GI tract: Mouth

Congenital defects: **Cleft mouth and cleft palate**

- The most common congenital disorder of the oral cavity (1/800 births)
- Pathophysiology:
    - A malformation due to failure of midline fusion of the face
    - Most are spontaneous. If starting diagnosis with antenatal imaging, up to 30% are syndromic (none are common; most involve neuroectodermal abnormalities)
    - Pathology:
        - Cleft lip and palate: 50%
        - Cleft lip alone: 25%
        - Cleft palate alone: 25%
- Presentation:
    - Antenatal imaging: soft tissues of the face cannot be well seen until the second semester. Examination of the upper lip is a standard part of the ultrasonography. This allows for search for syndromic origin and possible pregnancy termination for severe disease.
    - Post-delivery: visual, self-evident
- Natural history
    - Most significant in resource-poor nations as suckling is necessary for the milk let-down reflex. Children with palate defects usually require adaptive feeding equipment. Cleft lip only can usually generate enough negative pressure to suckle.
    - Complications:
        - Eustachian tube dysfunction leads to recurrent otitis media
        - Speed problems
    - Treatment: surgery
        - Cleft lip after 3 months
        - Cleft palate after 6 months.

Infectious/inflammatory: **HIV-related oral infections**

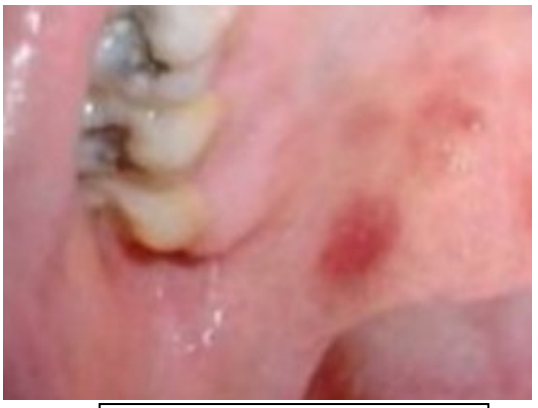
- Candidiasis (most common)
- Aphthous ulcers (aka canker sores)
    - Unknown origin
    - Often stress-induced

- P/E: painful/tender ulcers covered by the necrotic debris of the ulcer base which forms a shaggy grey exudate.

Membrane versus a pseudomembrane

A membrane is part of the epithelium and so it does not remove easily. When torn off, there is bleeding. A pseudomembrane is the sticky exudate that forms with necrosis, such as the base of an ulcer. It can be wiped off with gauze. Oral candidiasis (aka thrush) forms white plaques that are pseudomembranes.

- Hairy leukoplakia
  - The presence of white painless plaques along the lateral edges of the tongue is one of the first manifestations of HIV infection.
  - These are membranes formed by squamous hyperplasia due to reactivation of ENV infection with immunodeficiency.
- Kaposi sarcoma
  - A neoplasm of the endothelial cell due to human herpesvirus 8 (HHV8).
  - Red patches are seen, most commonly on the hard palate



