

## **PATHOLOGY OF SELECTED HEAD AND NECK LESIONS**

Except for the common upper respiratory infectious diseases, most of the lesions which will be covered in this lecture usually are seen clinically by Otolaryngologists. The shorthand term used for this field is ENT (Ear, Nose, Throat).

In this lecture, certain organs and structures will be covered, including oral cavity, nasal cavity, paranasal sinuses, nasopharynx, middle ear, pharynx, hypopharynx, and larynx. The lecture will be divided into two parts: first part will cover infectious, inflammatory and developmental lesions, and the second part will cover neoplastic lesions.

**Part I: Infectious, inflammatory and developmental disorders** (Excerpted from: Robbins and Cotran, Pathologic Basis of Disease)

### **NOSE**

Inflammatory diseases, mostly in the form of the common cold, are the most common disorders of the nose and accessory sinuses. Most of these inflammatory conditions are viral in origin, but they are often complicated by superimposed bacterial infections.

#### ***Infections:***

##### ***Zygomycosis (Mucormycosis)***

Zygomycosis (mucormycosis, phycomycosis) is an opportunistic infection caused by "bread mold fungi," including *Rhizopus*, *Absidia*, *Cunninghamella*, and *Mucor*, which belong to the class Zygomycetes. These fungi are widely distributed in nature and infect immunosuppressed patients. Predisposing factors are: neutropenia, corticosteroid use, diabetes mellitus and breakdown of the cutaneous barrier (e.g., burns, surgical wounds, trauma).

Zygomycetes are transmitted by airborne asexual spores. Most commonly, inhaled spores produce infection in the sinuses and the lungs, but spores can also lead to infection following percutaneous exposure or ingestion. Macrophages provide the initial defenses by phagocytosis and oxidative killing of germinating spores. Neutrophils have a key role in killing fungi during established infection.

Zygomycetes form nonseptate, irregularly wide (6 to 50  $\mu\text{m}$ ) fungal hyphae with frequent right-angle branching, which are readily demonstrated in the necrotic tissues by hematoxylin and eosin or special fungal stains. Most commonly in diabetics, the fungus may spread from nasal sinuses to the orbit and brain, giving rise to rhinocerebral mucormycosis. The zygomycetes cause local tissue necrosis, invade arterial walls, and penetrate the periorbital tissues and cranial vault. Meningoencephalitis follows, sometimes complicated by cerebral infarctions when fungi invade arteries and induce thrombosis.

#### ***Inflammatory Lesions:***

##### ***Allergic Rhinitis and Nasal Polyps***

Allergic rhinitis (hay fever) is initiated by sensitivity reactions to one of a large group of allergens, most commonly the plant pollens, fungi, animal allergens, and dust mites. It affects 20% of the U.S. population. Allergic rhinitis is an Ig E-mediated immune reaction

characterized by marked mucosal edema, redness, and mucus secretion, accompanied by a leukocytic infiltration in which eosinophils are prominent.

Recurrent attacks of rhinitis eventually lead to focal protrusions of the mucosa, producing so-called nasal polyps, which may reach 3 to 4 cm in length. On histologic examination, these polyps consist of edematous mucosa having a loose stroma, often harboring hyperplastic or cystic mucous glands and infiltrated with a variety of inflammatory cells, including prominently neutrophils, eosinophils, and plasma cells. When multiple or large, the polyps may encroach on the airway and impair sinus drainage.

### ***Wegener Granulomatosis:***

Wegener granulomatosis is a necrotizing vasculitis characterized by the triad of (1) acute necrotizing granulomas of the upper respiratory tract (ear, nose, sinuses, throat), the lower respiratory tract (lung), or both; (2) necrotizing or granulomatous vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries), most prominent in the lungs and upper airways but affecting other sites as well; and (3) renal disease in the form of focal necrotizing, often crescentic, glomerulitis. Some patients who do not manifest the full triad are said to have "limited" Wegener granulomatosis, in which the involvement is restricted to the respiratory tract.

