REACTIVE, INFECTIOUS AND BENIGN LESIONS OF SALIVARY GLAND- A REVIEW

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ABSTRACT

Salivary gland tumors are relatively uncommon and account for approximately 3-6 percentage of all neoplasms of the head and neck. Tumors of salivary glands usually occur in the major salivary glands (parotid, submandibular, sublingual), however, a small percentage occur in the minor salivary glands located within the oral mucosa, palate, uvula, floor of the mouth, tongue, pharynx, larynx and paranasal sinuses. The salivary glands are subject to a number of pathologic conditions. These include inflammatory infective diseases such as viral, bacterial, or allergic sialadenitis, a variety of benign tumors. In this review we summarize the various reactive, infectious and benign lesions of salivary gland for better understanding with the recent references and current literature.

KEYWORDS: Salivary gland tumors, reactive, infectious, metabolic,
INTRODUCTION
The salivary glands are a group of compound exocrine glands secreting saliva. All salivary glands develop similarly as initial discrete thickenings of the epithelium of the stomodeum. The parotid and submandibular glands are actually located subcutaneously, below and front of the ears. The submandibular gland is located under the floor of the mouth, close to the mandible. The sublingual gland is located in the floor of the mouth, anterior to the submandibular gland. The minor salivary glands line the mucosa of the lips, tongue, oral cavity and pharynx. The chief function of salivary gland is the secretion of saliva.

Salivary gland tumors are relatively uncommon and account for approximately 3-6 percentage of all neoplasms of the head and neck.\(^1\) Tumors of salivary glands usually occur in the major salivary glands but a small percentage occur in the minor salivary glands too. Approximately 80% of salivary gland tumors are benign and the most common benign tumor is pleomorphic adenoma. Salivary gland disorders include inflammatory, bacterial, viral and neoplastic etiologies. The presentation can be acute, recurrent, or chronic. Acute suppurrative sialadenitis presents as rapid-onset pain and swelling and is treated with antibiotics, salivary massage, hydration and sialagogues such as lemon drops or vitamin C lozenges. Recurrent or chronic sialadenitis is more likely to be inflammatory than infectious; examples include recurrent parotitis of childhood and sialolithiasis. Inflammation is commonly caused by an obstruction such as a stone or duct stricture. Viral etiologies include mumps and human immunodeficiency virus, and treatment is directed at the underlying disease. Benign and malignant tumors can occur in the salivary glands and usually present as a painless solitary neck mass.\(^2\)

Diagnosis is made by imaging (e.g., ultrasonography, computed tomography, magnetic resonance imaging) and biopsy as a diagnostic procedure (initially with fine-needle aspiration).\(^3\) Diagnosis of salivary gland neoplasm includes immunohistochemistry, ultrasonography of salivary glands, Point of care technology, measuring biofilm activity, oral fluid nanosensor test. Molecular testing in anatomic pathology is becoming standardized and can contribute valuable diagnostic, therapeutic, and prognostic information for the clinical management of patients.\(^4\) Overall, most salivary gland tumors are benign and can be treated with surgical excision.
DISCUSSION

Classification of salivary gland disorders (Regezi)

Reactive lesions
Mucous extravassation phenomenon
Mucous retention cyst
Maxillary sinus retention cyst/ pseudo cyst
Necrotizing sialometaplasia

Infectious sialadenitis
Mumps
Cytomegalovirus sialadenitis
Bacterial sialadenitis
Sarcoidosis

Benign neoplasm
Mixed tumour (pleomorphic adenoma)
Monomorphic adenoma
Ductal papilloma

Reactive lesions

Mucocele is a clinical term that includes mucus extravasation phenomenon and mucus retention cyst, because each has a distinctive pathogenesis and microscopy, they are considered separately[^5]. Ranula is a clinical term that also includes mucus extravasation phenomenon and mucus retention cyst, but it occurs specifically in the floor of the mouth.

Mucus Extravasation Phenomenon
Mucus extravasation phenomenon presents as a relatively painless smooth-surfaced mass ranging in size from a few millimeters to 2 cm in diameter. It has a bluish color when mucin is superficially located. Adolescents and children are more commonly affected than adults.[^6] Lesions may fluctuate in size because of mucosal rupture over the pooled mucin. Continued production of mucin leads to recurrence.

Etiology and pathogenesis. The cause of mucus extravasation phenomenon is traumatic severance of salivary gland excretory duct, resulting in mucus escape, or extravasation, into the surrounding connective tissue. An inflammatory reaction of neutrophils followed by
macrophages ensues. Granulation tissue forms a wall around the mucin pool and the contributing salivary gland undergoes inflammatory change. Ultimately, scarring occurs in and around the gland.\(^7\)

**Clinical features.** Common location for these lesions in the oral cavity is lower lip however, it also presents on other locations like tongue, buccal mucosa, soft palate, retromolar pad and lower labial mucosa. It is more common in children and young adults.\(^8\) Lesions are uncommonly found in other introral regions where salivary glands are located, probably because of lower susceptibility to trauma.

