Non Neoplastic Salivary Gland Disorders

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ABSTRACT

Non-neoplastic salivary gland disorders make up about 6% of diseases of the salivary glands. These disorders are divided into the following groups: developmental, obstructive, infectious / systemic, idiopathic and auto-immune. Clinically these lesions may mimic a neoplastic process involving salivary gland and the treatment process may vary accordingly. Sialadenosis is distinguishable from sialadenitis by its clinical, radiological, and morphological characteristics. Mucoceles represent the majority of these cysts (75%). HIV-associated salivary gland disease includes lymphoepithelial lesions and cysts involving the salivary gland tissue and/or intraglandular lymph nodes, and Sjogren's syndrome-like conditions, diffuse interstitial lymphocytosis syndrome, and other reported lesions of the major salivary glands. This review article discusses the clinical features, histopathological features and treatment of various non-neoplastic salivary gland diseases.

Keywords: Non-neoplastic enlargement, sialadenosis, sjogren's syndrome, labial biopsy.

Introduction

Tumors of salivary glands constitute a heterogeneous group of lesions of great morphologic variations. Tumors of salivary glands have a annual incidence of around 1-6.5 cases per 100,000 individuals. Non neoplastic disorders of the salivary glands are divided into the following groups;[1]

a. Salivary duct cysts
b. Sialadenosis
c. Sialolithiasis
d. Sialadenitis
e. HIV associated salivary gland diseases
f. Oncocytosis
g. Necrotizing sialometaplasia

WHO classification of tumor like lesions of the salivary gland;[2]

1. Sialadenosis
2. Oncocytosis
3. Necrotizing sialometaplasia
4. Benign lymphoepithelial lesions
5. Salivary gland cyst
6. Chronic sclerosing sialadenitis

Table 1: Classification of Salivary gland disorders;[3,4,5]

1.	DEVELOPMENTAL
	a. Aplasia
	b. Hyperplasia
	c. Developmental lingual mandibular salivary gland depression'
	d. Anterior lingual depression
	e. Heterotopic salivary gland tissue
	f. Accessory salivary gland tissue
	g. Oncocytosis
	h. Adenomatoid glandular hyperplasia
	i. Polycystic disease of the parotid gland
1.	NON NEOPLASTIC
	a. OBSTRUCTIVE
	i. Mucus escape phenomenon
	ii. Mucus retention phenomenon
	iii. Sailolithiasis
	b. INFECTIOUS & SYSTEMIC DISEASES
	i. Tuberculosis
	ii. Cat-scratch disease
	iii. Cytomegalovirus
	iv. Salivary gland cyst as a manifestation of HIV
	v. Mumps
	vi. Sarcoidosis
	vii. Cystic fibrosis
	viii. Sialdenosis
	c. IDIOPATHIC
	i. Necrotizing sialometaplasia
	ii. Benign cyst of salivary gland
	iii. Angiolymphoid hyperplasia and Kimura's disease
	iv. Chelitis glandularis
	d. AUTOIMMUNE
	i. Sjogren syndrome
	ii. Mikulicz disease

Developmental Salivary Gland Disoders

1. APLASIA (Agenesis): Any one or group of salivary glands may be absent, unilaterally or bilaterally. It manifest with the development of xerostomia. A diagnosis of salivary gland aplasia is made after the exclusion of the common causes of xerostomia medications, sjogren syndrome and radiation. CT scan and MRI will indicate the gland's absence. This condition occurs as a unknown cause or may develop along with associated syndromes such as Hemifacial microstomia or LADD syndrome or Treacher Collins syndrome.

2. PALATAL GLAND HYPERPLASIA: An unusual localized hyperplasia or hypertrophy of minor accessory salivary glands in the palate can occur. The causes for this alteration are endocrine disorders, gout, dm, menopause, hepatic diseases, starvation, alcoholism, sjogrens syndrome, adiposity and aging process.