The upper respiratory tract lesions range from inflammatory sinusitis resulting from mucosal granulomas to ulcerative lesions of the nose, palate, or pharynx, rimmed by necrotizing granulomas and accompanying vasculitis. Microscopically, the granulomas reveal a geographic pattern of necrosis surrounded by lymphocytes, plasma cells, macrophages, and variable numbers of giant cells. In association with such lesions there is a necrotizing or granulomatous vasculitis of small and sometimes larger arteries and veins.

Males are affected more often than females, at an average age of about 40 years, with peak incidence in the fifth decade. Clinical features include persistent pneumonitis with bilateral nodular and cavitary infiltrates (95%), chronic sinusitis (90%), mucosal ulcerations of the nasopharynx (75%), and evidence of renal disease (80%). Untreated, 80% of patients die within 1 year. c-ANCA are present in the serum in up to 95% of patients with active generalized disease, and this appears to be a good marker for disease activity.

## **PHARYNX**

The nasopharynx lies above and behind the soft palate. The oropharynx lies posterior to the oral cavity, below the nasopharynx and above the hypopharynx. The most anterior portion of the oropharynx contains the tonsils. The hypopharynx, the most inferior portion, connects to the esophagus.

### **Tonsils**

Pharyngitis and tonsillitis are frequently part of the usual viral upper respiratory infections. There is reddening and slight edema of the nasopharyngeal mucosa, with reactive enlargement of the related lymphoid structures. Bacterial infections may be superimposed or primary. The most common offenders are the  $\beta$ -hemolytic streptococci, but sometimes *Staphylococcus aureus* or other pathogens may be implicated. Particularly

severe forms of pharyngitis and tonsillitis are seen in infants and children and in immunosuppressed adults. The major importance of streptococcal "sore throats" lies in the possible development of late sequelae, for example, rheumatic fever and glomerulonephritis. Histologically, the tonsils are composed of a series of crypts lined by non-keratinizing squamous epithelium and surrounded by lymphoid tissue with germinal centers, but without sinuses. During the course of repeated viral and bacterial infections, the tonsillar lymphoid tissue may undergo marked hyperplasia with prominent germinal centers, leading to tonsillar enlargement. Acute tonsillitis may be complicated by a peritonsillar abscess.

### **Adenoid**

Lymphoid tissue is normally found in the subepithelial connective tissue of the nasopharynx. This lymphoid tissue usually undergoes hyperplasia as the result of repeated viral and bacterial infections. In small children, these hyperplastic lymphoid masses may obstruct the nasopharynx leading to difficulty in breathing. In addition, one or both Eustachian Tubes may drain poorly, leading to middle ear infections. As a result, many children are treated with adenoidectomy (curettage of hyperplastic nasopharyngeal lymphoid tissue).

The lymphoid tissue of the nasopharynx is part of Waldeyer's ring, which includes the lymphoid tissue of the oropharynx (tonsils), posterior tongue (lingual tonsils), uvula, and hypopharynx. The tissues of Waldeyer's ring are composed of collections of lymphoid tissue with germinal centers, but no sinuses are seen. Lymph nodes have central and marginal sinuses.

## **LARYNX**

### ***Inflammatory Lesions:***

Laryngitis is commonly part of an upper respiratory tract infection or the result of heavy exposure to tobacco smoke. Although most infections are self-limited, they may at times be serious, especially in infancy or childhood. In particular, laryngoepiglottitis, caused by *Haemophilus influenzae* or  $\beta$ -hemolytic streptococci in infants and young, may induce such sudden swelling of the epiglottis and vocal cords that a potentially lethal medical emergency is created. Croup is the name given to laryngotracheobronchitis in children, in which the inflammatory narrowing of the airway produces the inspiratory stridor.

### **Reactive Nodules (Vocal Cord Nodules And Polyps)**

Reactive nodules, also called polyps, sometimes develop on the vocal cords, most often in heavy smokers or in individuals who strain their vocal cords (singers' nodules). Adults, predominantly men, are affected. These nodules constitute smooth, rounded, sessile or pedunculated excrescences, generally only a few millimeters in greatest dimension, located usually on the true vocal cords. They are typically covered by squamous epithelium that may become keratotic, hyperplastic, or even slightly dysplastic. The core of the nodule is a loose myxoid connective tissue that may be variably fibrotic or punctuated by numerous vascular channels. Because of their strategic location, they often cause progressive hoarseness. They virtually never give rise to cancers.

