# Pathology sheet

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Diseases of the oral cavity:

1- Diseases of Teeth and supporting structures
2- Inflammatory/ Reactive lesions
3- Infections
4- Oral manifestations of systemic diseases
5- Precancerous and cancerous lesions
6- Odontogenic cysts and tumors
7- Salivary gland disease

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Inflammatory/Reactive Lesions

- **Aphthous Ulcers** (Canker Sores):
  - common, often recurrent, painful, superficial oral mucosal ulcerations
  - unknown etiology
  - most common in the first 2 decades of life.
  - tend to be prevalent within certain families
  - may also be associated with immunologic disorders including celiac disease, inflammatory bowel disease, and Behçet disease.
  - The lesions appear as single or multiple
  - The lesions typically resolve spontaneously in 7 to 10 days, but may sometimes persist for weeks, particularly in immunocompromised patients.

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*An ulcer is a discontinuity of the epithelium. It can be found anywhere in the body. When found in the
oral cavity its called "Apthous Ulcer"
Most of the Aphthous Ulcers are benign and self limited as they resolve spontaneously in 7-10 days, but they could also persist for a longer period of time; in that case there would be an underlying cause (pathology)

*Morphology of an aphthous ulcer --> covered by whitish exudate that consists of inflammatory cells shallow hyperemic ulcerations covered by a thin exudate rimmed by a narrow zone of erythema
irritation fibroma:
- also called traumatic fibroma
- occurs primarily on the buccal mucosa along the bite line or the gingiva
- It is believed to be a reactive proliferation caused by repetitive trauma.
- Treatment is complete surgical excision.

*Irratation fibroma is a benign lesion, usually 1 cm, that could be self limited. If the fibroma persisted it can be removed completely by surgical excision. Irratation --> caused by inflammatory or reactive lesion. Irratation fibroma occurs primarily on the buccal mucosa along the Bite Line.
Bite line: the line where people commonly bite themselves accidentally while eating.

Rules in naming tumors:
A) Epithelial cells
- Benign: add -OMA at the end, ex: Fibroma
- Malignant: add -CARCINOMA at the end
B) Mesenchymal cells
- Benign: add -OMA
- Malignant: add -SARCOMA
but there are exceptions; ex: Malenoma --> malignant
tumor

Differentiating tumors grossly by their surrounding border:
A) well defined border --> Benign
B) ill-defined border (irregular) --> Malignant

A fibroma has well defined borders which means that it's a circumscribed tumor --> Benign lesion

*Pyogenic Granuloma (also known as pregnancy tumor)
a vascular lesion (arising from blood vessels) that occurs on mucosa/skin, and appears as an overgrowth (increased angiogenesis) due to a physical trauma/hormonal factors. It is a misnomer -- it's not a tumor-granuloma but it's a capillary hemangioma.

During pregnancy there's increased levels of progesterone that could sometimes trigger the growth of this lesion.

Oral Manifestations of Systemic Disease

- **Hairy Leukoplakia:**
  - is a distinctive oral lesion on the lateral border of the tongue that is usually seen in immunocompromised patients (cancer therapy, transplant associated immunosuppression, advancing age, HIV).
  - is caused by Epstein-Barr virus (EBV).
  - It can be observed in patients infected with the human immunodeficiency virus (HIV) and may portend the development of AIDS.
  - takes the form of white, confluent patches of fluffy ("hairy"), hyperkeratotic thickenings, almost always situated on the lateral border of the tongue. Unlike thrush, the lesion cannot be scraped off.
• **Erythroplakia:**
  - less common
  - The risk of malignant transformation is much higher than in leukoplakia.
  - The histologic changes in erythroplakia only rarely demonstrate orderly epidermal maturation; virtually all (approximately 90%) disclose severe dysplasia, carcinoma in situ, or minimally invasive carcinoma.
  - Often, an intense subepithelial inflammatory reaction with vascular dilation is seen that likely contributes to the reddish clinical appearance.