1. HETERTOPIC SALIVARY GLAND: Salivary gland tissue located in sites other than those of normal anatomical locations. "Willis et al" proposed three reasons for heterotopias;

a. Abnormal persistent & development of vestigial structures
b. Dislocation of a portion of a definitive organ
c. Abnormal differentiation of the normal tissues.

Locations: Paraparotid lymphnodes, Middle ear, Intraosseous hetertopic salivary gland tissue, External auditory canal, Mediastinum, Pituitary gland, Prostate, Thyroid and parathyroid gland.

2. ACCESSORY PAROTID GLANDS: Refers to lobules of the parotid salivary gland tissue that are separated from the main body of the gland but drain into stenson's duct. "Frommer et al" pointed out that anterior extensions of the parotid gland tissue along the parotid duct are normal variants and are not considered accessory. It arranges from 0.5 to 3cms and may be superior or ablong. Clinically, lesions of accessory parotid tissue present as masses in the cheek that occur in the central third of a line drawn from the mid tragus to the point midway between the ala of the nose

and vermillion lip border. The histologic features are similar to that of the primary parotid gland tissue.[6]

3. ONCOCYTOSIS: It is a metaplastic, sometimes hyperplastic, developmental or transformational process that is characterized by focal replacement of normal glandular tissue with enlarged eosinophilic epithelial cells with granular cytoplasm. Oncocytosis is seen with greater frequency in older people and is considered a squela of aging. The majority is of cases occur in parotid but it may be found in any major and minor salivary glands. Histologically, oncocytosis may present as scattered foci of enlarged, eosinophilic epithelial cells or as a solitary foci of metaplastic oncocytes. The cells retain their acinar arrangement. Oncocytosis stain with PTAH and with PAS. Ultrastructural findings are characterized by cytoplasm that is packed with large, pleomorphic mitochondria containing filamentous tubular and vesicular cristae. Oncocytes have been considered as a product of degenerative changes. Cells also contain high levels of mitochondrial enzymes because of increased mitochondria.[7,8]

4. POLYCYSTIC DISEASE OF THE PAROTID GLAND: Least common of the benign cystic lesions of the parotid gland and is a developmental malformation of the ductal system. Females are more commonly affected & occur bilaterally. Recurrent painless swelling of the involved gland occurs. Histopathologically, the architecture of the gland is preserved. Lobules are markedly distended. Honey combed or lattice like appearance. Cystic lumina contain flocculent, eosinophilic material and few scattered macrophages. Eosinophilic bodies with concentric and radial patterns similar to spheroliths and microliths.[9]

OBSTRUCTIVE SALIVARY GLAND DISORDERS

Most common disorders of the major and minor salivary glands.

Occurs as a result of:

a. Trauma to the salivary gland ducts
b. Stasis of saliva
c. Partial or complete obstruction of the ducts.

Three more common primary mechanical obstructive disorders are:

1. Mucus escape phenomenon
2. Mucus retention cyst
3. Sialolithiasis.

1. MUCUS ESCAPE PHENOMENON (MUCOCELE)

It is defined as a pooling of mucus in a cavity within a connective tissue that is not lined by a epithelium.

Traumatic severance of a duct with resultant pooling of mucus in the surrounding tissue is its cause. Clinically, Major and minor (common) salivary glands are affected. 96% affects the minor salivary glands in the lower lip. Superficial lesions present as raised soft tissue swelling with translucent bluish hue. Deeper lesions appear nodular with overlying normal mucosa. Painless mucosal swelling will appear from few days to weeks.

Ranula – Swelling in the floor of the mouth most commonly associated with sublingual glands but submandibular gland can also be affected. *(Plunging or Cervical ranula).* Histologically, Non epithelial lined (Not a true cyst). Circumscribed cavity in soft tissue filled with eosinophilic material staining positive for mucin staining. Presence of acute and chronic inflammatory cells. Consists of compressed fibrovascular connective tissue. As the lesion matures, granulation tissue progressively grows into the cavity and slowly obliterates the defect & is known as *"Organizing mucocele".*

Treatment: Removal of both the lesion and the adjacent minor salivary glands and its duct.[10,11]

2. MUCUS RETENTION CYST: It is a true salivary gland cyst lined by a epithelium. "Eversole et al" termed this lesion as an "Oral Sialocyst". This lesion develops as a result of partial obstruction of a duct and buildup of presence may cause its dilatation without the rupture and is responsible for the proliferation of the ductal epithelium.

