Objectives

- Describe the pathology of common diseases of the oral cavity, nasopharynx, larynx and salivary gland

Outline

I. Oral Cavity

a. **Inflammatory and infectious lesions:** *Aphthous ulcers, HSV, Candidiasis*
b. **Oral manifestations of systemic disorders**
c. **Squamous epithelial lesions:** *Squamous papilloma, Leukoplakia/Erythroplakia, Squamous cell carcinoma*

II. Nose, Nasopharynx and Larynx

a. **Inflammatory nasal lesions:** *Rhinitis, Nasal polyps*
b. **Necrotizing lesions of the Nose and Upper Airways:** *Extranodal NK/T-cell lymphoma*
c. **Nasopharyngeal carcinoma**
d. **Laryngeal squamous papilloma and papillomatosis**
e. **Laryngeal carcinoma**

III. Salivary Glands

a. **Inflammation (sialadenitis) and sialolithiasis**
b. **Neoplasms:** *Pleomorphic adenoma, Warthin tumour, Mucoepidermoid carcinoma, Adenoid cystic carcinoma*

IV. Others

a. **Branchial cyst**
b. **Thyroglossal duct cyst**

References

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***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. ORAL CAVITY

Inflammatory and infectious lesions

Aphthous ulcers (canker sores)

- Single or multiple, shallow, mucosal ulcerations that are common, often recurrent and painful
- Can be associated with immunologic disorders e.g. inflammatory bowel disease
- Usually self-resolve in a week but may persist for longer especially in immunocompromised patients

Herpes simplex virus infection

- Oral herpes usually caused by HSV-1 but HSV-2 (genital herpes) can also occur
- In children, usually present as **acute herpetic gingivostomatitis** (usually between 2-4 yo) with vesicles and ulceration of the oral mucosa
- In adults, usually presents as **acute herpes pharyngitis**
- After acute infection, the virus treks along regional nerves and becomes latent within local ganglia. Reactivation results in **recurrent herpetic stomatitis**
- In immunocompromised, can persist as **chronic mucocutaneous infection**

Oral candidiasis (thrush)

- Most common fungal infection of the oral cavity
- Thrush refers to the pseudomembranous form of oral candidiasis, in which there is a superficial gray-white inflammatory membrane composed of matted organisms in a fibrinosuppurative exudate that can be scrapped off, showing an erythematous inflammatory base
- Usually not invasive except in the setting of immunosuppression

Oral manifestations of systemic disorders

Oral lesions can be seen in blood dyscrasias (e.g. folic acid or vitamin B12 deficiency), mucocutaneous diseases (e.g. lichen planus, pemphigus vulgaris, systemic lupus erythematosus), chemotherapy

Squamous epithelial lesions

The spectrum of squamous lesions include benign, premalignant and malignant lesions.

Squamous papilloma

- Most common benign epithelial neoplasm in the oral cavity, usually in adults
- Up to 70% associated with low-risk HPV subtypes (HPV-6 and 11)
- **Microscopy**: Exophytic papillary proliferation of hyperplastic stratified squamous epithelium with branching fibrovascular core. Should not have dysplasia

Leukoplakia and erythroplakia

- **Leukoplakia** = "white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease"
    - Clinical term; as 5-25% are premalignant, all leukoplakias are considered premalignant until otherwise proven by histologic evaluation
    - Histology: spectrum of epithelial change from hyperkeratosis to severe dysplasia
- **Erythroplakia** = red velvety area within the oral cavity (+/- eroisions)
    - Clinical term; higher risk of malignant transformation compared to leukoplakia
    - Histology: almost all display severe display, carcinoma in-situ or minimally invasive carcinoma
- Often related to tobacco use

Squamous cell carcinoma (SCC)