**Histopathology.** Extravasation of free mucin incites an inflammatory response that is followed by connective tissue repair. Neutrophils and macrophages are seen and granulation tissue forms around the mucin pool. The adjacent salivary gland whose duct are transacted shows ductal dilation, chronic inflammation, acinar degeneration and interstitial fibrosis.

**Differential Diagnosis.** Although a history of a traumatic event followed by development of a bluish translucency of lower lip is characteristic of mucus extravasation phenomenon, other lesions might be considered when a typical history is absent. These include salivary gland neoplasm (especially mucoepidermoid carcinoma), vascular malformation, venous varix, and soft tissue neoplasm such a neurofibroma or lipoma.

**Treatment and Prognosis.** The treatment is surgical excision.\(^9\) Aspiration of fluid content provides no lasting clinical benefit. Removal of associated minor salivary glands along with the pooled mucus is necessary to prevent recurrence.

**Mucous retention cyst**

**Etiology and Pathogenesis.** Mucus retention cysts result from obstruction of salivary flow because of a sialolith, periductal scar, or impinging tumor. The retained mucin is surrounded by ductal epithelium, giving the lesion a cyst like appearance microscopically.

**Sialolithiasis:** Obstruction due to salivary stone, or sialolith, is usually associated with the submandibular gland. The sialolith(s) can be found anywhere in the ductal system from the gland parenchyma to the excretory duct orifice. A *sialolith* represents the precipitation of calcium salts primarily calcium phosphate in the form of hydroxyapatite, with small amount of magnesium, carbonate, and ammonium.\(^10\)
Clinical features. Mucus retention cyst is less common than mucus extravasational phenomenon. Most retention cysts are asymptomatic.\textsuperscript{[11]} It usually appears in older age-group and is most commonly seen in palate, cheek and floor of the mouth. Lesions present as asymptomatic swellings, usually without antecedent trauma. They vary from size from 3 to 7 mm and on palpation are mobile and nontender. The overlying mucosa is intact and of normal color.

Histopathology. The cyst like cavity of mucus retention cyst is lined by normal but compressed ducal epithelial cells. The type of lining formed by the epithelial cells ranges from pseudostratified to stratified squamous. The cyst lumen contains inspissated mucin or a calcified sialolith. The connective tissue around the lesion is minimally inflamed, although the associated gland shows obstructive change.

Differential Diagnosis. Salivary gland neoplasms, mucus extravasation phenomenon, and benign connective tissue neoplasms should be included in a clinical differential diagnosis. Dermoid cyst might also be included for lesions in the floor of the mouth.

Treatment and Prognosis. Treatment requires removal of mucus retention cyst and the associated minor salivary gland to avoid postoperative mucus extravasation phenomenon. Lesions of major salivary glands can be treated in similar way or, on occasion, only by removal of the obstruction (sialolith) if it occurs in the distal part of the ductal system. The sialolith is either surgically removed or milked through the duct orifice. Newer methods include cryosurgery, CO2 laser ablation, intralesional corticosteroid injection, marsupialization and electrocautery. The advantage in CO2 laser is that it minimizes the relapses and complications.\textsuperscript{[12]}

Maxillary Sinus Retention Cyst/Pseudocyst

Etiology and pathogenesis. Retention cysts are thought to arise from blockage of an antral seromucous gland, resulting in a ducal epithelium-lined cystic structure filled with mucin. Pseudocysts are inflammatory in origin and result from fluid accumulation within the sinus membrane. They may be related to infection or allergy. Bacterial toxins, anoxia, or other factors presumably cause leakage of protein into surrounding soft tissue, thus raising the extravascular osmotic pressure with subsequent fluid increase.
Clinical Features. The great majority of these lesions are asymptomatic, although there maybe some slight tenderness in the mucobuccal fold or, more rarely, palpable buccal expansion in this region. With age group between 18-35 years.\(^{13}\) It is more common in female In panoramic and periapical radiographs, retention cysts and pseudocysts of the maxillary sinus are hemispheric, homogeneously opaque, and well delineated. They usually demonstrate an attachment to the floor of the antrum, with size being a function of the anatomic space rather than of duration, Uncommonly these lesions may appear bilaterally.

Histopathology. The pathogenesis of the two forms of antral cysts is reflected in the histologic appearance. The retention cyst is lined by pseudostratified columnar epithelium with occasional mucous cells interspersed. The supportive elements are minimally inflamed. The pseudocyst shows no evidence of an epithelial lining but, rather, pools of mucoid material surrounded by slightly compressed connective tissue is seen.

Differential Diagnosis. A clinical differential diagnosis of cysts and pseudocysts arising within the mucosa of the maxillary sinus would include polyps, hyperplasia of the sinus lining secondary to odontogenic infection, maxillary sinusitis and neoplasms arising within the soft tissues of the antral lining.

Treatment. Antral retention cysts and pseudocysts are generally left untreated because they are limited in growth and are not destructive and most spontaneously rupture. Therefore periodic observation is all that is required.