Clinical features: Parotid gland is the commonest site of involvement. Affects individual from first to ninth decades of life. Has slight predilection. Lesion appears as slowly enlarging, painless, circumscribed often fluctuant soft tissue swelling that may persist from months to yrs.

Pathological features: Presence of a overlying epithelial lining. Unilocular / multilocular / multicystic patterns. Lining epithelium consists of cuboidal to low columnar cells of non keratinizing stratified squamous epithelium. Presence of inflammatory infiltrates.

Treatment: Surgical excision of the true cyst. [2,12]

3. SIALOLITHIASIS: Sialoliths are calcified masses that develop in the ductal system of the salivary glands.

Also known as:

a. Salivary gland calculi
b. Salivary gland stones

Sialoliths grow by a rhythmic deposition of inorganic and organic components around a mineralized nucleus.

Clinical features: May develop in the ductal system of major and minor salivary gland. Submandibular gland is the most commonly affected gland due to its course of the ductal system. Has slight female predilection. Swelling and pain in the area of the affected gland may be present. Swelling may be located by bimanual palpation in the affected area.

Pathological features: They are round oval or cylindrical calcified masses that may vary in colour from white to yellow brown. The surface texture may be smooth or irregular Changes in the ductal wall includes squamous, oncocytic or mucous cell metaplasia of the epithelium. Saliva stasis may lead to retrograde infections via its ducts. Longterm obstruction may lead to fibrosis or subsequent loss of secretory functions.

Treatment: Conservative therapy:

a. Moist heat therapy
b. Increased intake of fluids

c. Sialagogues
d. Use of pilocarpine to increase the salivary flow.[13,14]

Infectious and Systemic Diseases

The salivary glands are involved when the pathogens or other systemic processes affect the gland parenchyma, its stroma or intraglandular lymphnodes. Lymphnodes are the primary factor involved in most of these diseases.

Table 2: Classification of Sialadenitis[15]

1.	Bacterial sialadenitis
2.	Viral sialadenitis
3.	Radiation induced sialadenitis
4.	Electrolytic sialadenitis
5.	Chronic sclerosing sialadenitis (Kuttner's tumor)
6.	Immune sialadenitis.

Tuberculosis

Tuberculoses lymphadenitis is the most common extrathoracic form of the disease and cervical lymphnodes including lymphnodes in and around the major salivary glands.[16] Infection of the salivary glands and lymphnodes occurs in one of the two ways: A focus of mycobacterium TB in oral cavity break through the mucous membrane that ascend to the salivary glands. Hematogenous or lymphatic spread.

Clinical features: Parotid gland is the most commonly affected. Females are most commonly affected. Clinically the lesion appears as painless, cystic or solid nodule that is upto 5cms in diameter. Intracutaneous injection of PPD shows positivity with 10mm or more of indurations in 48hrs.

Histopathologic features: Gland & lymphnodes demonstrate multiple granuloma. Central necrosis surrounded by giant cells of both langhan's and foreign body types, epitheloid cells and lymphocytes.

Treatment: Multi drug anti-TB therapy.

CYTOMEGALOVIRUS: CMV is DNA virus of Herpes viridae family. It is the most common viral disorder of the salivary glands & affects the newborns.
Clinical features: CMV infection is seen in one of the four clinical settings;
1. Congenital infections
2. Perinatal infections
3. CMV mononucleosis
4. In immune compromised patients

Histologic features: Consists of large cells around 25 – 40 micrometers that exhibits central basophilic nuclear inclusions and cytoplasmic inclusions.

Treatment: Antiviral chemotherapy.

