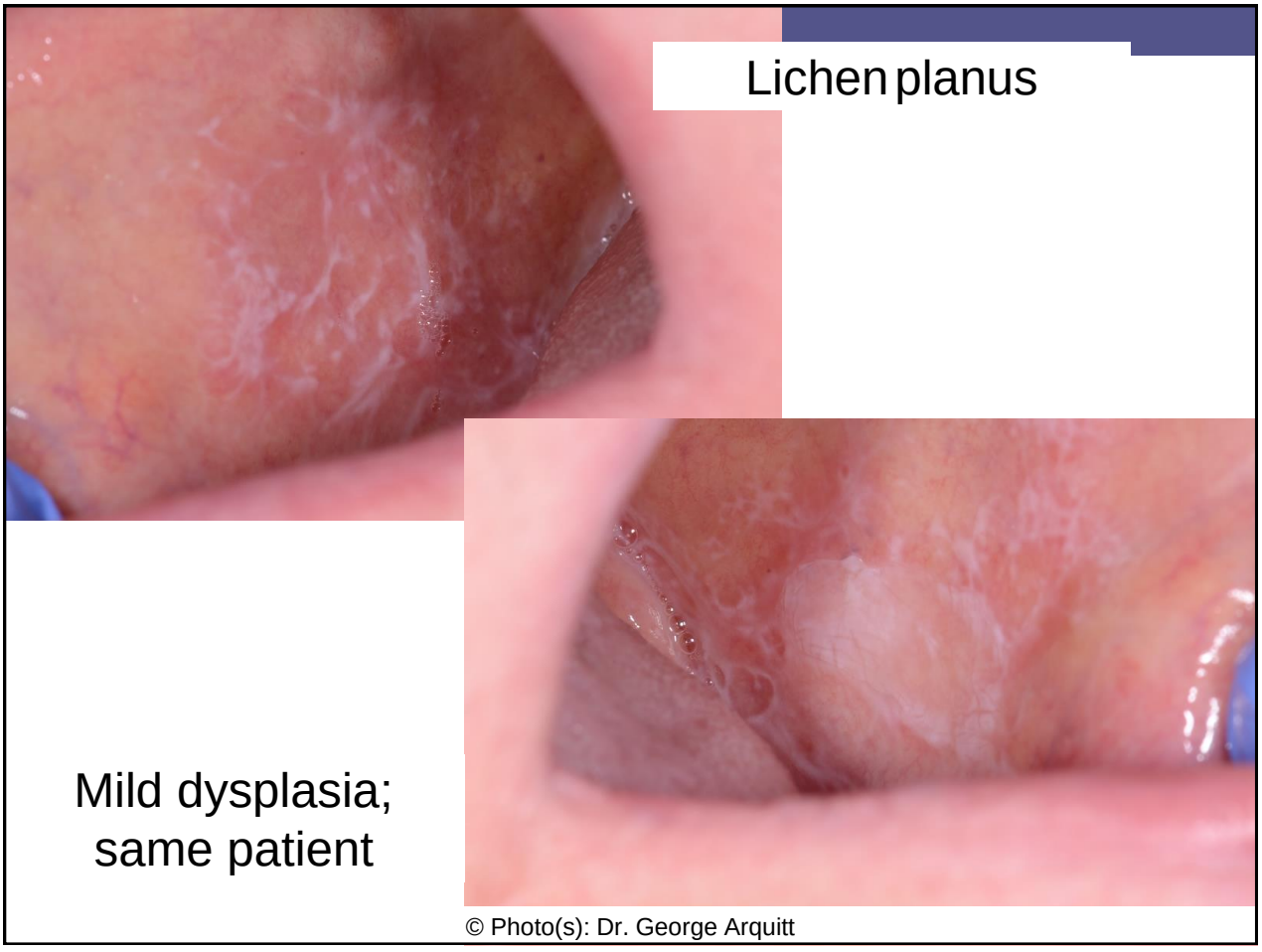

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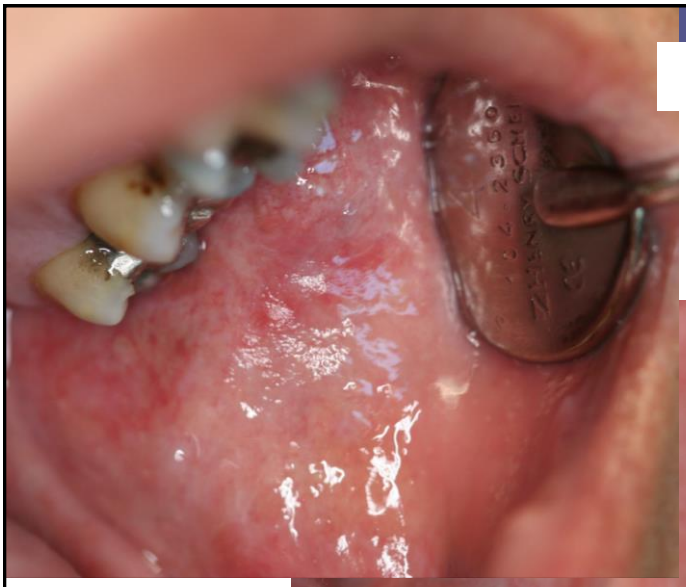
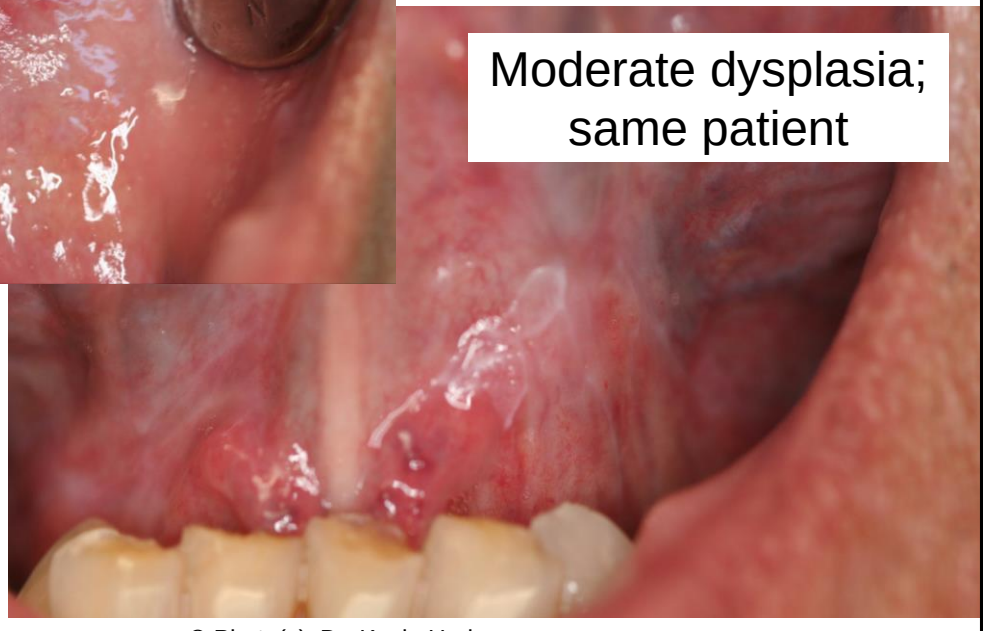