Necrotizing sialometaplasia

Necrotizing sialometaplasia is a benign condition that typically affects the palate and rarely other sites containing salivary glands. It was defined by Abrams et al. in 1973 as a reactive necrotizing inflammatory process involving minor salivary glands of the hard palate.\(^{14}\)

Etiology and Pathogenesis. The initiating event of necrotizing sialometaplasia is believed to be salivary gland ischemia precipitated by local trauma, surgical manipulation, or local anesthesia. Infarction of the gland follows and squamous metaplasia of ductal remnants eventually appears. This condition is believed to be due to local trauma or focal vascular compromise leading to discrete tissue necrosis in the area. Patients often have no history of a prior traumatic event.
Anneroth and Hansen proposed 5 histologic stages in the development and evolution of necrotizing sialometaplasia: infarction, sequestration, ulceration, repair and healing. They emphasized that these stages could overlap and would be dependent upon the extent and severity of damage.\textsuperscript{[15]}

**Clinical Features.** Intraorally, necrotizing sialometaplasia is characterized by a seemingly spontaneous appearance, most commonly at the junction of the hard and soft palates. It is more common in adults; the mean age of onset is 46 years. Males are commonly affected nearly twice as often as females.\textsuperscript{[16]} Early in its evolution, the lesion may be noted as a tender swelling, often with a dusky erythema of the overlying mucosa.

Subsequently the mucosa breaks down, with the formation of a sharply demarcated deep ulcer with a yellowish gray lobular base but few cases manifest as non-ulcerated swelling or mass.\textsuperscript{[17]} In the palate the lesion may be unilateral or bilateral, with individual lesions ranging from 1 to 3 cm in diameter.

**Histopathology.** Submucosa adjacent to an ulcer shows necrosis of salivary glands and squamous metaplasia of salivary duct epithelium. Preservation of the lobular architecture of salivary glands serves to distinguish this process from neoplasia.\textsuperscript{[18]} The characteristic ductal squamous metaplasia shows no cytologic atypia, but the pattern may be misinterpreted as squamous cell carcinoma. When this metaplasia is seen in the presence of residual viable salivary gland, the lesion may be mistaken for mucoepidermoid carcinoma.

**Differential Diagnosis.** Clinically, squamous cell carcinoma and malignant minor salivary gland neoplasms must be ruled out, usually by a biopsy. Syphilitic gummas and deep fungal infections must likewise be ruled out, since they may present as punched-out lesions of the palate. Findings from serology, biopsy and/or culture are usually needed to exclude these entities. In medically compromised patients, such as those with poorly controlled diabetes, opportunistic fungal infections such as mucormycosis may cause a similar clinical picture.

The entity *subacute necrotizing sialadenitis* has recently been described as a nonspecific, inflammatory condition of minor salivary glands of unknown etiology. It is characterized by an abrupt onset of pain and localized swelling, usually of the hard or soft palate, but unlike necrotizing sialometaplasia, is self-limiting without an ulcerative or metaplastic component.
Treatment and Prognosis. This condition is a benign, self-limiting process that does not require surgical intervention. However, an incisional biopsy should be performed to establish a definitive diagnosis. Diagnosis may be further supplemented via immunohistochemistry, demonstrating focal to absent immunoreactivity for p53, low immunoreactivity for MIB1 (Ki-67) and the presence of 4A4/p63- and calponin-positive myoepithelial cells.\(^{[19]}\) Healing takes place over several weeks by secondary intention. Patient reassurance, wound irrigation using a bland baking soda-and-water mouth rinse, and occasional use of analgesics are the only management steps necessary.

Adenomatoid Hyperplasia

Adenomatoid hyperplasia was first described by Giansanti et al. in 1971.\(^{[20]}\) It is a non neoplastic enlargement of the minor salivary glands of the hard palate. The cause is unknown, although there is some evidence to suggest that trauma plays a role.\(^{[21]}\)

Clinical Features. The palate is the chief site of involvement of this salivary gland hyperplasia. There is a male predominance, and age ranges from 24 to 63 years.(adenomatoid hyperplasia of oral minor salivary glands,) The clinical presentation is a unilateral swelling of the hard and/or soft palate. This lesion is asymptomatic, broad based, and covered with intact mucosa of normal color and quality.\(^{[22]}\)

Histopathology. Lobules of hyperplastic mucous glands extend beyond the submucosa and into the lamina propria. Individual acinar clusters are more numerous and larger than normal. Ducts exhibit a slight increase in relative prominence. The cytologic and morphologic features of acinar and ductal elements are within normal limits. There is generally no significant inflammatory cell infiltrate.

Differential Diagnosis. A clinical differential diagnosis would include salivary neoplasms, lymphoma and extension of nasopharyngeal or sinonasal disease into the oral cavity. Periapical inflammatory disease should be excluded.

Treatment and Prognosis. Subsequent to identification by means of an incisional biopsy, no treatment is necessary, given the purely benign nature of this process. There is no neoplastic potential. There have been no recurrence reported in the literature yet.\(^{[23]}\)
Infectious sialadenitis

Mumps

Mumps is an infectious, acute viral sialadenitis affecting primarily the parotid glands. Considered the most common of all salivary gland diseases before the advent of routine immunization.