- Squamous cell carcinomas account for ~95% of all head and neck cancers (i.e. oral cavity, pharynx, larynx, nasal cavities, thyroid and salivary glands)
- **Pathogenesis**: Multifactorial; depends partly on tumour location. A growing proportion have no known risk factors
    - **Oropharynx**: high-risk human papillomavirus (HPV) infection (esp. HPV-16)
    - **Oral cavity**: smoked tobacco, alcohol, chewing of betel quid (India and Asia)
    - **Lower lip**: Actinic radiation (sun exposure) and pipe smoking
- **Clinical features**: Male preponderance. Patients with HPV-positive SCC tend to be younger and have better long term survival compared to non-HPV associated SCC. Multiple primary tumours can occur due to "field cancerisation", often with worse outcomes, necessitating early detection
- **Gross**: HPV-associated SCC tend to be easily overlooked small primary tumours but accompanied by significantly enlarged cervical lymph nodes, while non-HPV associated SCC appear as raised firm plaques or roughed areas of mucosal thickening that can enlarge to form ulcerated masses with indurated borders +/- background leukoplakia or erythroplakia
- **Microscopy**: HPV-associated SCC are **non-keratinizing SCC** – nests and lobules of basaloid cells which are p16 immunostain positive. Non-HPV associated SCC tend to be **keratinizing SCC** that may begin as dysplastic lesions

II. NOSE, NASOPHARYNX AND LARYNX

Nose

Rhinitis

- Can be **infectious** ('common cold'; due to viruses) or **allergic** ('hay fever'; due to hypersensitivity to allergens such as plant pollen, fungi, animal allergens, dust mites)
- **Chronic rhinitis** occurs after repeated episodes of microbial or allergic rhinitis, eventually resulting in superimposed bacterial infection

Nasal polyps

- Polypoid protrusions of oedematous nasal mucosa after recurrent attacks of rhinitis
- Can encroach on the airway and impair drainage of secretions from the sinuses when large or multiple

Necrotizing lesions of the nose and upper airways

Includes infectious conditions (e.g. acute fungal infections like Mucormycosis particularly in diabetics and immunosuppressed patients), inflammatory conditions (e.g. granulomatosis with polyangiitis) and neoplastic entities (e.g. extranodal NK/T-cell lymphoma)

Extranodal NK/T-cell lymphoma (ENKTL), nasal type

- Nasal subtype accounts for 80% of ENKTL, and is characterised by vascular damage and prominent necrosis at initial sites of involvement in the nose and upper respiratory tract, which can extend to cause local destruction with complications, regional spread to lymph nodes and, later, systemic spread
- Occurs predominantly in East Asia or Latin America; associated with EBV
- Aggressive disease; better outcomes for localised disease with chemoradiotherapy

Nasopharynx

Nasopharyngeal carcinoma (NPC)

- Carcinoma strongly associated with EBV infection and a distinctive geographic distribution (high in southern China, South-east Asia and lower in other parts of the world)
- **Pathogenesis**: Multifactorial, with viral, environmental and genetic components, including diets high in nitrosamines (salted fish, fermented foods) and smoking in addition to EBV infection
- **Clinical features**: Often clinically occult until advanced stage when they present with nasal obstruction, epistaxis and lymph node metastases. Usually treated with radiotherapy, but the keratinising subtype is less radiosensitive and has poorer outcomes
- **Microscopy**: Non-keratinising squamous cell carcinoma is the commonest subtype of NPC; other subtypes include keratinising SCC and basaloid SCC. NK-NPC is often closely associated with lymphocytes and plasma cells (when abundant, traditionally called lymphoepithelial carcinoma), and almost always positive with EBV in-situ hybridisation (EBER-ISH)

Larynx

Squamous papilloma and papillomatosis

- Benign squamous epithelium lesion resembling that seen in the oral cavity, usually located on the true vocal cords
- Usually solitary in adults but can be multiple in children (“juvenile laryngeal papillomatosis”) - may recur but usually regress spontaneously at puberty

Laryngeal carcinoma

- 95% are squamous cell carcinoma
- **Pathogenesis**:
    - Usually follows hyperplasia – dysplasia – carcinoma in-situ – invasive carcinoma sequence. Non-dysplastic hyperplasia has almost no potential for malignant transformation, while the risk of malignant transformation increases with grade of dysplasia
    - Most often related to tobacco smoke exposure (epithelial changes can regress prior to malignant transformation with smoking cessation); synergistic effect with alcohol. Other risk factors include diet, irradiation, HPV infection
- **Clinical features**: Older males presenting with persistent hoarseness, dysphagia, dysphonia. Prognosis depends on clinical stage
- **Gross**: Usually arise on vocal cords but can also develop above or below the cords. Appear as mucosal plaques that can progress into ulcerated fungating masses
- **Microscopy**: Typical features of squamous cell carcinoma, often with foci of dysplasia / carcinoma in-situ in the adjacent mucosa