Lichen planus



Moderate dysplasia; same patient

SMOKELESS TOBACCO KERATOSIS

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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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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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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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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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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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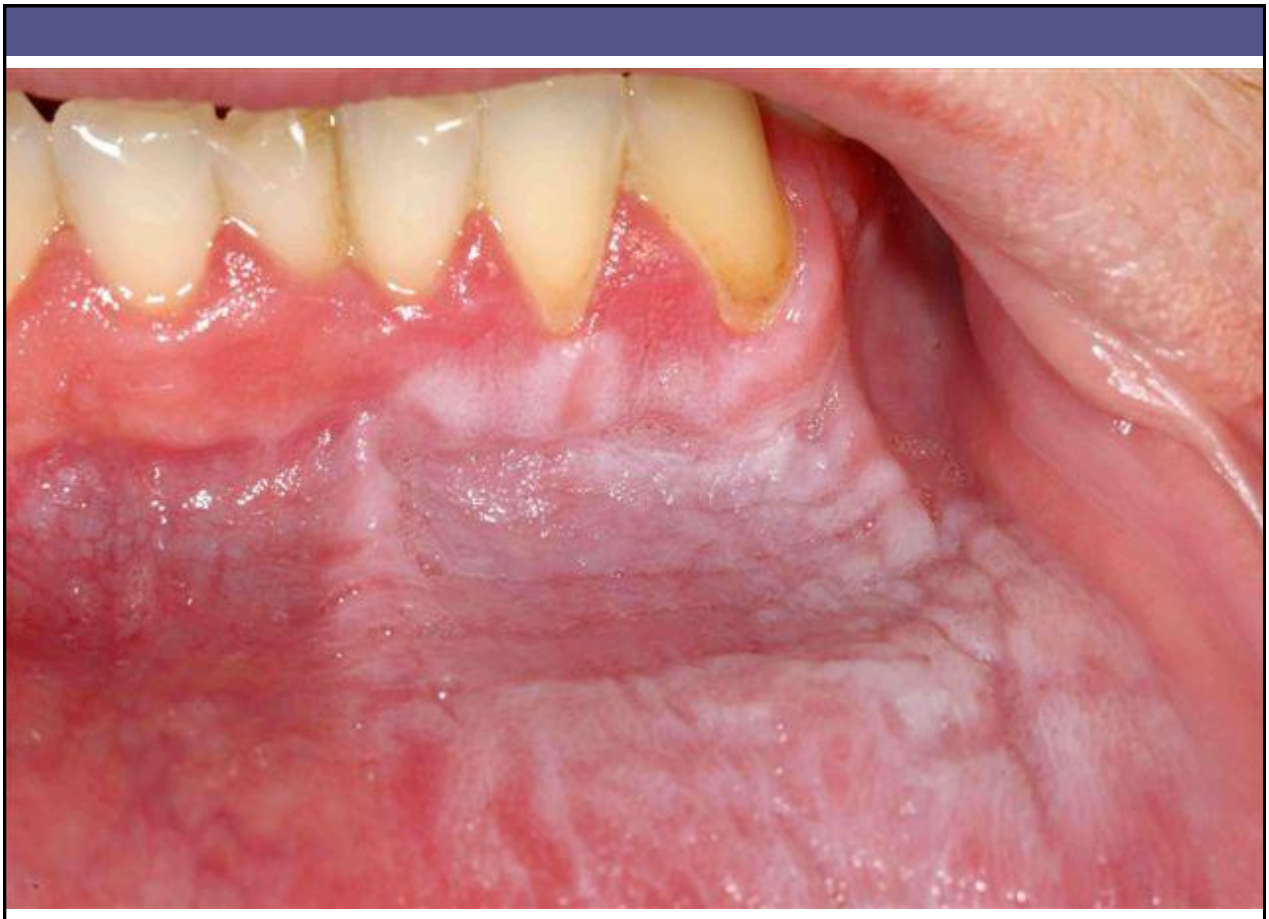

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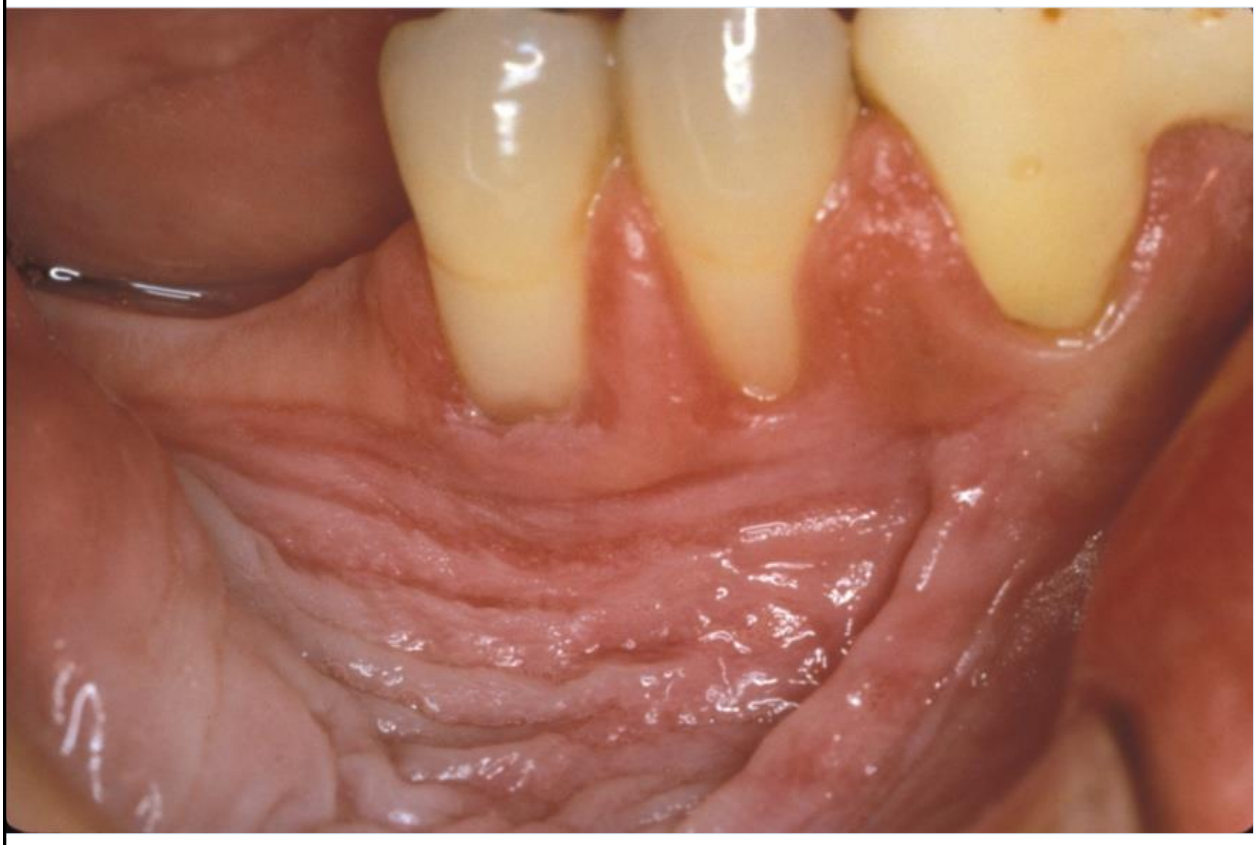