Etiology and Pathogenesis. The causative agent of mumps is a paramyxovirus. It is tubelike, helically symmetrical nucleocapsid contains a monopartite, single-stranded, negative-sense RNA genome and an RNA-directed RNA polymerase. A 2- to 3-week incubation period precedes clinical symptoms. Transmission is by direct contact with salivary droplets.

Clinical Features. Patients develop fever, malaise, headache and chills in addition to preauricular pain. In salivary glands, parotid is commonly involved which demonstrates 70% incidence of bilateral infection.[24] The parotid swelling tends to be asymmetric at the outset, reaching maximum proportions within 2 to 3 days. Severe local pain is often noted, especially on movement of the jaws in talking and chewing. Stensen's duct may become partially occluded as the gland swells, with sharp pain secondary to the stimulation of the secretory mechanism by food or drink.

Perceptible diminution of swelling is noted approximately 10 days after the onset of symptoms. The disease affects males and females equally, especially young adults and children. Potentially serious complications (orchitis or oophoritis) can occur in adults. Mumps is a systemic infection, as evidenced by the widespread involvement of glandular and other tissues in the body, including the liver, pancreas, kidney and nervous system.

Treatment and Prognosis. Treatment is symptomatic and includes bed rest. Analgesics are prescribed and in severe cases corticosteroids may be used. Complete recovery is generally the rule, although fatalities have been associated with viral encephalitis, myocarditis and nephritis.

Nerve deafness and bilateral testicular atrophy have been noted but are uncommon.[25] Prevention of the disease is now possible using a live attenuated vaccine that induces a noncommunicable, subclinical infection. Antibody conversion occurs in approximately 90% of susceptible individuals and immunity is lifelong. Although mumps is the most common form of viral sialadenitis, it is important to note that parotitis may also be caused by other
viral agents, including coxsackie A virus, echovirus, choriomeningitis virus, cytomegalovirus and parainfluenza virus types 1.

**Cytomegaloviral sialadenitis**

It is an infection of salivary glands, or so-called cytomegalic inclusion disease. It is a rare condition that affects neonates as a result of transplacental infection. When encountered in adults who are immunosuppressed (e.g., human immunodeficiency virus [HIV] infection, organ transplants), infection may cause fever, salivary gland enlargement, hepatosplenomegaly, pneumonitis and lymphocytosis.[26]

Retinitis can be a serious complication of this infection.[27] Cytomegalovirus can be demonstrated in biopsy material, and with the use of in situ hybridization methods its presence can be easily confirmed in the tissue sections. Oral aphthous like ulcers, particularly those arising in immunocompromised patients, may contain the virus, but the importance is undetermined. In severely infected immunocompromised patients, ganciclovir may be used to control cytomegalovirus infections.

Adults who are not immunosuppressed may also be infected with cytomegalovirus, as evidenced by demonstration of antibodies in serum.[28] Symptomatology may be nonexistent, or there may be slight to debilitating fever and malaise. The significance of cytomegalovirus infections in this population is poorly understood.

**Bacterial sialadenitis**

**Etiology and Pathogenesis.** Bacterial infections of salivary glands are generally due to microbial overgrowth in association with a reduction in salivary flow. Such reduction in flow may be noted subsequent to dehydration and debilitation.

Traditionally, bacterial sialadenitis has been a common postoperative complication of surgery related to inadequate hydration. Numerous drugs associated with a decreased salivary flow rate likewise contribute to infections of the major salivary glands, especially the parotid. Other possible causes include trauma to the duct system and hematogenous spread of infection from other areas.

The most commonly isolated organisms in parotitis are penicillin-resistant *Staphylococcus aureus*, *Streptococcus viridans*, and *Streptococcus pneumoniae*. [29] It is of interest to note the
marked reduction in the overall incidence of acute parotitis after the introduction of antibiotic preparations.

**Clinical Features.** Clinical features are chiefly characterized by the presence of a painful swelling, low-grade fever, malaise and headache. Laboratory studies disclose an elevated erythrocyte sedimentation rate (ESR) and leukocytosis. The involved gland is extremely tender, with the patient often demonstrating guarding during examination.

Trismus is often noted and purulence at the duct orifice may he produced by gentle pressure on the involved gland or duct. If the infection is not eliminated early, suppuration may extend beyond the limiting capsule of the parotid gland. Extension into surrounding tissues along fascial planes in the neck or extension posteriorly into the external auditory canal may follow.

**Treatment and Prognosis.** Management of bacterial sialadenitis is directed at elimination of the causative organism coupled with rehydration of the patient and drainage of purulence, if present. Culture and sensitivity testing of the exudate at the orifice of the duct is the first step in antibiotic management.

After a culture is obtained, all patients should empirically be placed on a regimen of a penicillinase-resistant antibiotic such as semisynthetic penicillin. A biopsy and retrograde sialography should be avoided. The former may cause sinus tract formation and the latter may allow infection to proceed beyond the boundaries of the gland into surrounding soft tissues. With prompt and effective treatment, recurrence is generally avoided.

In cases of recurrent parotitis, considerable destructive glandular changes can be seen. In the so-called juvenile, variant, of parotitis, intermittent unilateral or bilateral painful swelling is accompanied by fever and malaise.

