Oral pathology

Contents:

1. General structure of teeth
2. Common structural inflammatory lesions
3. Tumor like lesions
4. Infections
5. Oral manifestations of systemic disease
6. Tumors of oral cavity
7. Odontogenic tumors

1. Teeth are firmly implanted in the jaw and are surrounded by the gingival mucosa.
2. The anatomic crown of the tooth projects into the mouth and is covered by enamel, a hard, inert, acellular tissue—the most highly mineralized tissue in the body.
3. The enamel rests upon **dentin**, which is a specialized form of connective tissue that makes up most of the remaining hard-tissue portion of the tooth.

4. **Unlike enamel, dentin is cellular** and contains numerous dentinal tubules, which contain the **cytoplasmic extensions of odontoblasts**.

5. These cells line the interface between the dentin and the pulp and can, **when properly stimulated, produce new (secondary) dentin** within the interior of the tooth.

6. The pulp chamber itself is surrounded by the dentin and consists of loose connective tissue stroma rich in nerve bundles, lymphatics, and capillaries.

**Common structural inflammatory lesions**

There are mainly 3 topics in this subject. They are:

1. Dental caries
2. Gingivitis
3. Periodontitis

**Dental caries (Tooth decay)**

- Dental caries, caused by focal degradation of the tooth structure, is one of the most common diseases throughout the world and is the most common cause of tooth loss before age 35.
- Carious lesions are the result of **mineral dissolution of tooth structure by acid metabolic end products from bacteria** that are present in the oral cavity and are capable of fermenting sugars.
- Fluoride incorporates into the crystalline structure of enamel, forming **fluoroapatite**, and contributes to **resistance to degradation** by bacterial acids. So fluoridation of water has marked reduced the risk of dental caries.
Gingivitis

- Gingiva is the designation of the squamous mucosa in between the teeth and around them.
- Gingivitis is inflammation of the mucosa and the associated soft tissues. It occurs at any age but is most prevalent and severe in adolescence (ranging from 40% to 60%).
- Typically, the development of gingivitis is the result of a lack of proper oral hygiene, leading to an accumulation of dental plaque and calculus.
- **Dental plaque** is a sticky, usually colorless biofilm that **builds in between and on the surface of the teeth**. It is formed by a complex of:
  1. Oral bacteria,
  2. Proteins from the saliva, and
  3. Desquamated epithelial cells.
- **If plaque continues to build and is not removed, it becomes mineralized to form calculus (tartar).**
- Complications:
  1. The bacteria in the plaque release acids from sugar-rich foods, which erode the enamel surface of the tooth.
  2. Repeated erosions may lead to dental caries.
  3. Chronic gingivitis is characterized by gingival erythema, edema, bleeding, changes in contour, and loss of soft-tissue adaptation to the teeth.

Periodontitis

- **Periodontitis refers to an inflammatory process that affects the supporting structures of the teeth: periodontal ligaments, alveolar bone, and cementum.**
• With progression, periodontitis can lead to serious sequelae, including the loss of attachment caused by complete destruction of the periodontal ligament and alveolar bone.
• Causes of adult periodontitis:

<table>
<thead>
<tr>
<th>Causes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>1. Actinobacillus,</td>
<td></td>
</tr>
<tr>
<td>2. Porphyromonas, and</td>
<td></td>
</tr>
<tr>
<td>3. Prevotella.</td>
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<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>1. AIDS</td>
<td></td>
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<tr>
<td>2. Leukemia</td>
<td></td>
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<tr>
<td>3. Crohn’s disease</td>
<td></td>
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<tr>
<td>4. Diabetes Mellitus</td>
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<tr>
<td>5. Down syndrome</td>
<td></td>
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<tr>
<td>6. Sarcoidosis</td>
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<tr>
<td>7. Syndromes associated</td>
<td></td>
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<tr>
<td></td>
<td>with polymorphonuclear defects.</td>
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<tr>
<td>Systemic conditions</td>
<td></td>
</tr>
<tr>
<td>1. Infective endocarditis</td>
<td></td>
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<tr>
<td>2. Pulmonary abscess</td>
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<td>3. Brain abscess</td>
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</tbody>
</table>