Kaposi sarcoma of palate

Pigmentation abnormalities of the mouth

- Peutz-Jeghers syndrome

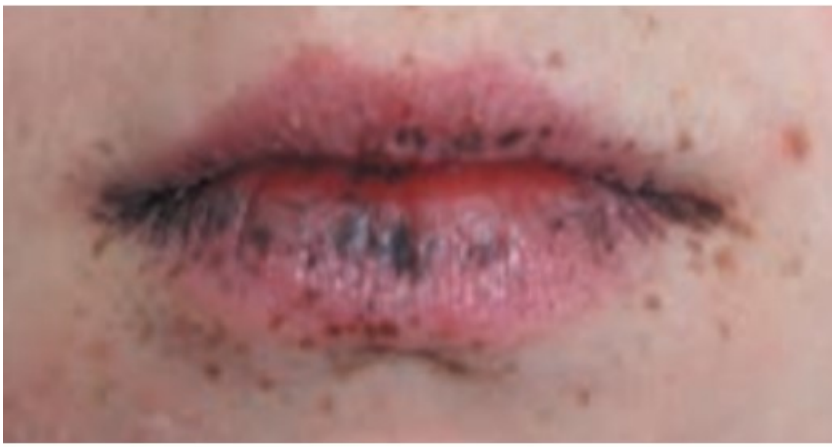


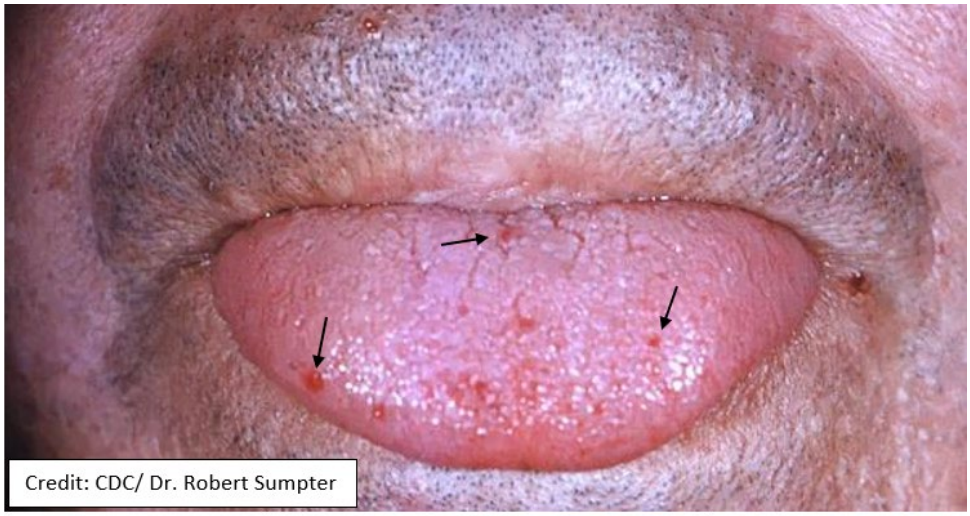
Image from: Sbutega, Isidora, et al, Serbian Journal of Dermatology and Venereology 2012; 4 (2): 77-80

- Freckles (aka lentigines) of the lips and oral mucosa
- Autosomal dominant
- Loss of a tumor suppressor STK11 leads to formation of hamartomas and a lifetime risk of invasive adenocarcinoma of >80%.
    - Cancers can occur in any ductal organ but mostly GI tract.

Hamartoma

A cellular proliferation with benign cells arranged in an abnormal architecture. While not neoplastic themselves, they can be associated with an increased risk of malignancy. Peutz-Jeghers is a model disease in which numerous hamartomatous polyps are found in the bowel and can present in childhood as obstruction.

- Hereditary hemorrhagic telangiectasia (HHT, Weber-Rendu-Osler syndrome)
    - Autosomal dominant gene (HHT) with defect in **TGF-β**, required for vascular remodeling
    - Two basic pathologies:
        - Arteriovenous malformations (50% lung, 10% brain)
        - Telangiectasias (mucocutaneous)

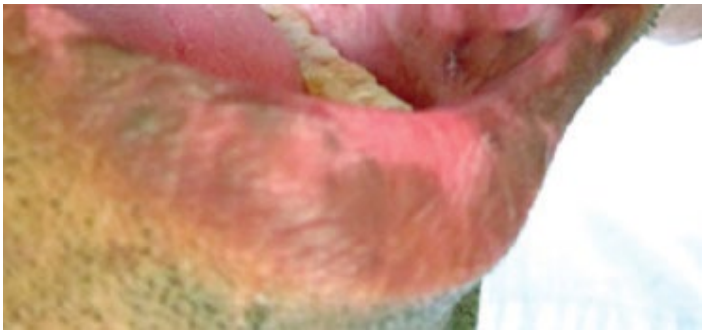


Hereditary hemorrhagic telangiectasia

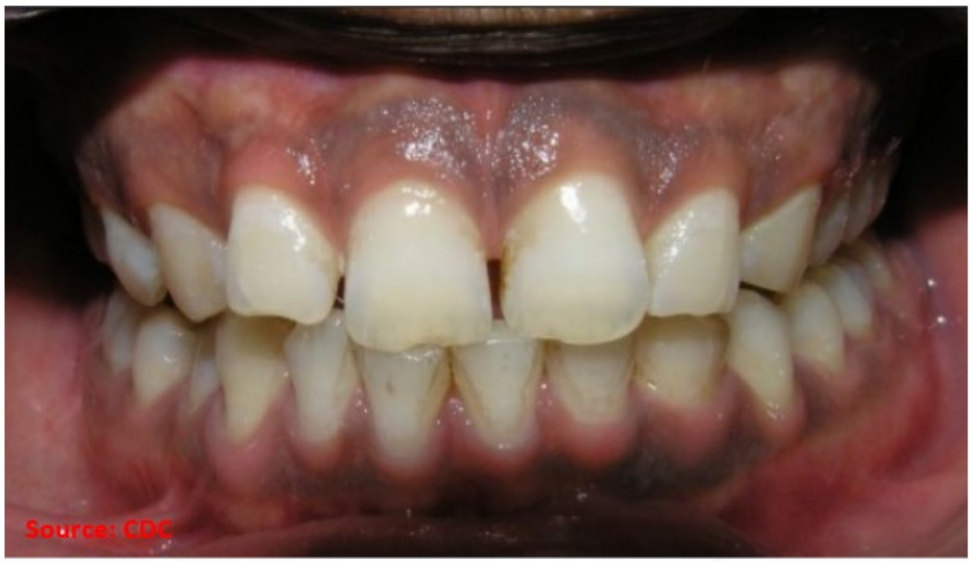
    - Presentation: epistaxis, iron deficiency anemia, telangiectasias
        - Diagnosis is made by having 3 of 4 of: any the above findings and/or a (+) family history.
    - Natural history: risk of severe and recurrent hemorrhages