**Sarcoidosis**

**Etiology.** Sarcoidosis is a granulomatous disease of undetermined origin. Although no specific cause has been identified, it has been suggested that this disease represents an infection or a hypersensitivity response to atypical mycobacteria. As many as 90% of patients
in some studies showed significant titers of serum antibodies to these organisms. In some patients with sarcoidosis, a transmissible agent from human sarcoid tissue has been identified.

With the use of molecular biologic techniques, mycobacterial DNA and RNA have been identified in sarcoid tissues, raising the possibility of *Mycobacterium tuberculosis* or a related organism as a causative agent. Susceptibility related to human leukocyte antigens has been studied. Patients with some histocompatibility antigens (HLA-B7, HLA-B5, HLA-A9) may have a greater incidence of sarcoidosis than do others.

**Clinical Features.** The protean manifestations of this disease are well known. Clinical courses range from spontaneous resolution to chronic progression. The disease may affect individuals at any age, although most are affected in the second to fourth decades. Females show a higher incidence than do males, and African-Americans are more commonly affected than whites.

Sarcoidosis is usually a self-limiting, benign disease with an insidious onset and protracted course. Patients may complain of lethargy, chronic fatigue and anorexia, with specific signs and symptoms related to the organ involved.

Pulmonary manifestations are the most characteristic of this disease. They are typified by bilateral, hilar and less commonly, paratracheal lymphadenopathy. The disease may stabilize at this point, or it may advance to pulmonary fibrosis and a more ominous prognosis. The most serious complications of sarcoidosis are pulmonary hypertension, respiratory failure, and cor pulmonale. The skin may be involved in approximately 25% of cases; most commonly, an erythema nodosum of acute onset and short duration is seen. Skin plaques characterized by nontender, dark purple, elevated areas on the limbs, abdomen and buttocks may appear.

Another form of cutaneous pathology includes lesions known as *lupus pernio*, a term used to describe symmetric, infiltrative, violaceous plaques on the nose, cheeks, ears, forehead and hands. Ocular involvement is variable, with inflammation of the anterior uveal tract most commonly seen. This may be associated with parotid gland swelling and fever, so-called *uveoparotid fever* or *Heerfordt's syndrome*.

Oral soft tissue lesions of sarcoidosis are nodular and generally indistinguishable from those seen in Crohn's disease. Parotid swelling may occur either unilaterally or bilaterally with
about equal frequency. This is often associated with fever, gastrointestinal upset, joint pains, and night sweats, which may precede glandular involvement by several days to weeks. Other salivary glands may also be involved in the granulomatous inflammatory process, leading to xerostomia. Granulomas may also occur in the nasal sinuses, pharynx, epiglottis and larynx. Serum chemistry, radiographic studies, and biopsy are useful laboratory tests.

**Histopathology.** Consistent microscopic findings of sarcoidosis are noncaseating granulomas. The granulomas may be well demarcated and discrete or confluent. Within the granulomas are epithelioid macrophages and multinucleated giant cells, which may contain stellate inclusions (asteroid bodies) and concentrically laminar calcifications (Schaumann bodies). A diffuse lymphocytic infiltrate may be seen around the periphery of the granulomas. A lip biopsy may occasionally provide evidence of sarcoid involvement of minor salivary glands in support of a clinical impression of pulmonary disease.

**Diagnosis.** The Kveim test has traditionally been used to establish the diagnosis of sarcoidosis; however, this test is no longer used. Of considerable value is a laboratory assay for angiotensin I—converting enzyme.

Serum chemistry studies should include calcium (for evidence of hypercalcemia) and angiotensin I-converting enzyme, lysozyme and adenosine deaminase levels (for evidence of macrophage activity within granulomas). Gallium scintiscanning and routine chest radiographs and intraoral films may be used to demonstrate bone involvement. Elevation of this enzyme in conjunction with a positive chest radiograph has a high diagnostic reliability. The histologic differential diagnosis includes tuberculosis, Crohn's disease, leprosy, cat-scratch disease, fungal infections.

**Treatment and Prognosis.** Spontaneous resolution occurs in a significant number of patients. Corticosteroids are generally considered beneficial and remain the drugs of choice in treating symptomatic pulmonary sarcoidosis.

**Benign lesions**

**Pleomorphic adenoma**

**Etiopathogenesis.** The mixed tumor, or pleomorphic adenoma, is the most common neoplasm involving both the major and minor salivary glands. The histogenesis of mixed tumor, or pleomorphic adenoma, relates to a dual proliferation of cells with ductal or
myoepithelial features, separating it from monomorphic adenomas composed of only one cell type.

The myoepithelial-differentiated cell assumes an important role in determining the overall composition and appearance of mixed tumors. A range of cell types and microscopic patterns are seen in mixed tumors - those composed almost completely of epithelial cells at one end of a spectrum and those composed almost completely of myoepithelial cells at the other end. Between these two extremes, less well developed cells with features of both myoepithelial and ductal elements may be seen. Alternatively, it has been theorized that rather than simultaneous proliferation of neoplastic epithelial and myoepithelial cells, a single cell with the potential to differentiate toward either epithelial or myoepithelial cells may be responsible for these tumors.