**TUMOR LIKE LESIONS**

There are mainly 3 lesions:

1. Irritation fibroma and,
2. Pyogenic granuloma,
3. Peripheral giant cell granuloma,
4. Apthous ulcers.
Irritation fibroma

- It primarily occurs in the buccal mucosa along the bite line or at the gingivodental margin.
- It consists of a nodular mass of fibrous tissue, with few inflammatory cells, covered by squamous mucosa.
- Treatment is complete surgical excision.

Pyogenic granuloma

- The pyogenic granuloma is a highly vascular pedunculated lesion.
- It usually occurs in the gingiva of children, young adults, and, commonly, pregnant women (pregnancy tumor).
- The surface of the lesion is typically ulcerated and red to purple in color.

- Histologically these lesions demonstrate a highly vascular proliferation that is similar to granulation tissue. Because of this histologic picture, pyogenic granulomas are considered by some authorities to be a form of capillary hemangioma.
They either regress, particularly after pregnancy, or undergo fibrous maturation, and they may develop into a **peripheral ossifying fibroma**. (It is a relatively common growth of the gingiva that is considered to be reactive in nature rather than neoplastic and of unknown aetiology. Complete surgical excision down to the periosteum is the treatment of choice.)

- Treatment is complete surgical excision.

**Peripheral giant cell granuloma**

- It is a relatively common lesion of the **gingiva**.
- It is generally covered by intact gingival mucosa, but it may be ulcerated.
- The clinical appearance of peripheral giant-cell granuloma can be similar to that of pyogenic granuloma, but which is generally more **bluish purple in color** while the pyogenic granuloma is more bright red.
- Histologically, however, these lesions are distinct. Peripheral giant-cell granuloma is made up of a **striking aggregation of multinucleate, foreign body–like giant cells** separated by a **fibroangiomatous stroma**.
- Although not encapsulated, these lesions are usually well delimited and easily excised.
- They should be differentiated from central giant-cell granulomas found within the maxilla or the mandible and from the histologically similar but frequently multiple “**brown tumors**” seen in **hyperparathyroidism**.

**APHTHOUS ULCERS**

- They are extremely common superficial ulcerations of the oral mucosa.
• The lesions appear as single or multiple, shallow, hyperemic ulcerations covered by a thin exudate and rimmed by a narrow zone of erythema.

• The underlying inflammatory infiltrate is at first largely mononuclear, but secondary bacterial infection introduces numerous neutrophils.

• The lesions may spontaneously resolve in 7 to 10 days or be stubbornly persistent for weeks.

• **Note:**
  Recurrent apthous ulcers may be associated with celiac disease and inflammatory bowel disease.

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**INFECTIONS**

This topic includes:

1. HSV infections
2. Oral candidiasis (Oral thrush).

**Herpes Simplex Virus Infection**

• The main causative agent is HSV1, but nowadays, there is an increase in the prevalence of HSV2 also due to changes in sexual habits. The disease typically occurs in children of age group 2 and 4.

• Approximately 10% to 20% of the time, primary infection presents as *acute herpetic gingivostomatitis*, in which there is an abrupt
onset of vesicles and ulcerations throughout the oral cavity, especially in the gingiva. These lesions are also accompanied by:
1. Lymphadenopathy,
2. Fever,
3. Anorexia and
4. Irritability.

Morphology:

- The vesicles range from lesions of a few millimetres to large bullae and are at first filled with a clear, serous fluid, but they often rupture to yield extremely painful, red-rimmed, shallow ulcerations.
- On microscopic examination there is intracellular and intercellular edema (acantholysis), yielding clefts that may become transformed into macroscopic vesicles.
- Individual epidermal cells in the margins of the vesicle or lying free within the fluid sometimes develop eosinophilic intranuclear viral inclusions, or several cells may fuse to produce giant cells (multinucleate polykaryons), changes that are demonstrated by the diagnostic Tzanck test, based on microscopic examination of the vesicle fluid.
- The vesicles and shallow ulcers usually spontaneously clear within 3 to 4 weeks, but the virus treks along the regional nerves and eventually becomes dormant in the local ganglia (e.g., the trigeminal).