## **EAR**

The middle ear is connected to the nasopharynx by the Eustachian Tube. The tympanic membrane separates the middle ear from the external auditory canal.

### ***Inflammatory Lesions:***

Inflammations of the ear—otitis media, acute or chronic—occur mostly in infants and children. They usually produce a serous exudate (when viral in origin) but may become suppurative with superimposed bacterial infection. The most common offenders are *Streptococcus pneumoniae*, nontypeable *H. influenzae*, and *Moraxella catarrhalis*. Cholesteatomas, associated with chronic otitis media, are cystic lesions 1 to 4 cm in diameter, lined by keratinizing squamous epithelium and filled with amorphous debris (derived largely from desquamated epithelium). It is proposed that chronic inflammation and perforation of the eardrum with ingrowth of the squamous epithelium or metaplasia of the secretory epithelial lining of the middle ear are responsible for the formation of a squamous cell nest that becomes cystic. A chronic inflammatory reaction surrounds the keratinous cyst. These lesions, by progressive enlargement, can erode into the ossicles, the labyrinth, the adjacent bone, or the surrounding soft tissue and sometimes produce visible neck masses.

## **NECK**

### ***Branchial Cyst (Lymphoepithelial Cyst):***

These benign cysts, usually appearing on the anterolateral aspect of the neck, arise either from remnants of the branchial arches or from developmental salivary gland inclusions within cervical lymph nodes. They are circumscribed unilocular cysts, 2 to 5 cm in diameter, with fibrous walls usually lined by stratified squamous or pseudostratified columnar epithelium surrounded by well-developed lymphoid tissue with reactive follicles. The cystic contents may be clear, watery to mucinous fluid or may contain desquamated, granular cellular debris. The vast majority of patients present before the age of 30. Be wary of making the diagnosis in older patients particularly above 50. The leading diagnosis in that age group is metastatic squamous cell carcinoma.

### ***Thyroglossal Tract Cyst:***

Embryologically, the thyroid anlage begins in the region of the foramen cecum at the base of the tongue; as the gland develops, it descends to its definitive location in the anterior neck. Remnants of this developmental tract may persist, producing midline cysts, 1 to 4 cm in diameter, that move with tongue protrusion and may be lined by stratified squamous epithelium, or by pseudostratified columnar epithelium. The connective tissue wall of the cyst may harbor lymphoid aggregates or remnants of recognizable thyroid tissue. The treatment is excision, with removal of the central portion of the hyoid bone (Sistrunk procedure).

## **SALIVARY GLANDS**

There are three major salivary glands—parotid, submandibular, and sublingual—as well as innumerable minor salivary glands distributed throughout the mucosa of the oral cavity. On histologic examination, salivary glands are composed of variable combinations of serous and mucinous cells.

### ***Inflammation (Sialadenitis):***

Sialadenitis may be of traumatic, viral, bacterial, or autoimmune origin. The most common form of viral sialadenitis is mumps, in which usually the major salivary glands, particularly the parotids, are affected. Autoimmune disease underlies the inflammatory salivary changes of Sjögren syndrome leading to xerostomia. Associated involvement of the lacrimal glands produces dry eyes—keratoconjunctivitis sicca.

### ***Sialolithiasis and Nonspecific Sialadenitis:***

Nonspecific bacterial sialadenitis, most often involving the submandibular glands, is common, usually secondary to ductal obstruction by stones (sialolithiasis). Stone formation is sometimes related to obstruction of the orifices of the salivary glands by impacted food debris or by edema about the orifice after some injury. Frequently, the stones are of obscure origin. Unilateral involvement of a single gland is the rule. The inflammatory involvement causes painful enlargement and sometimes a purulent ductal discharge.