Some regions in this tumors can be composed of principally of ducts with associated myoepithelial cells, others composed largely of modified myoepithelial cells, and still others are composed of a combination of the two cell types, forming solid or cellular zones. Variable production of basal lamina and glycosaminoglycans leads to the gradual separation of the tumor cells and to the formation of the myxoid regions in different degrees, both within each pleomorphic adenoma and between different examples. Metaplastic processes associated with the development of myxomatous areas results in the chondroid component.

Clinical features. The mixed tumor, or pleomorphic adenoma, is the most common tumor of the major and minor salivary glands. The tumor is typically lobulated and enclosed within a connective tissue pseudocapsule that varies in thickness The parotid gland accounts for approximately 85% of these tumors, whereas the submandibular gland and the intraoral minor salivary glands account for 8% and 7%, respectively. Mixed tumors occur at any age, males are more affected than females and are most prevalent in the fourth to sixth decades of life. They constitute approximately 50% of all intraoral minor salivary gland tumors. Generally, they are mobile except when they occur in the hard palate.

They appear as firm, painless swellings and, in the vast majority of cases, do not cause ulceration of the overlying mucosa. The palate is the most common intraoral site, followed by the upper lip and buccal mucosa. When they arise within the parotid gland, mixed tumors are generally painless and slow growing. They are usually located below the ear and posterior to
the mandible. Some tumors may be grooved by the posterior extent of the mandibular ramus, with long-standing lesions capable of producing pressure atrophy on this bone.

When they are situated within the inferior pole or tail of the parotid, the tumors may present below the angle of the mandible and anterior to the sternocleidomastoid muscle. Mixed tumors range in size from a few millimetres to centimetres.

**Histopathology.** Microscopically, mixed tumors demonstrate a wide spectrum of histologic features. The pleomorphic patterns and the variable ratios of ductal to myoepithelial cells are responsible for the synonym *pleomorphic adenoma*. Approximately one third of mixed tumors show an almost equal ratio of epithelial and mesenchymal elements (believed to be derived from myoepithelial differentiated cells). The epithelial component may appear as ducts, tubules, ribbons and solid sheets and the mesenchymal component may appear as myxoid, hyalinized connective tissue. Infrequently, fat, cartilage and/or bone may be seen. Myoepithelial cells may appear as plasmacytoid cells or spindled cells.[35]

The plasmacytoid cells, when seen, are highly characteristic of mixed tumors and are almost never found in other salivary gland tumors. The pseudocapsule surrounding mixed tumors may demonstrate islands of tissue within it or extending through it. These islands represent outgrowths or pseudopods continuous with the main tumor mass and likely contribute to recurrences, particularly in the parotid.

**Treatment and Prognosis.** The treatment of choice is surgical excision. Enucleation of parotid mixed tumors is not advisable because of the risk of recurrence due to extension of tumor through capsular defects. Removal of mixed tumors arising within the parotid gland is complicated by the presence of the facial nerve.

Any surgical approach, therefore, must include preservation of the uninvolved facial nerve. In most cases superficial parotidectomy (lateral lobectomy) with preservation of the facial nerve is the most appropriate management for those tumors arising within the parotid.

Resection of the submandibular gland is the preferred treatment for mixed tumors in this location. Lesions of the palate or gingiva often involve or abut, periosteum or bone, making complete removal difficult unless some bone is removed. Other oral benign mixed tumors can be more easily excised, preferably including tissue beyond the pseudocapsule. Inadequate initial removal of mixed tumors in major glands may result in recurrence, often with multiple,
discrete tumor foci. These recurrent lesions may be widely distributed within the area of previous surgery and may occur in association with the surgical scar. In most instances the recurrent tumor maintains the original pathology.

However, with each recurrence there is an increased possibility of malignant transformation (carcinoma ex-mixed tumor). If lesions are untreated for an extended length of time, typically years to decades, up to 25% may undergo malignant transformation. The probability of malignant change also increases if the area has previously been treated with surgery or radiotherapy. Myoepithelial cells in mixed tumors have shown to be immunoreactive for keratin, S-100 protein, glial fibrillary acidic protein, actin, and vimentin.

**Monomorphic adenoma**

Monomorphic adenomas are composed of an isomorphic epithelial cell population and lack the neoplastic connective tissue elements that characterize mixed tumors. The classification scheme is based on the histologic pattern.

**Basal Cell Adenomas.** Basal cell adenomas constitute approximately 1% to 2% of all salivary gland adenomas. About 70% are found within the parotid. In minor salivary glands, mostly the upper lip, followed in palate, buccal mucosa, and lower lip are affected.

**Clinical Features.** Basal cell adenomas generally are slow growing and painless. The lesions tend to be clinically distinct on palpation, but they can be multifocal and multinodular. The age range of patients is between 35 and 80 years, with a mean age of approximately 60 years. A distinct male predilection is noted.

The *membranous adenoma (dermal analog tumor)* variant occurs in the parotid gland in more than 90% of cases, with no cases reported in the intraoral minor glands. These lesions vary from 1 to 5 cm in greatest dimension and generally present as an asymptomatic swelling. Several patients with this particular finding in the parotid gland have presented with synchronous or metachronous adnexal cutaneous tumors, including dermal cylindroma, trichoepithelioma, and eccrine spiradenoma.