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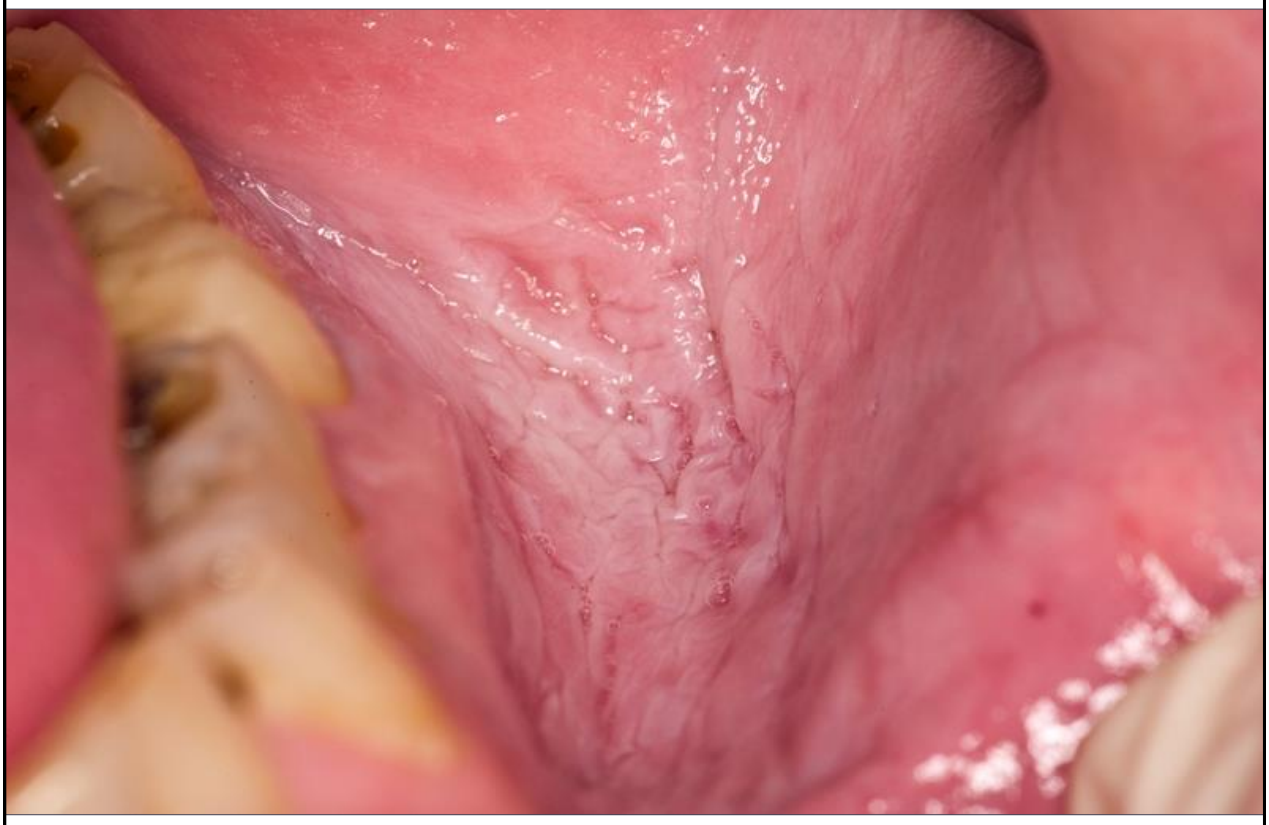

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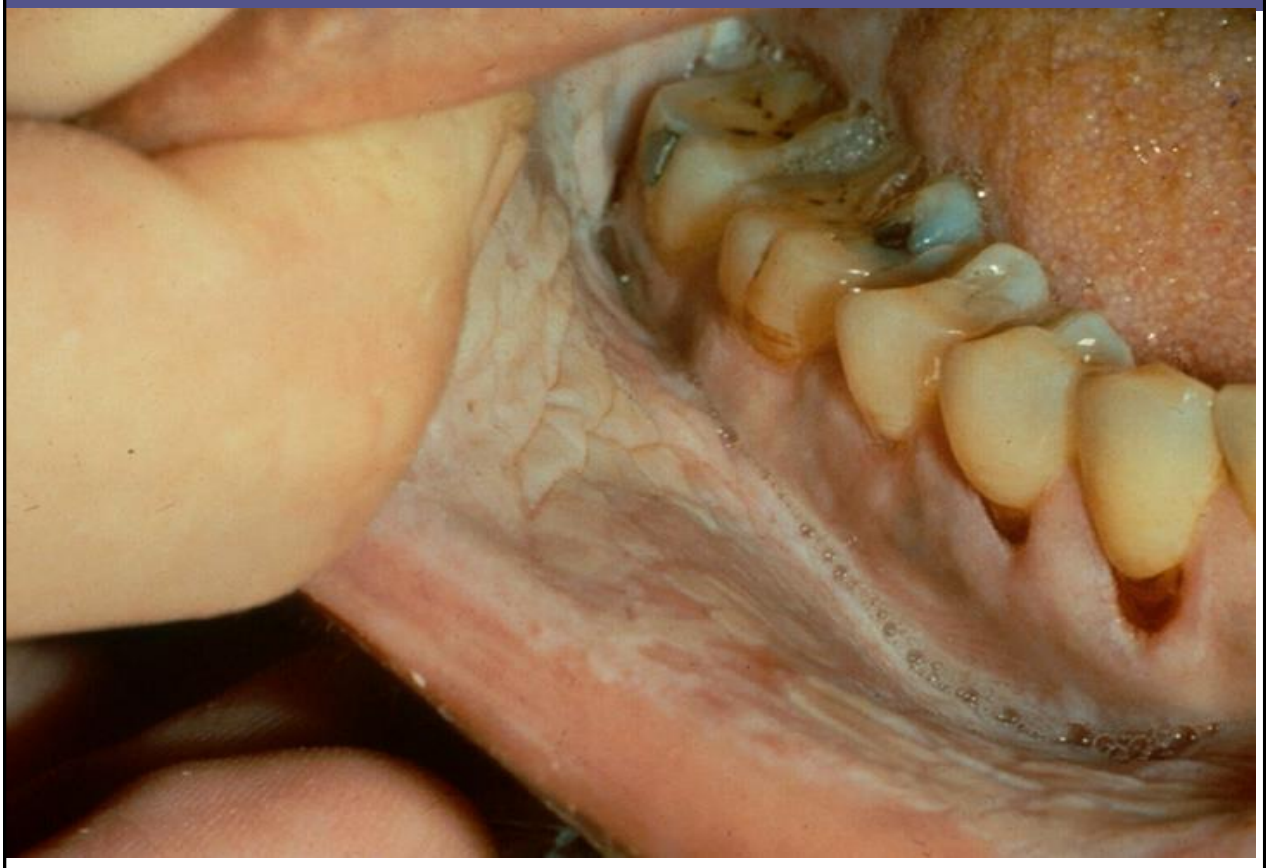