**Speckled leukoerythroplakia:**
Intermediate forms that have the characteristics of both leukoplakia and erythroplakia.

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**Precancerous and Cancerous Lesions**

• **Leukoplakia:**
  - defined by the WHO as “a white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease.”
  - This clinical term is reserved for lesions that are present in the oral cavity for **no apparent reason**.
  - 5% to 25% of these lesions are premalignant. Thus, until proven otherwise by means of histologic evaluation, all leukoplakias must be considered precancerous.
  - On histologic examination they present a spectrum of epithelial changes ranging from hyperkeratosis overlying a thickened, acanthotic but orderly mucosal epithelium to lesions with markedly dysplastic changes sometimes merging into carcinoma in situ.
*Leukoplakia can't be scraped off (unlike fungal infections of the oral cavity which can be scraped off. Fungal infections are most commonly caused by candida which are called "Oral thrush / candidiasis")

Both erythroplakia and leukoplakia are lesions in the oral cavity with no definitive diagnosis, the only difference between them is their color: 
Leukoplakia is white 
Erythroplakia is red

Oral cavity tumors are either 
A)Squamous cell carcinoma - which is the most common one due to the lining of the oral cavity being non keratedened stratified squamous epitheluim 
B)Salivary gland tumors

Before oral cavity tumors appear, there will be precancerous lesions that could either be: leukoplakia or erythroplakia, they could be benign or malignant 
if its leukoplakia --> there's a 5-25% chance of it being malignant 
if its erythroplakia--> there's a 90% chance of it being malignant
Mitosis reached upper layers of epithelium
Disorderly organization of cells - not all cells are polarized to the surface

This didn't reach the cancer stage yet because the basement membrane is still intact

Microscopy of leukoplakia could reveal that it is: (changes are unpredictable)
1- Benign: hyperkeratosis, hyperplasia in epithelium (increase in the number of epithelial layers)
2- Precancerous lesion:
   * Squamous cell dysplasia --> disordely layers of cells, pleomorphism (different shapes and sizes), mitosis is no longer confined to the basal layer.
   * Carcinoma in situ: full thickness dysplasia
3- Cancer: Break in the basal membrane (the membrane that separates epithelium from the subepithelium)
Erythroplakia/Leukoplakia

- they are usually found in persons aged 40 to 70
- 2 : 1 male preponderance.
- Although these lesions have multifactorial origins, the use of tobacco (cigarettes, pipes, cigars, and certain forms of smokeless tobacco) is a common antecedent.
Squamous Cell Carcinoma

- Approximately 95% of cancers of the head and neck are squamous cell carcinomas (SCCs), with the remainder largely consisting of adenocarcinomas of salivary gland origin.

- Head and neck squamous cell carcinoma is the sixth most common neoplasm in the world

The pathogenesis of squamous cell carcinoma is multifactorial:

- Within North America and Europe:
  a disease of middle-aged individuals
  chronic abusers of smoked tobacco and alcohol.

- In India and Asia:
  the chewing of betel quid and paan (areca nut, slaked lime, and tobacco, wrapped in a betel leaf) is a major regional predisposing influence.

- Actinic radiation (sunlight) and, particularly, pipe smoking are known predisposing influences for cancer of the lower lip.

- In the oropharynx, as many as 70% of SCCs, particularly those involving the tonsils, the base of the tongue, and the pharynx, harbor oncogenic variants of HPV, particularly HPV-16. Unlike the oropharynx, HPV-associated SCC of the oral cavity is relatively uncommon.
• The incidence of oral cavity SCC in individuals younger than age 40, who have no known risk factors (nonsmokers and not infected with (HPV)), has been on the rise. The pathogenesis in this group is unknown.

*The cause of SCC in individuals younger than 40 years is unknown genetic reasons.

• Survival is dependent on a number of factors including the specific etiology of SCC.
• The 5-year survival rate of “classic” (smoking and alcohol related) early-stage SCC is approximately 80%, while survival drops to 20% for late-stage disease.
• Patients with HPV-positive SCC have greater long-term survival than those with HPV-negative tumors.
• The frequent development of multiple primary tumors markedly decreases survival.