**Histopathology.** In the *solid* variety of monomorphic adenoma, islands or sheets of basaloid cells often show peripheral palisading, with individual cells at the periphery appearing cuboidal to low columnar in profile. The *trabecular-tubular* form of basal cell adenoma exhibits trabecular cords of epithelial cells or tubular epithelial elements.
Membranous adenoma grows in a nodular fashion with variable-sized islands of tumor tissue surrounded by a thick periodic-acid-Schiff (PAS)-positive hyaline membrane. Similar, if not identical, eosinophilic hyaline material is also noted in droplet form within the intercellular areas of the tumor islands, similar to those noted in so-called collagenous spherulosis of the breast and polycystic adenosis of salivary glands. Membranous adenomas may also contain foci of normal salivary gland, giving the erroneous impression of invasive ness and necessitating separation from adenoid cystic carcinoma. Nuclei are regular in shape and uniformly basophilic, and the amount of cytoplasm is generally slight.

**Treatment and Prognosis.** Except for membranous adenoma, monomorphic adenomas are benign and rarely recur. The membranous form of basal cell adenoma has a significant rate of recurrence because of its growth pattern and multifocal nature. Preferred management is conservative surgical excision including a margin of normal uninvolved tissue.

Canalicular Adenoma. *Canalicular adenoma* is generally separated from other monomorphic adenomas because it occurs almost exclusively within the oral cavity, commonly in the upper lip, and has distinctive histologic features. Its biologic behavior is, however, similar.

**Clinical Features.** A narrow age range is noted in patients with canalicular adenomas. Most patients tend to be older than 50 years of age, and most patients are women. The upper lip is by far the most common site for canalicular adenomas, with one series reporting 81% of lesions located in this region. The lesions tend to be freely movable and asymptomatic and range in size from a few millimeters to 2 to 3 cm. Canalicular adenomas occasionally may not be totally encapsulated, and more than 20% of cases are also multifocal.

**Histopathology.** Characteristically, canalicular adenomas show bilayered strands of basaloid cells that branch and anastomose within a delicate stroma that is highly vascular and contains few fibroblasts and little collagen. Individual cells are characteristically cuboidal to columnar, with moderate to abundant amounts of eosinophilic cytoplasm.

**Treatment and Prognosis.** The treatment of choice for canalicular adenoma is surgical excision.
Myoepithelioma

Etiopathogenesis. Benign salivary gland tumors composed entirely of myoepithelial cells are called myoepitheliomas. Although these tumors are of epithelial origin, the phenotypic expression of the tumor cells is more closely related to that of smooth muscle.

Reflective of this is the immunohistochemical staining of myoepithelioma cells with antibodies to actins, cytokeratin and S-100 protein. Most myoepitheliomas arise within the parotid gland and, less commonly, the submandibular gland and intraoral minor salivary glands.

Clinical features. Myoepitheliomas present as circumscribed painless masses. Most myoepitheliomas arise within the parotid gland and, less commonly, the submandibular gland and intraoral minor salivary glands. Lesions appear from the third through ninth decades (median age, 53 years) and in both genders equally.

Histopathology. Microscopically, sheets of either plasmacytoid or spindle cells make up these lesions. Approximately 70% of cases contain spindle cells and 20% are composed of plasmacytoid cells. Occasionally, both cell forms may be seen in equal quantity.

Myoepithelial differentiation of tumor cells has been confirmed with immunohistochemical and electron microscopic studies. Rarely, clear cells may dominate the histologic presentation, leading to the designation of a "clear cell variant." of this entity.

Treatment and prognosis of this benign lesion is identical to that of the benign mixed tumor. Conservative excision of lesions arising in minor salivary glands is advised, including a thin rim of surrounding normal tissue. When lesions are noted within the parotid gland, superficial parotidectomy is indicated. The overall prognosis is excellent, and recurrences are not reported.

Oncocytoma

Etiopathogenesis. Oncocytoma, or oxyphilic adenoma, is a rare lesion seen predominantly in the parotid gland. This lesion is composed of oncocytes, large granular acidophilic cells filled with mitochondria. Such cells are normally found in salivary glands in the intralobular ducts, and they usually increase in number with age.
The histogenetic origin of this lesion is believed to be from the salivary duct epithelium, in particular the striated duct.

**Clinical features.** Oncocytomas are solid, ovoid encapsulated lesions usually less than 5 cm in diameter when they are noted within the major salivary glands. In some instances bilateral occurrence may be noted. These lesions are rarely seen intraorally. Within individual glands (most often the parotid) a non neoplastic and multicentric cellular change known as oncocyotosis may be seen. As oncocytic foci enlarge, confusion with oncocytoma may occur.