**Part II: Neoplastic disorders** (Excerpted from Robbins and Cotran, Pathologic Basis of Disease)

**ORAL CAVITY**

Precancerous Lesions

***Leukoplakia And Erythroplakia:***

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." Approximately 3% of the world's population have leukoplakic lesions. A wide spectrum of lesions may show leukoplakia, including 1) simple hyperplasia with hyperkeratosis, 2) dysplasia, 3) carcinoma in-situ, and 4) invasive carcinoma. Somewhere between 5% and 25% of these lesions are premalignant.

Related to leukoplakia, but much less common and much more ominous, is erythroplakia. It represents a red, velvety, possibly eroded area within the oral cavity that usually remains level with or may be slightly depressed in relation to the surrounding mucosa. The epithelium in such lesions tends to be markedly atypical, incurring a much higher risk of malignant transformation than that seen with leukoplakia.

Intermediate forms are occasionally encountered, termed speckled leukoerythroplakia. Both leukoplakia and erythroplakia may be seen in adults at any age, but they are usually found between ages 40 and 70, with a 2:1 male preponderance. Although these lesions have multifactorial origins, the use of tobacco (cigarettes, pipes, cigars, and chewing tobacco) is the most common antecedent.

***Squamous Cell Carcinoma:***

At least 95% of cancers of the head and neck are squamous cell carcinomas (HNSCC), arising most commonly in the oral cavity. HNSCC is the sixth most common neoplasm in the world and approximately 40,000 cases in the United States and more than 500,000 cases worldwide will be diagnosed each year. The long-term survival has remained at less than 50% for the past 50 years due to a number of factors. Oral cancer is often diagnosed at an advanced stage (5-year survival for early-stage: ~ 80%; for late-stage: ~19%). The frequent development of multiple primary tumors markedly decreases survival (rate of second primary tumors: 3% to 7% per year). This observation has led to the concept of "field cancerization." It is postulated that multiple individual primary tumors develop independently in the upper aerodigestive tract as a result of years of chronic exposure of the mucosa to carcinogens.

The pathogenesis of squamous cell carcinoma is multifactorial.

Within North America and Europe, it is a disease of middle-aged men who have been chronic abusers of smoked tobacco and alcohol. With increased cigarette usage, the incidence of oral cancer in women is on the rise.

In addition, at least 50% of oropharyngeal cancers, particularly those involving the tonsils and the base of tongue, harbor oncogenic variants of HPV.

There is in epidemiologic evidence that a family history of head and neck cancer is a risk factor for the disease.

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

Outside of North America and Europe, a major regional predisposing influence is the chewing of betel quid and paan in India and parts of Asia.

The incidence of oral cancer in individuals under age 40 who have no known risk factors has been on the rise for the past several years. The basis of this is not understood.

Squamous cell carcinoma may arise anywhere in the oral cavity, but the favored locations are the ventral surface of the tongue, floor of the mouth, lower lip, soft palate, and gingiva. In the early stages, cancers of the oral cavity appear either as raised, firm, pearly plaques or as irregular, roughened, areas of mucosal thickening. As these lesions enlarge, they typically create ulcerated and protruding masses that have irregular, firm, and indurated (rolled) borders.

Squamous cell carcinomas range from well-differentiated keratinizing neoplasms to anaplastic, sometimes sarcomatoid, tumors, and from slowly to rapidly growing lesions. As a group, 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.

## **NASAL CAVITY AND PARANASAL SINUSES**

### ***Nasopharyngeal Angiofibroma:***

This is a highly vascular tumor that occurs almost exclusively in adolescent males. Despite its benign nature, it may cause serious clinical problems because of its tendency to bleed profusely during surgery.

### ***Sinonasal Papillomas:***

These are benign neoplasms arising from the sinonasal mucosa and are composed of squamous or columnar epithelium. Although their etiology is still unproven, HPV types 6 and 11 have been identified in the lesions. These occur in three forms: exophytic, inverted, and oncocytic.