- Chronic adrenal insufficiency (aka Addison) disease
    - There is often a delay because the onset is insidious, with nonspecific symptoms:

        - Fatigue
        - Weight loss
        - GI complaints (nausea & vomiting, pain)
    - The most reliable finding on physical exam is hyperpigmentation. While this is general, it is most prominent in areas exposed to sunlight (e.g. lower lip, seen in image)
        - This is due to stimulation of melanocytes by MSH (melanin stimulating hormone) which is formed from the cleavage of POMC, a precursor in ACTH synthesis).

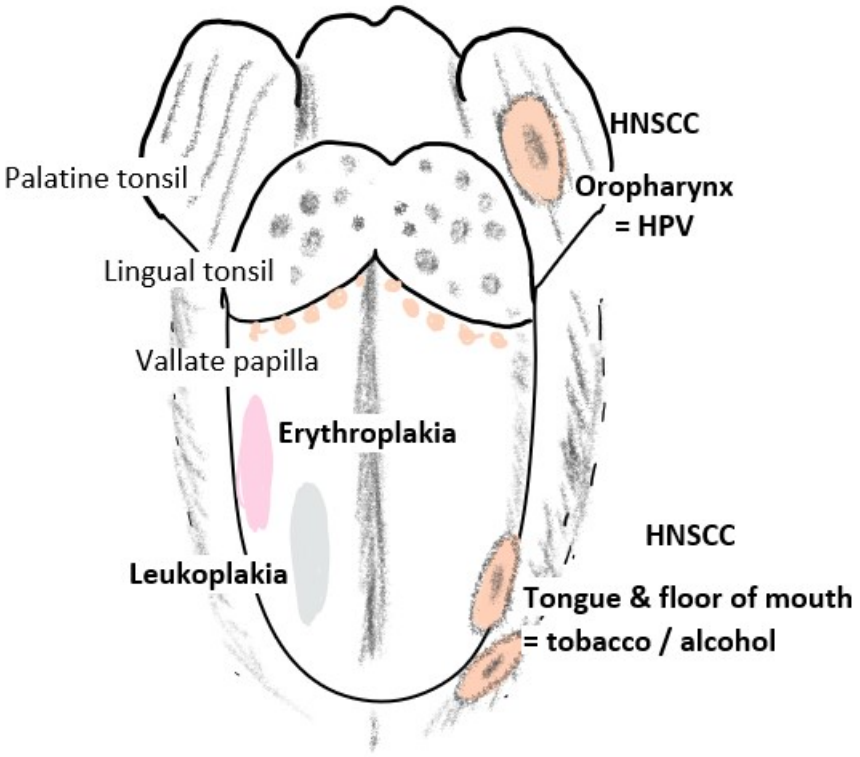


- Lead poisoning:
    - In the past, this had an eponym of Burtonian “lead line”
    - A rare finding
    - Due to interaction of lead with oral bacteria that form lead sulfide, which has a blue-gray color.



Lead poisoning: gingival lead line

Neoplasia of the oral cavity



Head and neck squamous cell carcinoma

Leukoplakia and erythroplakia

- Pathophysiology
  - Refers to any colored patch (flat) or plaque (raised)
    - Leukoplakia: white
    - Erythroplakia: red
    - Leukoerythroplakia: mixed
  - The critical difference is hyperplasia versus dysplasia