III. SALIVARY GLANDS

Inflammation (sialadenitis) and sialolithiasis

- **Sialolithiasis** = salivary duct obstruction by stones (usually idiopathic)
- Causes of **sialadenitis**
    - **Trauma**: usually manifests as a mucocele (fluctuant bluish swelling) resulting from either blockage or rupture of a salivary gland duct with mucus extravasation
    - **Viral infections**: especially mumps
    - **Bacterial infections**: non-specific bacterial sialadenitis is usually caused by infection with S.aureus and Streptococcus viridans following sialolithiasis
    - **Autoimmune disease**

Neoplasms

- 65-80% of all salivary gland neoplasms arise in parotid, 10% in submandibular gland and rest in the minor salivary glands. However, majority of parotid tumours are benign, while higher proportions of submandibular and minor salivary gland tumours are malignant
- Most common **benign** salivary gland tumours are **pleomorphic adenoma** and **Warthin tumour**, while the most common **malignant** tumour is **mucoepidermoid carcinoma**

Pleomorphic adenoma (mixed tumours)

- Most common salivary gland neoplasm (parotid gland >> submandibular gland >> minor salivary glands)
- Consist of a mixture of ductal (epithelial) and myoepithelial cells within a chondromyxoid or fibrous (mesenchymal) stroma; associated with *PLAG1* or *HMGA2* alterations

- **Clinical features**: Usually presents as painless slow-growing mobile discrete mass. May recur; low rate of malignant transformation (increases with age of lesion)
- **Gross**: Circumscribed lobulated mass with tan, white, translucent or gelatinous cut surface

Warthin tumour

- 2nd most common salivary gland neoplasm; arises almost exclusively in the parotid gland
- Consist of oncocytic epithelial cells lining ductal, papillary and cystic structures associated with a lymphoid-rich stroma
- **Clinical features**: 40-60yo M>F, particularly in smokers. Rarely recurs unless incompletely excised
- **Gross**: Usually unifocal but can be multifocal/bilateral. Well-circumscribed round to oval mass with pale gray surface and cystic/cleft-like spaces +/- papillary projections filled with mucinous secretions

Mucoepidermoid carcinoma

- Most common primary malignant tumour of salivary glands (mostly in parotid gland, but also account for a large proportion of salivary gland neoplasms in the other salivary glands)
- Consist of mucous, intermediate and epidermoid (squamous) epithelial cells forming solid and cystic areas; associated with *MAML2* gene rearrangement
- **Clinical features**: Wide age range including children. Prognosis depends on histologic grade
- **Gross**: Pale gray-white firm to soft solid tumours +/- cystic areas, may appear circumscribed or infiltrative

Adenoid cystic carcinoma

- Approximately half occur in the minor salivary glands; can also occur in sites outside of the salivary glands e.g. nose, upper airways, lung, breast
- Consist of basaloid cells forming tubular, solid or cribriform growth patterns with basophilic or hyaline matrix / basement membrane material; associated with *MYB*, *MYBL1* or *NFIB* rearrangement
- **Clinical features**: Usually older patients. Tends to be slow-growing but can have rapid course in the presence of high grade transformation. Frequent perineurial invasion
- **Gross**: Poorly circumscribed tan-gray/white firm solid mass

IV. OTHERS

Branchial cyst

- 20-40 yo; thought to arise from remnants of the second branchial arch
- Located on the upper lateral aspect of the neck along the sternocleidomastoid muscle
- Well-circumscribed cysts with a fibrous wall containing reactive lymphoid tissue, lined by squamous or pseudostratified columnar epithelium
- Differential diagnosis: Metastatic cystic squamous cell carcinoma

Thyroglossal duct cyst

- Develops from the remnants of descent of the thyroid gland from the base of the tongue to the midline of the anterior neck
- Cyst with a fibrous wall containing lymphoid tissue or thyroid remnants, lined by squamous or pseudostratified columnar epithelium