Salivary Gland Cysts as Manifestations of HIV[17]

Persistent generalized lymphadenopathy (PGL) is defined as palpable lymphadenopathy at 2 or more extrainguinal sites that persists for more than 3 months in absence of any infections. In some cases, the initial manifestations may be localized rather than generalized lymphadenopathy that may precede to months or even years. Parotid swelling can be unilateral or bilateral for a period of 1 to 4 yrs. Presence of multiple parotid swelling or cysts which are frequently bilateral.

Histologic features: Monomorphic round (clear cells) focally pack medullary sinuses or form aggregates along the blood vessels, fibrous septa and peripheral lymphnodes. Mitoses are absent. Lymphnodes in and around the salivary glands contain squamous lined cysts and epimyoepithelial islands.

MUMPS: Mumps virus is an RNA virus of paramyxoviridae family and is the most common viral infective agent of the salivary glands. Mumps is an acute, contagious disease that is endemic in all areas of the world.
Clinical features: Usually spreads from human reservoirs by airborne droplets of infected saliva. After incubation period, the condition manifests as pain and rapid swelling of one or moth parotid glands during a period of 1 to 3 days.[18] Tasting citrus fruits or other sour liquids that stimulates salivation intensifies the pain. The swelling & systemic symptoms gradually subside in 3 – 7 days.

Histopathologic features: Three sets of changes:
a. Interstitial changes
b. Acinar cell changes
c. Ductal epithelial changes
Other features are dilated ducts with lumina filled with clumps of secretion & desquamated epithelium.

Treatment: Self-limiting condition.

Cystic Fibrosis: It is the most common fatal inherited, autosomal condition. Past few years, new concepts concerning the cause of cystic fibrosis has emerged. Previously it was thought to be a disease of abnormal mucus products and now considered to be involving abnormal fluid and electrolyte transports across the exocrine gland epithelium. Chronic obstructive pulmonary disease, impaired digestive & absorptive & elevated concentrations of salt in sweats. Salivary gland acini are mainly mucous in types, are affected. Sublingual gland shows more pathologic alterations. Consists of ductal ectasia, microliths abd interstitial fibrosis.

Treatment: Aggressive respiratory & physical therapy as well as administration of appropriate antibiotics.

SIALADENOSIS: Non neoplastic and non inflammatory enlargement of the salivary glands. Usually bilateral and may manifest reoccurrence or pain or both.

Table 3: Classification of sialadenosis[19]

a.	Hormonal sialadenosis
b.	Neurohumoral sialadenosis
c.	Dysenzyamtic sialadenosis
d.	Malnutritional sialadenosis
e.	Mucoviscidosis
f.	Drug induced sialadenosis

Slowly evolving, undulating & recurrent swelling affecting fourth decades of life. Hypertrophy of acinar cells and terminal ducts branching yields sialographic *"leafless tree"* patterns.

Histopathologic features: ***"Donath and Seifert et al"*** described as swelling is due to acinar enlargements. Diameter of the acinar cells increase 2-3 times than that of normal. The nuclei tend to be basally situated. Inflammatory cells are absent.

Treatment: Dependent on controlling the underlying cause.

IDIOPATHIC SALIVARY GLAND DISORDERS: These are unrelated group of lesions for which the causes are generally remains unknown.

NECROTIZING SIALOMETAPLASIA: Necrotizing sialometaplasia is non neoplastic, inflammatory, self limiting condition of the salivary glands. Most commonly misdiagnosed as carcinomas, mainly squamous cell carcinoma or mucoepidermoid carcinoma. This pitfall in diagnosis can be avoided if one is familiar with the clinical and histopathological findings.

Clinical features: Mostly involves the minor salivary glands of the hard palate. Etiology: Trauma, radiation therapy or ill fitting dentures. Presents as deep, crater like ulcers of 1-3cms. These ulcers are usually unilateral but may occur bilateral also. Asymptomatic but numbness, pain & burning sensation can be present. Cause is usually unknown, but most of them favors on ischemic pathogenesis.

Histologic features described by ***"Abrams et al"*** includes:

1. Coagulative necrosis of glandular acini
2. Squamous metaplasia of the ductal epithelium
3. Pseduoepitheliomatous hyperplasia
4. Mucus pooling with an associated granulomatous inflammatory responses.