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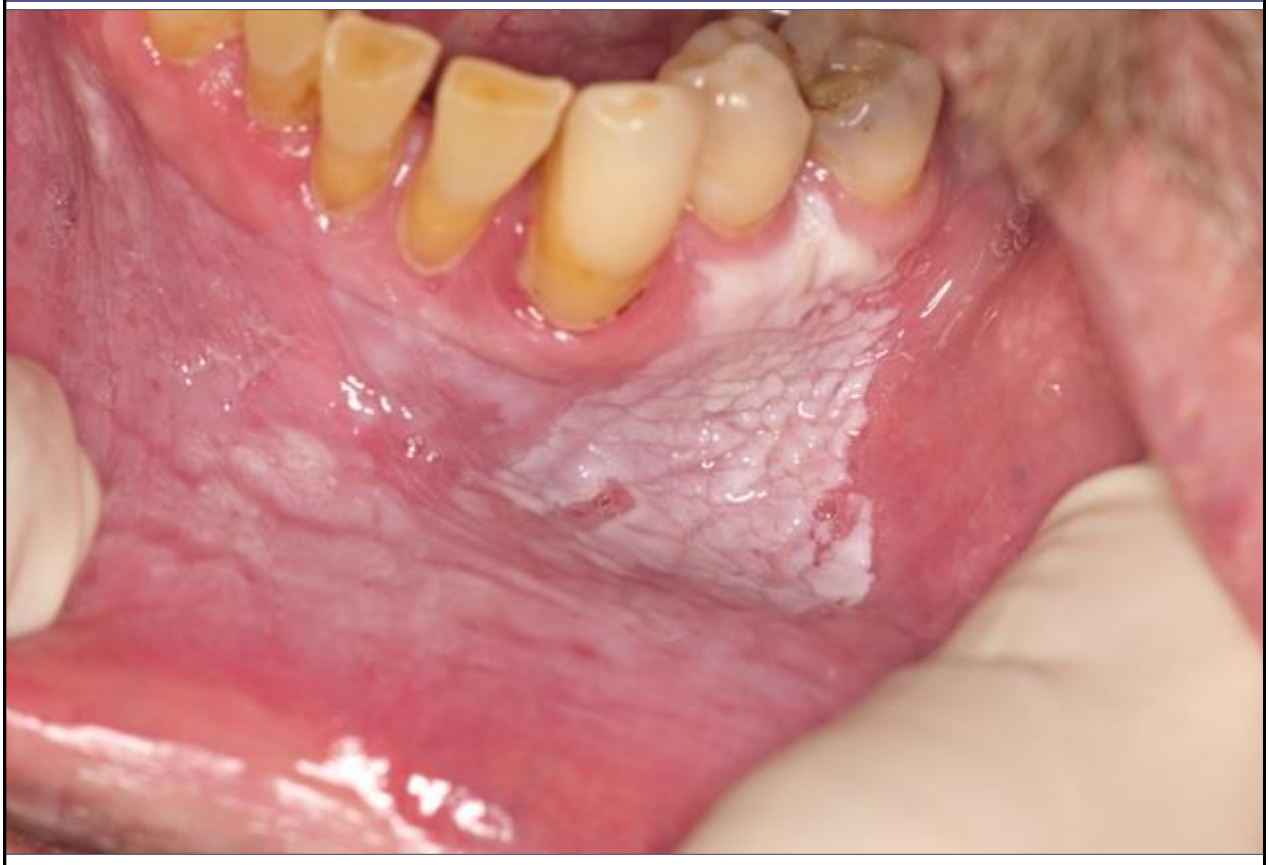

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ACTINIC CHEILITIS

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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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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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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

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

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

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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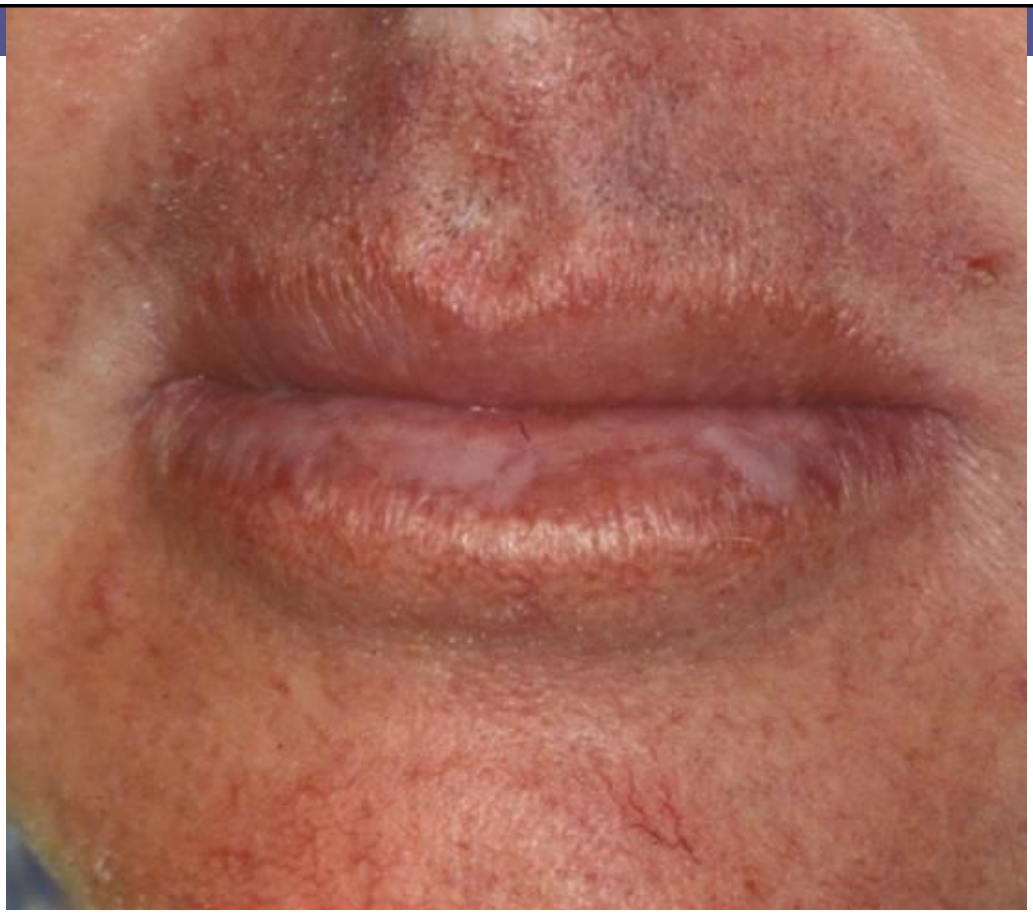