Inverted papillomas are benign but locally aggressive neoplasms occurring in both the nose and the paranasal sinuses. As the name implies, the papillomatous proliferation of squamous epithelium, instead of producing an exophytic, extends into the mucosa, that is, it is inverted. If not adequately excised, it has a high rate of recurrence, with the potentially serious complication of invasion of the orbit or cranial vault; rarely, frank carcinoma may also develop in 5-10% of patients with inverted papillomas.

### ***Nasopharyngeal Carcinomas:***

This tumor is characterized by a distinctive geographic distribution, a close anatomic relationship to lymphoid tissue, and an association with EBV infection. The WHO classification divides them into: (1) keratinizing squamous cell carcinomas, (2) nonkeratinizing squamous cell carcinomas that can be either differentiated or undifferentiated (with abundant lymphoid infiltration) and (3) basaloid squamous cell carcinoma. Risk factors: EBV, diet (Nitrosamines particularly as a child), genetics. Nasopharyngeal carcinomas are particularly common in parts of Africa, where they are

the most frequent childhood cancer. In contrast, in southern China, they are very common in adults but rarely occur in children. In the United States, they are rare in both adults and children. The EBV genome has been identified in the tumor epithelial cells (not the lymphocytes) of most nonkeratinizing (differentiated and undifferentiated) squamous cell nasopharyngeal carcinomas.

On histologic examination, the keratinizing and nonkeratinizing squamous cell lesions more or less resemble usual well-differentiated and poorly differentiated squamous cell carcinomas arising in other locations. The undifferentiated variant is composed of large epithelial cells with oval or round vesicular nuclei, prominent nucleoli, and indistinct cell borders. Admixed with the epithelial cells are abundant, mature, normal-appearing lymphocytes. The three histologic variants present as masses in the nasopharynx or sometimes in other locations, such as the tonsils, posterior tongue, or upper airways. Nasopharyngeal carcinomas tend to grow silently until they have become unresectable and have often spread to cervical nodes or distant sites. Radiotherapy is the standard modality of treatment, yielding in most studies about a 50% to 70% 3-year survival rate. The undifferentiated carcinoma is the most radiosensitive and the keratinizing the least radiosensitive.

## **LARYNX**

### ***Squamous cell carcinoma:***

Similar to the oral cavity, precancerous changes precede the development of invasive carcinoma. These are termed, from one end of the spectrum to the other, hyperplasia, atypical hyperplasia, dysplasia, carcinoma in situ, and invasive carcinoma. The likelihood of the development of an overt carcinoma is directly proportional to the level of atypia when the lesion is first seen.

The various changes described are related to tobacco smoke, the risk being proportional to the level of exposure. However, alcohol is also clearly a risk factor.

About 95% of laryngeal carcinomas are typical squamous cell carcinomas. The tumor usually develops directly on the vocal cords, but it may arise above or below the cords. They begin as in situ lesions that later appear as pearly gray, wrinkled plaques on the mucosal surface, ultimately ulcerating and fungating. Adjacent mucosa may demonstrate squamous cell hyperplasia with foci of dysplasia or even carcinoma in situ.

Carcinoma of the larynx manifests itself clinically by persistent hoarseness. At presentation, about 60% of these cancers are confined to the larynx (better prognosis). Later, laryngeal tumors may produce pain, dysphagia, and hemoptysis. About one third die of the disease. The usual cause of death is infection of the distal respiratory passages or widespread metastases and cachexia.

### ***Squamous Papilloma And Papillomatosis:***

Laryngeal squamous papillomas are benign neoplasms, usually on the true vocal cords, that form soft, raspberry-like excrescences rarely more than 1 cm in diameter. On histologic examination, the papillomas are made up of multiple slender, finger-like projections supported by central fibrovascular cores and covered by an orderly, typical, stratified squamous epithelium.



Papillomas are usually single in adults but are often multiple in children, in whom they are referred to as juvenile laryngeal papillomatosis. However, multiple recurring papillomas also occur in adults. The lesions are caused by HPV types 6 and 11. They do not become malignant, but they frequently recur.