"Anneroth & Hansen" proposed five Histologic stages:[20]

1. Infarction (Necrotic) stage
2. Sequestration stage
3. Ulceration stage
4. Reparative stage
5. Healed stage

KIMURA'S DISEASE: It is a chronic inflammatory condition of unknown cause that is endemic in origin. The disease occurs predominately in young & middle aged adults. Typically the lesions are firm, rubbery, subcutaneous, tumor like nodules or masses over a period of one to two yrs. Most common in the peri-auricular regions, but misdiagnosed as salivary gland tumors. Microscopically, the lesions are unencapsulated & ill defined & are characterized by fibrocollagenous tissue, lymphoid tissue & mixed inflammatory infiltrates with numerous eosinophils. The enlarged regional lymphnodes in kimura's disease typically reveal florid follicular hyperplasia & eosinophilic infiltration & sclerosis.

Treatment: Surgical excision, radiation therapy and drug therapy.

CHELITIS GLANDULARIS: Chelitis glandularis was first described by ***"Volkman"***, to describe a condition characterized by a suppurative, inflammatory swelling of the lower lip. In 1914, ***"Suttan et al"***, postulated that the swelling was due to enlargement of the labial salivary gland. Hypertrophy of the salivary gland is noted. Most commonly affects middle aged and older man.

Chelitis glandularis has been classified into three types:

1. Simple type of chelitis glandularis
2. Superificial chelitis glandularis (Baclz's disease)
3. Deep suppurative (Chelitis glandularis apostematosa)

Pathophysiology: Although some have speculated that cheilitis glandularis represents a hereditary autosomal dominant condition, composite findings in most cases appear to indicate cheilitis glandularis represents a clinical reaction pattern to chronic irritation of the lip from a spectrum of highly diverse external causes. These include actinic damage, factitial injury, atopy, infection, and tobacco irritation. ***"Carrington and Horn"*** reported a case in which an elderly man developed cheilitis glandularis related to actinic damage following vermilionectomy for squamous cell carcinoma of the lower lip. These authors advocate clinical investigation in cases of cheilitis glandularis to rule out neoplastic, immune suppressive, or inflammatory changes due to local factors. This illustrates the concept that cheilitis glandularis is not a separate and distinct disease. Instead, it appears to be a descriptive phenomenon that could represent any one of a host of diverse clinicopathological entities. The possibility of a genetic predisposition for cheilitis glandularis has been raised by some authors. ***"Parmar and Muranjan"***, among others, described a genetic syndrome involving "double lip" of both lips in conjunction with ptosis and other physical abnormalities.[21]

Autoimmune Salivary Gland Disorders

BENIGN LYMPHOEPITHELIAL LESIONS / MIKULICZ DISEASE / MIKULICZ SYNDROME AND SJOGREN SYNDROME

The classification now is as follows:

(1) Primary Sjögren's syndrome (sicca complex) **-** this consists only of xerostomia and xerophthalmia with no connective tissue component.

2) Secondary Sjogren's syndrome **-** this consists of xerostomia, xerophthalmia and a connective tissue disease which in nearly 50% of cases is rheumatoid arthritis but may also be systemic lupus erythematosus, scleroderma and polymyositis

(3) Benign lymphoepithelial lesion, otherwise known as myoepithelial sialoadenitis, which is localized to the parotid glands and some regard as a prelymphomatous condition

(4) Aggressive type, lymphocytic behavior which again is confined to the parotid glands and is almost a pseudolymphoma.

Clinical features: Sjögren's syndrome is a multisystem disease affecting every system in the body but particularly the oral cavity, the eyes and the salivary apparatus.