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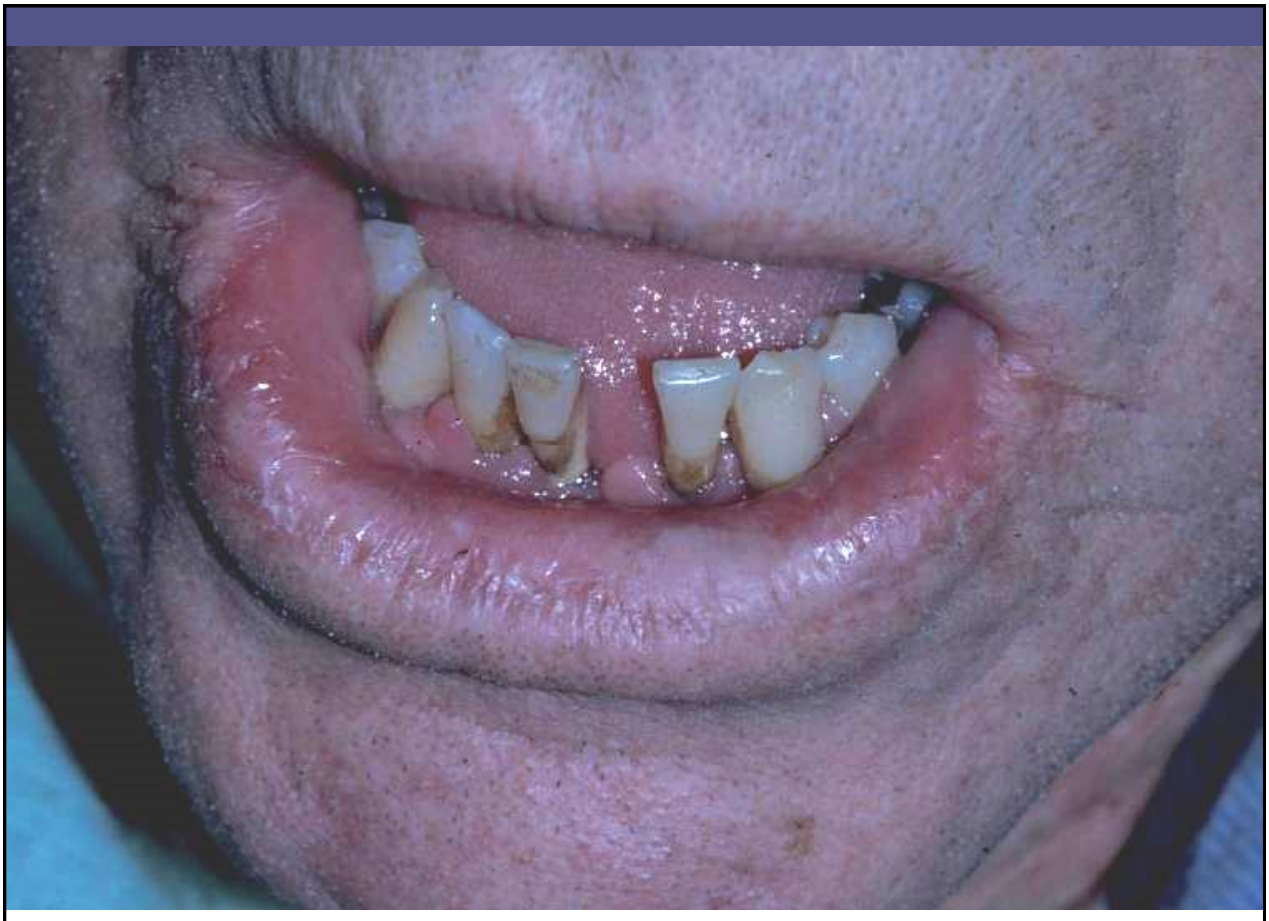

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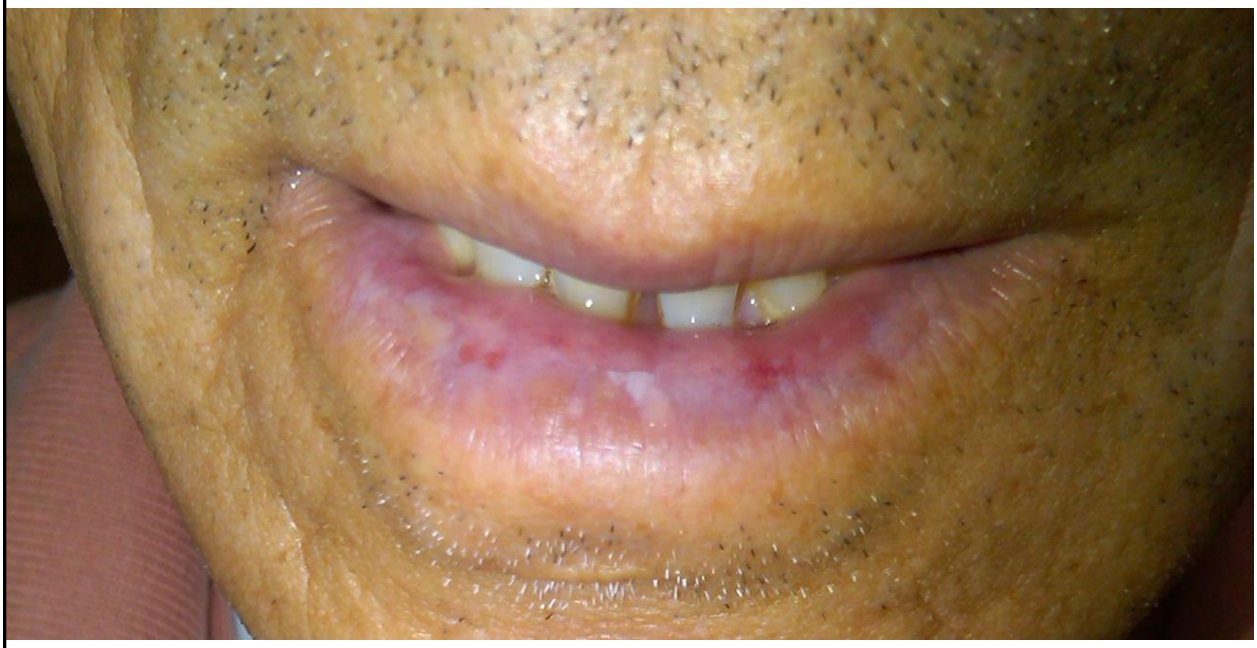