*Survival depends on:
A) Grade: how much the lesion under microscope resemble normal cells
   But most commonly it depends on
B) Stage: depends on tumor size and extent of tumor invasion to lymph nodes and other organs (can be seen by radiology)
There are two theories explaining why multiple primary tumors develop in different areas of upper aerodigestive tract:

A) Field cancerization --> exposure of these areas to the same carcinogenic material over the years

B) One lesion was originally present that later on underwent intraepithelial metastasis

Molecular Biology of Squamous Cell Carcinoma:

**Tobacco carcinogen induced cancers:**
mutations frequently involve the p53 pathway as well as proteins responsible for the regulation of squamous differentiation, such as p63 and NOTCH 1.

**HPV-associated SCCs:**
contain far fewer and different genetic alterations and typically overexpress p16, a cyclindependent kinase inhibitor. expression of the HPV oncoproteins E6 and E7, there is inactivation of the p53 and RB pathways

*Molecular changes in SCC:*
SCC results due to changes in cell cycle genes
either by stimulating oncogenic genes or by inhibiting tumor suppressor genes (P53, P16)

SCC in:
- Smokers --> inhibition of P53
- HPV infections --> overexpression of P16
(HPV secretes 2 proteins: E6 & E7; they both inhibit p53, RB (tumor suppressor genes). The inhibition of RB results in overexpression of P16.

Oral progression of cancer doesn't always follow this specific sequence.
MORPHOLOGY:
For the “classic” oral cavity SCC, the favored locations are the:
ventral surface of the tongue
floor of the mouth
lower lip
Soft palate
Gingiva

typically preceded by the presence of premalignant lesions

*Picture B --> represents squamous cell carcinoma due to the break in Basement membrane and invasion to the subepethelial layer
Pink material represents keratin (presence of keratin gives a clue that the carcinoma is of squamous cell origin)
And keratin production by squamous cell carcinoma means that it's a well differentiated tumor; Grade 1 (Low grade) as
it still looks like normal tissue.

- the degree of histologic differentiation, as determined by the relative degree of keratinization, is not correlated with behavior.
- these tumors tend to infiltrate locally before they metastasize to other sites.
- The favored sites of local metastasis are the cervical lymph nodes, while the most common sites of distant metastasis are mediastinal lymph nodes, lungs, liver, and bones.
- Unfortunately, such distant metastases are often already present at the time of discovery of the primary lesion.

**SALIVARY GLANDS**

- **Xerostomia:**
  - dry mouth
  - resulting from a decrease in the production of saliva.
  - It is a major feature of the autoimmune disorder **Sjögren syndrome**, in which it is usually accompanied by dry eyes (keratoconjunctivitis sicca).
  - Other causes: radiation therapy, medications
  - Complications: dental caries, candidiasis, difficulty in swallowing and speaking.

Salivary glands:
A)Major- parotid gland, submandibular gland, sublingual (3 paired glands)
B) Minor- distributed throughout the oral digestive system

**• Inflammation (Sialadenitis):**
Causes: - trauma
  - viral infection (Mumps---parotids)
  - bacterial infection
  - autoimmune disease

**• Mucocoele:**
- The most common type of inflammatory salivary gland lesion.
- It results from either blockage or rupture of a salivary gland duct, with consequent leakage of saliva into the surrounding connective tissue stroma.
- Most often found on the lower lip and are the result of trauma.
- Patients may report a history of changes in the size of the lesion, particularly in association with meals.
- Complete excision of the cyst and its accompanying minor salivary gland lobule is required, as incomplete excision may lead to recurrence.
- **Ranula** is a term reserved for epithelial-lined cysts that arise when the duct of the sublingual gland has been damaged.

*When a mucocoele is found in the sublingual gland its called "Ranula" which is a benign lesion.*

Causes of Mucocoele--> trauma, stones, inflammation
- blockage due to edema-
Most common complaint in Sialadenitis: Patient comes with a mobile mass in the oral cavity (no specific criteria for deciding if this is a malignant or benign tumor) but in some cases of malignancy this mass develops to form an elevation and becomes immobile.