The oral symptoms are those of dry mouth with secondary candidiasis, stomatitis, glossitis and subsequent dental caries. The eye symptoms are keratoconjunctivitis sicca; the patient has a foreign body sensation in the eye, burning, redness, itching, photosensitivity and an inability to tolerate contact lenses. Only 40% feel salivary gland enlargement and only 20% show it clinically. It is nearly always in the parotid and those patients with parotomegaly from Sjögren's disease have a much higher chance of developing lymphoma. Two-thirds of the patients never have salivary gland enlargement. Other associated systemic problems are primary biliary cirrhosis, chronic hepatitis, vasculitis, chronic graft versus host disease, cryoglobulinaemia, hypergammaglobulinaemic purpura and polyarteritis. Fifteen per cent will have thyroiditis and many will develop pancreatitis.

Investigations:

San Diego Diagnostic criteria for sjogren syndrome:[22]

I. Primary Sjogren syndrome

A. Symptoms and objective signs of ocular dryness

1. Schirmer's test less than 8mm wetting per 5 min
2. Positive rose Bengal staining of cornea or conjunctiva to demonstrate keratoconjunctivitis sicca

B. Symptoms and objective signs of dry mouth

1. Decreased parotid flow rate using Lashley's cups
2. Abnormal findings from biopsy of minor salivary glands

C. Serological evidence of systemic autoimmunity

1. Elevated Rh factor
2. Elevated ANA(AntiNuclearAntibody)
3. Presence of anti-SS-A or anti-SS-B

II. Secondary Sjogren syndrome

Characteristic signs and symptoms of primary SS along with clinical features sufficient enough to allow a diagnosis of rheumatoid arthritis, SLE, scleroderma or biliary cirrhosis.

1. Blood examination: The erythrocyte sedimentation rate is usually raised. A protein profile will show elevation of all the immunoglobulins especially IgG. Rheumatoid factor and antinuclear factor will probably be positive and there may well be a wide range of autoantibodies.

2. Specific immunological tests: When class 2 antigens such as HLA A1 and B8 and DR3 are examined, then almost three times as many patients with sicca syndrome have these antigens when compared with patients with the secondary syndrome. Specific antigens for Sjögren's syndrome are called SSA and SSB. Again these are more common in patients with the sicca syndrome than in those with secondary Sjögren's disease with rheumatoid arthritis.

3. Schirmer's test: This is carried out by putting special strips into the lower fornix. Wetting of less than 5 mm in 5 minutes represent a diagnosis of xerophthalmia. A diagnosis of keratoconjunctivitis sicca, however, cannot be made until the ophthalmologist examines the eye with Rose Bengal dye to see the filamentary keratitis.

4. Salivary flow rate: This is measured using Carlsson-Crittenden cups; these are suction cups placed over the parotid duct. Maximum stimulation is created by getting the patient to suck a lemon. A flow of less than 0.5 mL in a minute represents xerostomia.

5. Labial biopsy: This is performed by obtaining four globules of fat from the back of the lower lip. It can be performed under local anaesthetic and is the diagnostic test for Sjögren's disease. The pathologist must grade it according to the rules laid down.

Grade 1: slight lymphocytic infiltration
Grade 2: less than 50 lymphocytes per 4 mm2
Grade 3: 50 lymphocytes per 4 mm2
Grade 4: more than 50 lymphocytes per 4 mm2.

The distribution of lymphocytes is important also because they cannot be diffuse, but must be periductal. In this test, false positives can be obtained in rheumatoid arthritis, scleroderma, subacute lupus erythematosus, sarcoid, amyloid and graft versus host disease.[23]

6. Radiology: Sialography either shows a normal sialographic pattern or that of 'globular sialectasis'. This does not imply that the patients with Sjögren's disease have sialectasis. What it does imply is that there is an abnormality in the duct allowing leakage of lipiodol into the stroma of the gland.

Treatment: There is little of a specific nature that can be done to help these patients. Bouts of parotid swelling may be treated with steroids but the bouts are seldom so severe that they require other immunosuppressive drugs. Artificial tears and synthetic saliva provide limited comfort and bromhexine 40 mg/day sometimes helps a tenacious cough. The most important feature of treatment, however, is to put these patients on a lymphoma follow-up. Those who have parotid enlargement are at a higher risk of developing lymphoma and diagnostic parotidectomy should be considered.

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