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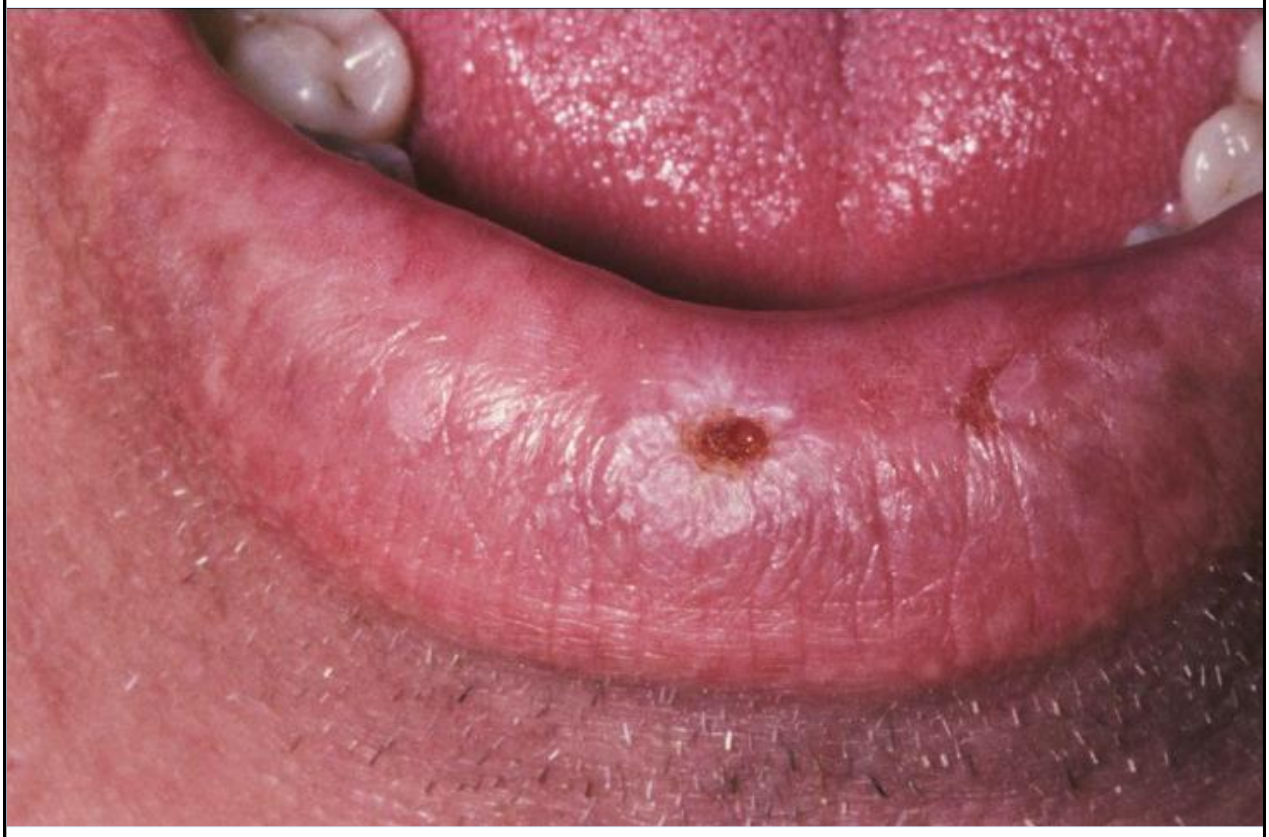

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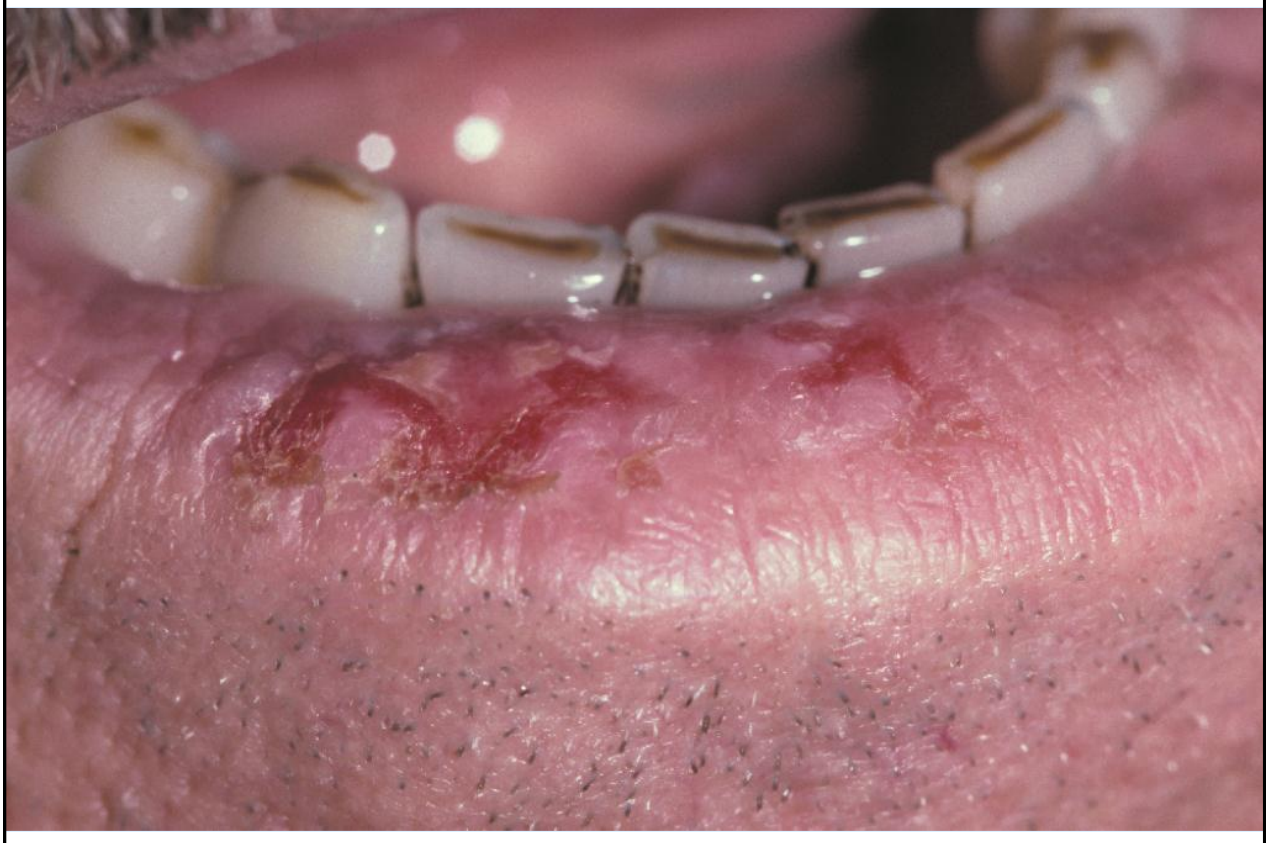

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ERYTHROPLAKIA

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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.