<u>Hyperplasia versus dysplasia</u>

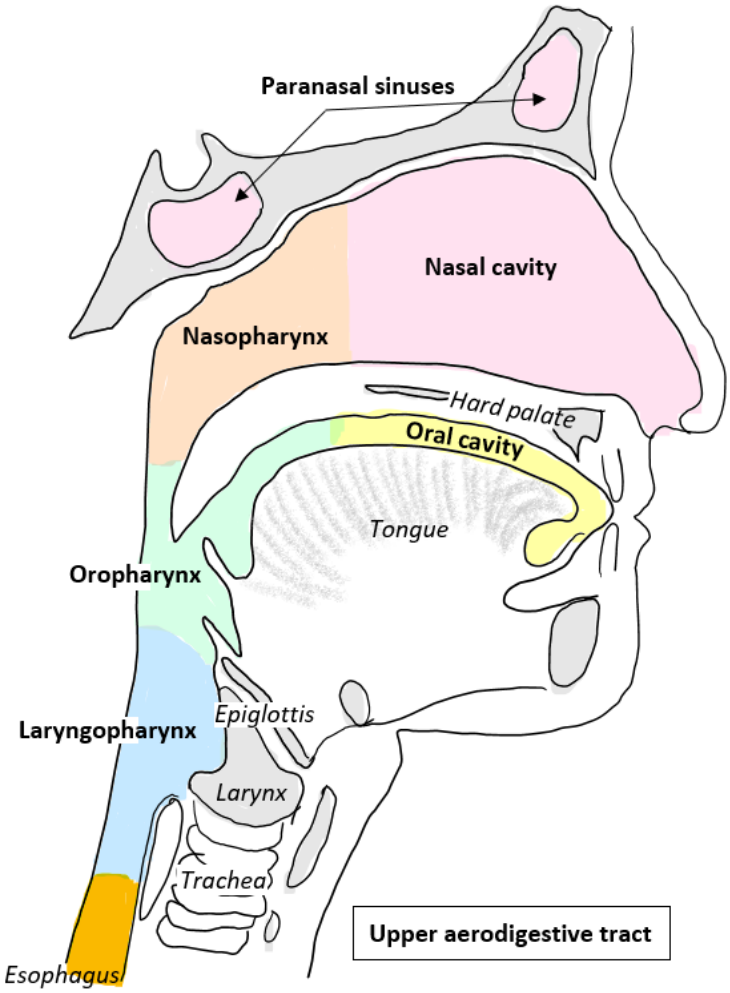
- Hyperplasia is a physiologic increase in the number of cells. The stimulation may be physiologic (e.g. callous) or pathologic (e.g. broken tooth edge) but the hyperplasia will regress with removal of the stimulus. It has a very low progression to neoplasia.
- Dysplasia is a precancerous condition with chromosomal abnormalities. It can be recognized on biopsy because it has nuclear atypia. Severe dysplasia has a general progression to invasive carcinoma of about 10% / decade. Does not typically regress.

    - Etiology**:** all forms of tobacco, alcohol, HPV infection

- Presentation:
    - Symptoms: none
    - P/E:
        - alcohol and cigarette plaques are most commonly found where there is the highest exposure to the carcinogens: side of the tongue and floor of the mouth. By comparison, HPV-related plaques are found in the oropharynx, especially the palatine tonsil.
        - These are true membranes and cannot be wiped off
    - Testing: **all oral plaques should be biopsied**
- Natural history:
    - Prognosis: leukoplakia has a lower likelihood of progression to invasive cancer than erythroplakia. The latter has progression to invasive squamous cell carcinoma as high as 60% lifetime.
    - Treatment: the need for complete excision rises with increasing severity of dysplasia. Carcinoma in situ requires complete excision.

Head and neck squamous cell carcinoma (HNSCC)

- Introduction:
    - These arise in the aerodigestive squamous mucosa. This describes the shared single tube that divides at the epiglottis (i.e. mouth, nasopharynx and oropharynx).



- Pathophysiology:
    - There are 2 major patterns of disease in the US
        - Alcohol and smoking
            - Each alone is carcinogenic and together they are synergistic
            - Cancers form where there is the greatest contact with the carcinogens, i.e. side of tongue and floor of mouth
        - HPV infection
            - There are 10-20 high risk HPV, the most important being types 16 and 18.
            - These cancers occur in the oropharynx, most commonly the palatine tonsil (50%).
            - HPV vaccination is protective against high risk HPV-related carcinomas, including HNSCC (as well as cervix, anal verge and distal esophagus)
    - Uncommon risk factors:

- Nasopharyngeal carcinomas are found in South East Asia from reactivation of EBV.
- Immunodeficiency: SCCs in all sites increase in incidence with immunodeficiency states