- **Nonspecific Sialadenitis:**
  - Most often involving the major salivary glands, particularly the **submandibular glands**.
  - Usually secondary to ductal obstruction produced by stones (**sialolithiasis**)
  - The common offenders are **S. aureus** and **Streptococcus viridans**.
  - **Unilateral involvement** of a single gland is the rule.
  - Other causes: Decreased secretory function (phenothiazines, dehydration—elderly/major surgery)
• usually occur in adults.
• with a slight **female** predominance------except Warthin tumors

• The benign tumors most often appear in the fifth to seventh decades of life. The malignant ones tend to appear somewhat later.

*Warthin tumors are more common in males due to it being related to smoking.

• Although benign tumors are known to have been present usually for many months to several years before coming to clinical attention, **cancers are generally detected more quickly because of their rapid growth.**

• Ultimately, however, there are no reliable clinical criteria to differentiate benign from malignant lesions.
Pleomorphic Adenoma

- Mixed tumors.
- They represent about 60% of tumors in the parotid.
- **radiation** exposure increases the risk.
- chromosomal rearrangements involving PLAG1 (increase cell growth).
- These tumors present as painless, slow-growing, mobile, discrete masses within the parotid or submandibular areas or in the buccal cavity.
- The recurrence rate (perhaps months to years later) with parotidectomy is about 4% but, with simple enucleation approaches 25%.

*Most common tumor of the salivary glands.
They are mixed tumors (composed of epithelial and
myoepithelial cells which means there's an epithelial and mesenchymal differentiation)
Treatment: Complete excision of both tumor and gland.

Figure 16-18. A, Mucoepidermoid carcinoma growing in nests composed of squamous cells as well as clear vacuolated cells containing mucin. B, Mucicarmine stains the mucin reddish pink.

- carcinoma ex pleomorphic adenoma or a malignant mixed tumor:
  - A carcinoma arising in a pleomorphic adenoma
  - The incidence of malignant transformation increases with time, being about 2% for tumors present less than 5 years and almost 10% for those present for more than 15 years.
  - Malignant mixed tumors are among the most aggressive of all salivary gland malignant neoplasms, producing mortality rates of 30% to 50% at 5 years.
Figure 16-15 Pleomorphic adenoma. A, Slowly enlarging nodule in the parotid gland of many years duration. B, The bisected, sharply circumscribed, yellow-white tumor can be seen surrounded by normal salivary gland tissue.

Figure 16-16 Pleomorphic adenoma. A, Low-power view showing a well-demarcated tumor with adjacent normal salivary gland parenchyma. B, High-power view showing epithelial cells and myoepithelial cells within a chondroid matrix material.
Warthin Tumor

- Papillary Cystadenoma Lymphomatosum.
- the second most common salivary gland neoplasm.
- arises almost *exclusively* in the parotid gland.
- Occurs more commonly in males than in females, usually in the fifth to seventh decades of life.
- 10% are multifocal
- 10% bilateral.
- **Smokers** have eight times the risk of nonsmokers for developing these tumors.
- These neoplasms are benign, with recurrence rates of only 2% after resection.

![Image of Warthin Tumor](image-url)
**Mucoepidermoid Carcinoma**

- represent about 15% of all salivary gland tumors.
- while they occur mainly (60% to 70%) in the **parotids**, they account for a large fraction of salivary gland neoplasms in the other glands, particularly the minor salivary glands.
- The most common form of primary malignant tumor of the salivary glands.
- **t(11,19)** -------------- MECT1, MAML2 genes

*Most common maligna*

*tumor in salivary glands.*
• The clinical course and prognosis depend on the grade of the neoplasm.

• Low-grade tumors: rarely do they metastasize and so yield a 5-year survival rate of more than 90%.

• High-grade neoplasms: are invasive and difficult to excise and so recur in about 25% to 30% of cases and, in 30% of cases, metastasize to distant sites. The 5-year survival rate in patients with these tumors is only 50%.

It's not until you fall that you fly😊