Recurrent herpes stomatitis:

- It occurs either at the site of primary inoculation or in adjacent mucosal areas that are associated with the same ganglion.
- It takes the form of groups of small (1–3 mm) vesicles.

- The most common locations for recurrent lesions are:
1. **Lips (Herpes labialis),**
2. **Nasal orifices,**
3. **Buccal mucosa,**
4. **Gingiva,**
5. **Hard palate.**

- They resemble those already described in the primary infections but are much more limited in duration, are milder, usually dry up in 4 to 6 days, and heal within a week to 10 days.

**Oral candidosis (Oral Thrush)**

- Candidiasis is by far the most common fungal infection in the oral cavity.
- **Candida albicans** is a normal component of the oral flora in approximately 50% of the population.

- There are three major clinical forms of oral candidiasis:
  1. **Pseudo-membranous** (thrush),
  2. **Erythematous,** and
  3. **Hyperplastic.**

- Only the pseudo-membranous form, the most common of these, also called as *thrush*, typically takes the form of a superficial, *gray to white inflammatory membrane* composed of matted organisms enmeshed in a *fibrinosuppurative exudate* that can be readily scraped off to reveal an underlying erythematous inflammatory base.

- This fungus causes mischief only in individuals who have some form of *immunosuppression*, as occurs in patients with:
  1. **Diabetes mellitus,**
  2. **Organ or bone marrow transplant recipients,**
  3. Those with *neutropenia*, or
  4. **AIDS.**
5. In addition, broad-spectrum antibiotics that eliminate or alter the normal bacterial flora of the mouth can also result in the development of oral candidiasis.

### ORAL MANIFESTATIONS OF SYSTEMIC DISEASES

<table>
<thead>
<tr>
<th>Systemic diseases</th>
<th>Oral manifestations</th>
</tr>
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<tbody>
<tr>
<td>Scarlet fever</td>
<td>red tongue with prominent papillae (raspberry tongue); white-coated tongue through which hyperemic papillae project (strawberry tongue)</td>
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<tr>
<td>Measles</td>
<td>Spotty enanthema in the oral cavity, ulcerations on the buccal mucosa about Stensen duct produce Koplik spots.</td>
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<tr>
<td>Infectious mononucleosis</td>
<td>Acute pharyngitis and tonsillitis that may cause coating with a gray-white exudative membrane; enlargement of lymph nodes in the neck, palatal petechiae.</td>
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<tr>
<td>Diphtheria</td>
<td>Characteristic dirty white, fibrinosuppurative, tough, inflammatory membrane over the tonsils and retropharynx.</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Opportunistic oral infections, particularly herpesvirus, Candida, and other fungi; oral lesions of Kaposi sarcoma and hairy leukoplakia.</td>
</tr>
<tr>
<td>Pancytopenia (agranulocytosis, aplastic anemia)</td>
<td>Severe oral infections in the form of gingivitis, pharyngitis, tonsillitis; may extend to produce cellulitis of the neck (Ludwig angina).</td>
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<tr>
<td>Leukemia</td>
<td>With depletion of functioning neutrophils, oral lesions may appear like those in pancytopenia.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>A friable, red, pyogenic granuloma protruding from the gingiva (&quot;pregnancy tumor&quot;).</td>
</tr>
<tr>
<td>Phenytoin ingestion</td>
<td>Striking fibrous enlargement of the gingiva.</td>
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<tr>
<td>Melanotic pigmentation</td>
<td>Seen in:</td>
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<tr>
<td></td>
<td>1. Addison disease,</td>
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<tr>
<td></td>
<td>2. Hemochromatosis,</td>
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<td></td>
<td>3. Fibrous dysplasia of bone (Albright syndrome),</td>
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<td>4. Peutz-Jegher syndrome (gastrointestinal polyposis).</td>
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Hairy leukoplakia

Hairy leukoplakia is a distinctive oral lesion that is usually seen in immunocompromised patients.