## EAR

Tumors of the ear are rare except for basal cell or squamous cell carcinomas of the pinna (external ear) associated with sun exposure. Those within the canal tend to be squamous cell carcinomas, which occur in middle-aged to elderly women and are not associated with sun exposure. Squamous cell carcinomas arising in the external canal may invade the cranial cavity or metastasize to regional nodes and, account for a 5-year mortality of about 50%.

## SALIVARY GLANDS

The salivary glands give rise to no fewer than 30 histologically distinct benign and malignant tumors.

**TABLE -- Histologic Classification and Approximate Incidence of Benign and Malignant Tumors of the Salivary Glands**

<b>Benign</b>	<b>Malignant</b>
Pleomorphic adenoma (50%) (mixed tumor)	Mucoepidermoid carcinoma (15%)
Warthin tumor (5%–10%)	Adenocarcinoma (NOS) (10%)
Oncocytoma (1%)	Acinic cell carcinoma (5%)
Other adenomas (5%–10%)	Adenoid cystic carcinoma (5%)
Basal cell adenoma	Malignant mixed tumor (3%–5%)
Canalicular adenoma	Squamous cell carcinoma (1%)
Ductal papillomas	Other carcinomas (2%)
NOS, not otherwise specified. <i>Data from Ellis GL, Auclair PL: Tumors of the Salivary Glands. Atlas of Tumor Pathology, Third Series. Washington, DC, Armed Forces Institute of Pathology, 1996.</i>	

A small number of neoplasms makes up more than 90% of salivary gland tumors. Overall, these neoplasms are relatively uncommon and represent less than 2% of tumors in humans. About 65% to 80% arise within the parotid, 10% in the submandibular gland, and the remainder in the minor salivary glands, including the sublingual glands. Fifteen percent to 30% of tumors in the parotid glands are malignant, in contrast to about 40% in the submandibular glands, 50% in the minor salivary glands, and 70% to 90% of sublingual tumors. The likelihood, then, of a salivary gland tumor being malignant is more or less inversely proportional to the size of the gland.

These tumors usually occur in adults, with a slight female predominance, but about 5% occur in children < 16 years. Being smoking related, Warthin tumors occur much more

often in males than in females. The benign tumors most often appear in the fifth to seventh decades of life. The malignant ones tend, on average, to appear somewhat later. Whatever the histologic pattern, neoplasms in the parotid glands produce distinctive swellings in front of and below the ear. In general, when they are first diagnosed, both benign and malignant lesions range from 4 to 6 cm in diameter and are mobile on palpation except in the case of neglected malignant tumors.

### **PLEOMORPHIC ADENOMA**

They represent about 60% of tumors in the parotid, are less common in the submandibular glands, and are relatively rare in the minor salivary glands. They are benign tumors that are derived from a mixture of ductal (epithelial) and myoepithelial cells. They reveal epithelial elements dispersed throughout a matrix along with varying degrees of myxoid, hyaline, chondroid (cartilaginous), and even osseous tissue.

Most pleomorphic adenomas present as rounded, well-demarcated masses < 6 cm. Although they are encapsulated, in some locations (particularly the palate) the capsule is not fully developed, and expansile growth produces tongue-like protrusions into the surrounding gland, rendering enucleation of the tumor hazardous. The cut surface is gray-white with myxoid and blue translucent areas of chondroid.

The dominant histologic feature is the great heterogeneity mentioned. The epithelial elements resembling ductal cells or myoepithelial cells are disposed in duct formations, acini, irregular tubules, strands, or sheets of cells. These elements are typically dispersed within a mesenchyme-like background of loose myxoid tissue containing islands of chondroid and, rarely, foci of bone.

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 adequate parotidectomy is about 4% but, with attempted enucleation, approaches 25% because of failure to recognize at surgery minute protrusions from the main mass. The incidence of malignant transformation increases with the duration of the tumor, being about 2% for tumors present less than 5 years and almost 10% for those of more than 15 years' duration. These cancers, when they appear, are among the most aggressive of all salivary gland malignant neoplasms, accounting for 30% to 50% mortality in 5 years.