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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 may other forms of pathology so please do not ignore them!

Reichart PA, Philipsen HP. Oral erythroplakia – A review. *Oral Oncology*. 2005;41:551-561.

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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.

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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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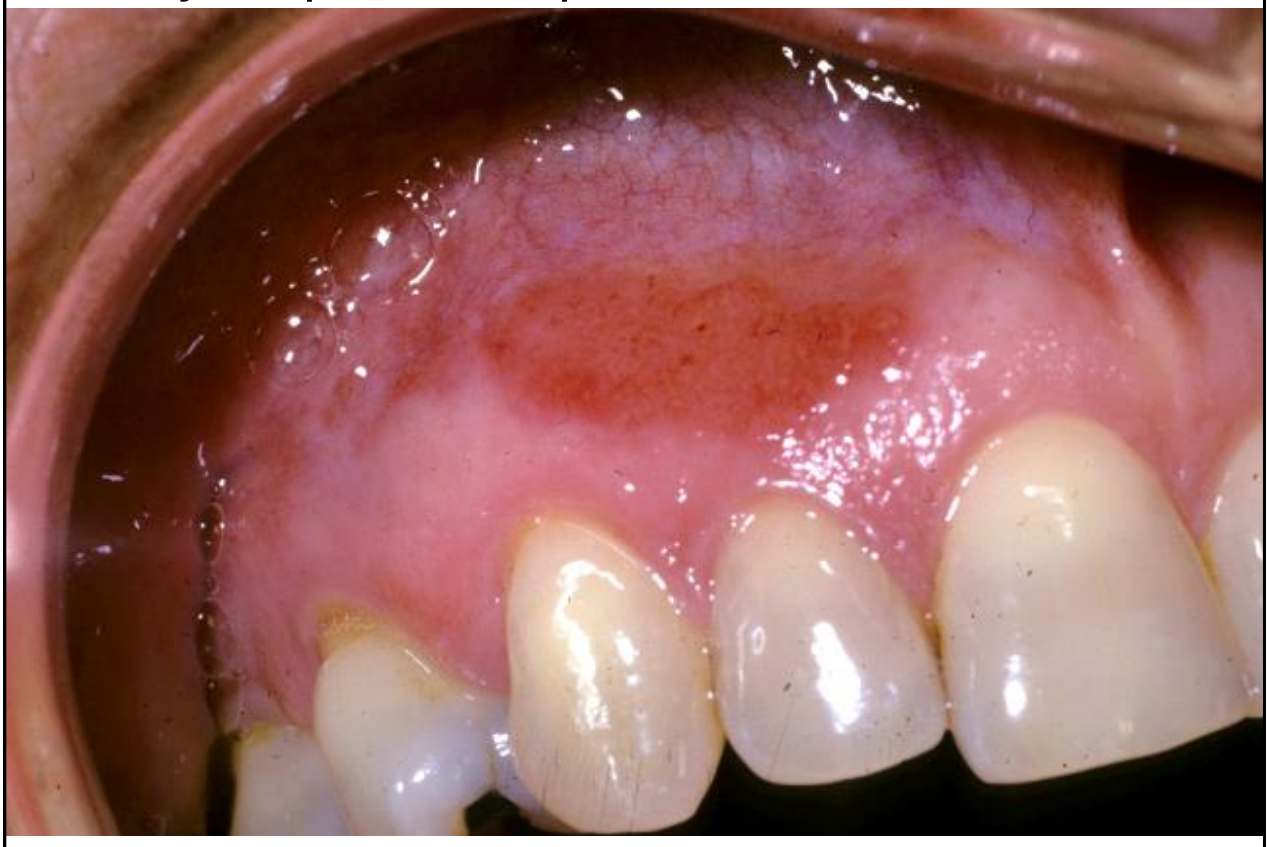
Erythroplakia – squamous cell carcinoma



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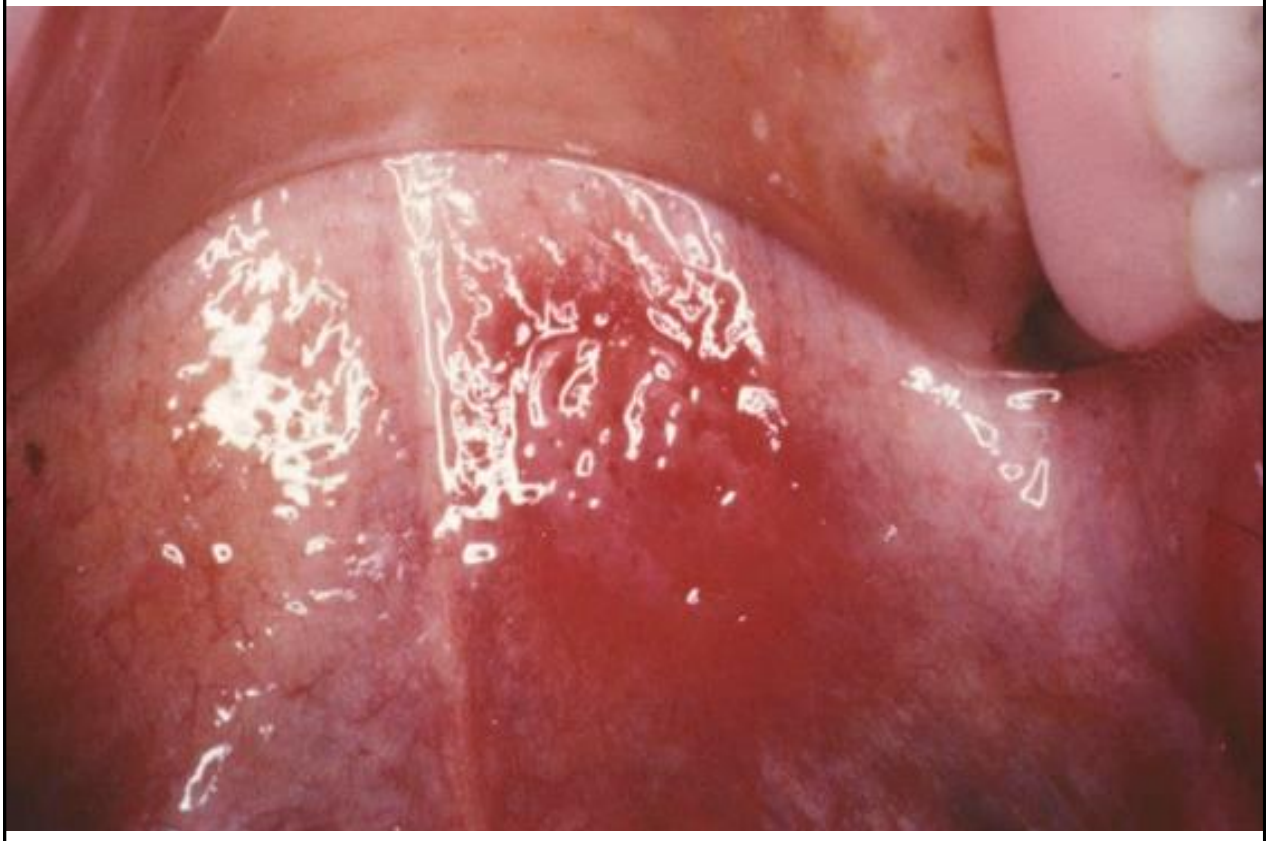
Erythroplakia – squamous cell carcinoma