Etiology:

1. HIV (in 80% of patients),
2. Immunocompromised for other reasons (20%: cancer chemotherapy/ transplantation patients).

Causative agent:

EBV is present in most cells and it is accepted as the causative agent of the lesion.

Characteristic lesion:

- Hairy leukoplakia 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.
- The distinctive microscopic appearance consists of hyperparakeratosis and acanthosis with "balloon cells" in the upper spinous layer.
- Sometimes there is koilocytosis of the superficial, nucleated epidermal cells, suggesting human papillomavirus (HPV) infection.

Note:

1. In HIV-positive individuals, with hairy leukoplakia, symptoms of AIDS follow in 2 to 3 years.
2. *Until it is proved otherwise via histologic evaluation, all leukoplakias must be considered precancerous.*
PRE-CANCEROUS LESIONS

1. LEUKOPLAKIA

Definition (WHO):
The term leukoplakia is defined by the World Health Organization as “a white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease.”

Simply put, if a white lesion in the oral cavity can be given a specific diagnosis it is not a leukoplakia.

Morphology:

- **Leukoplakias** may occur anywhere in the oral cavity but the favoured locations are:
  1. Buccal mucosa,
  2. Floor of the mouth,
  3. Ventral surface of the tongue,
  4. Palate, and
  5. Gingiva.

- They appear as solitary or multiple white patches or plaques, often with sharply demarcated borders.
- They may be slightly thickened and smooth or wrinkled and fissured, or they may appear as raised, sometimes corrugated, verrucous plaques.
- **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.**
- The more dysplastic or anaplastic the lesion, the more likely that a subjacent inflammatory infiltrate of lymphocytes and macrophages will be present.
Leukoplakia. Clinical appearance of leukoplakia is highly variable and can range from:

(A) smooth and thin with well-demarcated borders,

(B) diffuse and thick,

(C) irregular with a granular surface, to

(D) diffuse and corrugated.
Squamous Cell Carcinoma

General description:

- At least 95% of cancers of the head and neck are **squamous cell carcinomas** (HNSCCs), arising most commonly in the oral cavity.
- The remainder includes **adenocarcinomas** (of salivary gland origin), melanomas, various carcinomas, and other rarities.

Location:

Squamous cell carcinoma may arise anywhere in the oral cavity, but the favoured locations are:

1. The ventral surface of the tongue,
2. Floor of the mouth,
3. Lower lip,
4. Soft palate, and
5. Gingiva
Pathogenesis:

- The pathogenesis of squamous cell carcinoma is multifactorial. The main etiological agents associated are:
  1. Smoking tobacco
  2. Alcohol
  3. HPV
  4. Chewing of betel quid and paan
  5. Actinic radiation (sunlight)
  6. Pipe smoking.

- It should be noted, however, that patients with HPV-positive HNSCC do better than those with HPV-negative tumors.

Molecular biology:

Like all epithelial neoplasms, the development of squamous cell carcinoma is thought to be a multi-step process involving the sequential activation of oncogenes and inactivation of tumor suppressor genes in a clonal population of cells. The steps involved are:
• The first change is the loss of chromosomal regions of 3p and 9p21.
• Loss of heterozygosity (LOH) in conjunction with promoter hypermethylation at this locus results in the inactivation of the p16 gene, an inhibitor of cyclin-dependent kinase.
• This alteration is associated with the transition from normal to hyperplasia/hyperkeratosis and occurs before the development of histologic atypia,
• Subsequent LOH at 17p with mutation of the p53 tumor suppressor gene is associated with progression to dysplasia.
• Ultimately, amplification and overexpression of the cyclin D1 gene (located on chromosome 11q13), which constitutively activates cell cycle progression, is a common late event.
• This model does not take into account alterations in genes such as the epidermal growth factor receptor (EGFR), which is overexpressed in a high percentage of HNSCC and has been successfully targeted in the treatment of this disease.