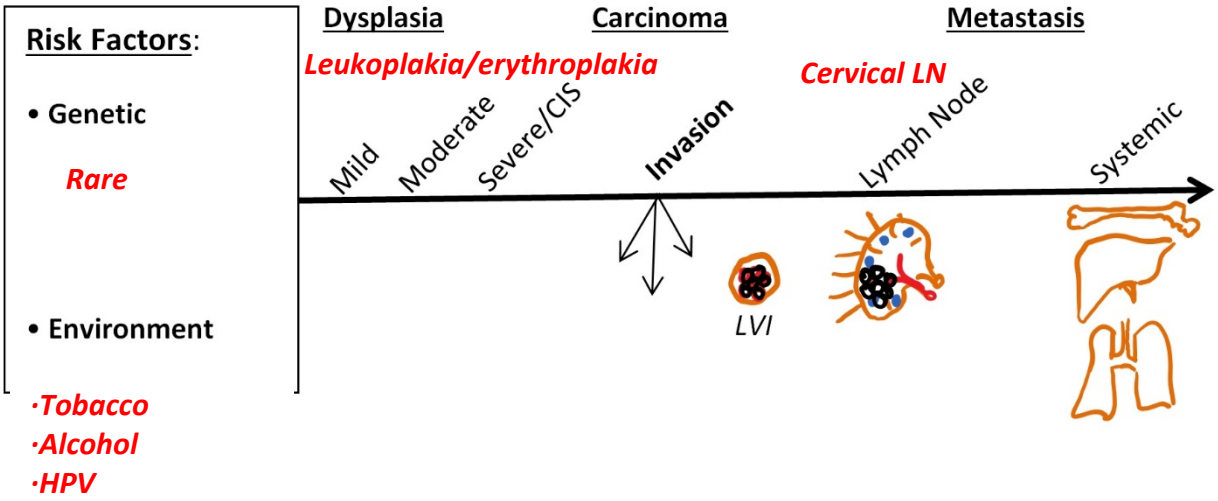
- Metastases spread first to the cervical lymph nodes

Neck masses: Rule of 80's

A new neck mass in a patient over 50 years old:

- 80% are lymph nodes
  - 80% of lymphadenopathy is malignant
    - 80% of the malignancy are HNSCC

- Progression of HNSCC



- Natural history:
  - Prognosis: depends on stage. HPV-related HNSCCs have a better prognosis
  - Treatment: surgery with chemotherapy and radiation in advanced cases

Salivary gland pathology

Sjogren syndrome

- Epidemiology
  - Usually female (20:1 female :male)
  - Peak onset just after menopause
  - Associated with viruses that infect the salivary glands (e.g. EBV).
  - Heredity: associated with HLA-DR, like other autoimmune diseases.
- Pathophysiology:
  - Autoimmune disease of **all exocrine glands** characterized by decreased function of the lacrimal and salivary glands. This results in dry eyes and dry mouth, called **sicca syndrome**.
  - The current working model is that damage to the glandular epithelium, perhaps by a virus, allows the SS-A antigen (aka Ro60 protein) to migrate to the cell membrane surface escaping apoptosis. When bound to an SS-A antibody, the immune complex is phagocytosed by an antigen presenting cells where it activates the intracytoplasmic TLRs (i.e. it is seen as viral-like). This stimulates an interferon response, giving the characteristic **interferon signature** of Sjogren syndrome.
  - Cycles of innate and adaptive immune response leads to extensive lymphoid infiltration of the glands with increasing dysfunction.
  - Characteristic auto-antibodies form: anti-SS-A (aka Ro) and anti-SS-B (aka La) in about 70% of cases.
- Presentation:
  - Symptoms:
    - Sicca (dry eyes and mouth)
    - Dryness of other organs: lung (cough), vagina (dyspareunia) and skin (xerosis ad pruritis)
    - Systemic: fatigue, neurologic dysfunction,
  - P/E: dry mouth and eyes
  - Testing:
    - Autoantibodies:
      - ANA (>90%)
      - Anti-SSA (Ro) and anti-SSB (La)
    - Labial salivary gland biopsy: lymphoid infiltrate with gland destruction
- Natural history

    - Prognosis: decreased quality of life, but probably normal life span
    - Complications:
        - Lymphoma: arises in 5% of cases
        - Pulmonary fibrosis
    - Treatment:
        - Fluid replacement for eyes and mouth
        - Immune modulation

Salivary gland neoplasms

- These occur in any salivary gland and present os masses.
    - Neoplasms in the large salivary glands are usually benign
    - Neoplasms in the minor salivary glands are usually malignant.