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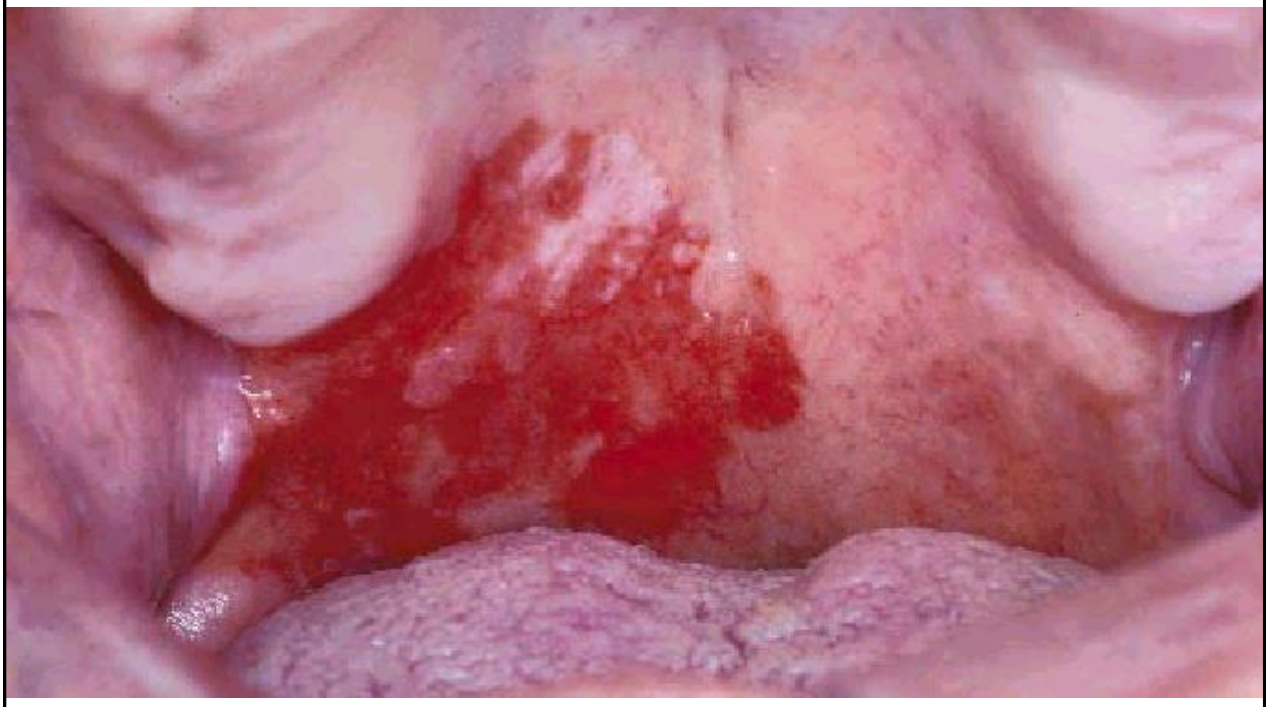
Erythroplakia – squamous cell carcinoma



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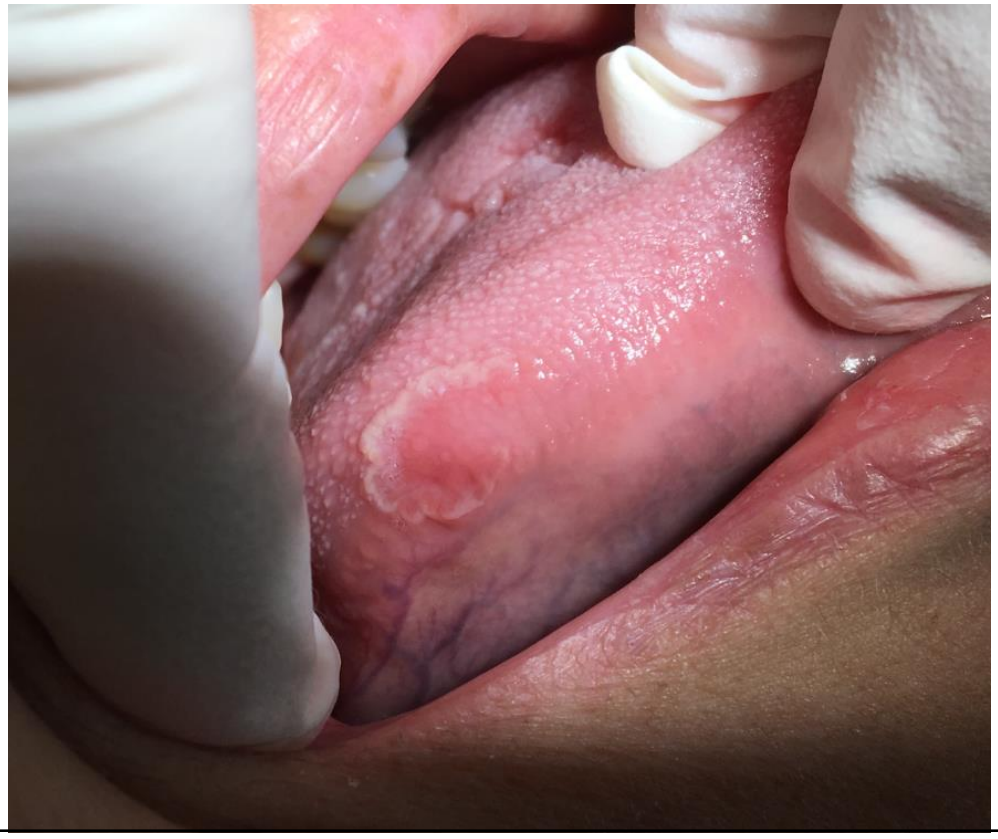
TREATMENT

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, 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):712-727.

Ashley Clark Exceptions



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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

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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

Reichart PA, Philipsen HP. Oral erythroplakia – A review. *Oral Oncology*. 2005;41:551-561.
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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):djz238.

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
    - Limited data is available for HPV-associated oral intraepithelial neoplasia; it has been reported to have about a 20% malignant transformation rate
  - 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*. 2009;31(12):1600-1609.

QUESTIONS?

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