Morphology:

• In the early stages, cancers of the oral cavity appear either as raised, firm, pearly plaques or as irregular, roughened, or verrucous areas of mucosal thickening, possibly mistaken for leukoplakia.
• As these lesions enlarge, they typically create ulcerated and protruding masses that have irregular and indurated (rolled) borders.

Histologically,

• On histologic examination, these cancers begin as dysplastic lesions, which may or may not progress to full-thickness dysplasia (carcinoma in situ) before invading the underlying connective tissue stroma.
• This difference in progression should be contrasted with cervical cancer in which, typically, full-thickness dysplasia, representing carcinoma in situ, develops before invasion.

• The degree of histologic differentiation, as determined by the relative degree of keratinization, is not correlated with behaviour.

• **As a group these tumors tend to infiltrate locally before they metastasize to other sites.**

• The routes of extension depend on the primary site. The favoured sites of local metastasis are the **cervical lymph nodes**, while the most common sites of distant metastasis are:
  1. Mediastinal lymph nodes,
  2. Lungs,
  3. Liver, and
  4. Bones.

• Unfortunately, such distant metastases are often occult at the time of discovery of the primary lesion.

**ODONTOGENIC TUMORS**

In contrast to the rest of the skeleton, epithelial-lined cysts are quite common in the jaws. The overwhelming majority of these cysts are derived from remnants of odontogenic epithelium present within the jaws. In general, these cysts are subclassified as either inflammatory or developmental.
Classification of odontogenic cyst:

**Dentigerous cyst:**

- The *dentigerous* cyst is defined as a cyst that *originates around the crown of an unerupted tooth* and is thought to be the result of a *degeneration of the dental follicle*.
- Radiographically, they are *unilocular lesions* and are most often associated with impacted *third molar (wisdom) teeth*.
- Histologically *they are lined by a thin layer of stratified squamous epithelium*.
- Often, there is a *very dense chronic inflammatory cell infiltrate* in the connective tissue stroma.
- Complete removal of the lesion is curative. This is important, since incomplete excision may result in *recurrence*. 
Odontogenic keratocyst (OKC):

- The *odontogenic keratocyst (OKC)* is an important entity to differentiate from other odontogenic cysts because *it is locally aggressive and has a high rate of recurrence.*
- OKCs can be seen at any age but are most often diagnosed in patients *between ages 10 and 40.*
- They occur most commonly in males *within the posterior mandible.*
- Radiographically, OKCs present as *well-defined unilocular or multilocular radiolucencies.*
- Histologically, the cyst lining consists of a thin layer of *keratinized stratified squamous epithelium* with a prominent basal cell layer and a corrugated appearance of the epithelial surface.
• **Treatment requires aggressive and complete removal of the lesion,** because recurrence rates for inadequately removed lesions can reach **60%**.

• Multiple OKCs may occur; these patients should be evaluated for **nevoid basal cell carcinoma syndrome** (Gorlin syndrome).

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**Periapical cyst/ radicular cyst:**

• These are extremely common lesions found at the **apex of teeth**.

• They develop as a result of **long-standing pulpitis**, which may be caused by advanced carious lesions or by trauma to the tooth in question.

• The inflammatory process may result in **necrosis of the pulpal tissue**, which can traverse the **length of the root** and exit the apex.
of the tooth into the **surrounding alveolar bone**, giving rise to a **periapical abscess**.

- Over time, like any chronic inflammatory process, a lesion with **granulation tissue** (with or without an epithelial lining) may develop.
- Periapical inflammatory lesions persist as a result of the **continued presence of bacteria** or other offensive agents in the area.
- Successful treatment, therefore, necessitates the **complete removal of offending material** and appropriate **restoration of the tooth** or **extraction**.