**Histopathology.** Microscopically, oncocytoma cells are polyhedral with granular eosinophilic cytoplasm. Nuclei are centrally placed and are typically vesicular. The histologic pattern is usually sheets of cells, although microcystic spaces and clear cell change may be seen. The histochemical stain phosphotungstic acid hematoxylin (PTAH), highlighting the intracytoplasmic mitochondria, is useful to confirm the diagnosis of oncocytooma. Antimitochondrial antibodies may also be used in an immunohistochemical approach to confirm diagnosis.

**Treatment and prognosis.** The treatment is conservative, with superficial parotidectomy as the treatment of choice for parotid lesions. In minor salivary glands, removal of the tumor with a margin of normal tissue is deemed to be adequate. Recurrence is rarely noted.

The malignant oncocytic tumor, or so-called malignant oncocytoma, is rare. The diagnosis is based on atypical nuclear changes in oncocyes in conjunction with an invasive pattern. Malignant change may arise de novo, or it may occur in a preexisting benign oncocytoma.

**Papillary Cystadenoma Lymphomatosum (Warthin’s Tumor).** Papillary cystadenoma lymphomatosum, also known as Warthin’s tumor, it is a benign neoplasm which accounts for approximately 7% of epithelial neoplasms of salivary glands. Most common synonyms used are cystic papillary adenoma, branchial cyst of parotid, oncocytoma, lymphoglandular cystome.

**Etiopathogenesis.** The pathogenesis of warthin’s tumor is not known and is still controversial in regards to the origin of both the epithelium and the lymphoid stroma. Warthin's tumor is thought to arise within lymph nodes as a result of entrapment of salivary gland elements early in development. This theory is supported by the occasional case of multicentricity, as well as normal lymph node architecture surrounding many early or
developing tumors. It is believed that some intraoral lesions may arise in an area of reactive lymphoid hyperplasia secondary to chronic inflammation. When it occurs in the parotid, this tumor presents typically as a doughy to cystic mass in the inferior pole of the gland, adjacent and posterior to the angle of the mandible.

**Clinical features.** Majority of the lesions occur within the parotid salivary gland. Intraorally, this lesion is rare. It is seen predominantly in men, typically between the fifth and eighth decades of life. Recent studies have shown a positive correlation between the development of Warthin's tumor and smoking. Rarely a malignant transformation to carcinoma, is seen as a complication of radiotherapy.

**Histopathology.** The combination of lymphoid matrix and papillations of eosinophilic epithelial cells forming cystic spaces presents a distinct and pathognomonic histopathologic picture. The epithelial cells are arranged in two cell layers of uniform rows. Tall columnar cells approximate the cystic space. The epithelial papillations projects into cystic spaces that are often filled with homogenous eosinophilic granular material that stains with periodic acid-schiff stain. Luminal lining cells are rarely ciliated but often have a “fuzzy” luminal surface, which is attributed to the presence of microvilli.

**Treatment and Prognosis.** The established treatment is surgical removal. The principal debate regarding treatment usually concerns the amount of normal tissue required to attain minimal recurrence rate. Two theories of surgical treatment are 1. Tumor enucleation with resection of minimal amount of surrounding tissue and 2. A somewhat more aggressive superficial parotidectomy. Enucleation may be sufficient treatment for warthin’s tumor.

**Ductal papillomas**
Ductal papillomas comprise sialadenomapapilliferum, inverted ductal papilloma, and intraductal papilloma. These rare tumors are thought to arise within the interlobular and excretory duct portion of the salivary gland unit.

**Sialadenoma papilliferum**
*Sialadenoma papilliferum* is an unusual benign salivary gland neoplasm that was first reported in 1969 by Abrams and Finch.

**Etiopathogenesis.** Sialadenoma is a distinct entity of minor and major salivary gland.
Clinical features. It is usually found intraorally, buccal mucosa and palate are the common sites involved. It presents as a painless exophytic papillary lesion. Most cases are seen in men between fifth to eighth decades of life. The clinical impression before removal is that of a simple papilloma, owing to its frequent keratotic appearance and papillary surface configuration.

Histopathology. Papillary processes develop, forming convoluted clefts and spaces. Each papillary projection is lined by a layer of epithelium approximately two to three cell layers thick and is supported by a core of fibrovascular connective tissue. The more superficial portions of the lesion demonstrate a squamous epithelial lining; deeper portions show more cuboidal to columnar cells, often oncocytic in appearance.

A related papillary lesion of salivary duct origin is inverted ductal papilloma This is a rare entity that presents as a nodular submucosal mass resembling a fibroma or lipoma. It is seen in adults and has an equal gender distribution. Microscopically, a marked proliferation of ductal epithelium is seen subjacent to intact mucosa. Crypts and cystlike spaces lined by columnar cells with polarized nuclei are interspersed with goblet cells and transitional forms of cuboidal to squamous cells.

The third form of ductal papilloma is intraductal papilloma This rare lesion arises from a greater depth within the ductal system, often presenting as a salivary obstruction. Histologically, a single or double layer of cuboidal to columnar epithelium covers several papillary fronds that project into a duct, with no evidence of proliferation into the wall of the cyst. Treatment for this lesion, as well as inverted ductal papilloma, is simple excision. There is little risk of recurrence.

Treatment and Prognosis. Management of lesion is by conservative surgery, with little chance of recurrence.

REFERENCES


