# Diseases of the salivary glands

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# Learning Outcomes

**Knowledge of diseases of the salivary glands including localized salivary gland disorders; iatrogenic salivary gland disorders and diseases with extra-oral manifestations that present with salivary gland disorders.**

1. Discuss the clinical features, diagnosis and treatment of salivary gland aplasia.

2. Describe the aetiology, pathogenesis, the clinical and histopathologic features and the diagnosis and treatment of:

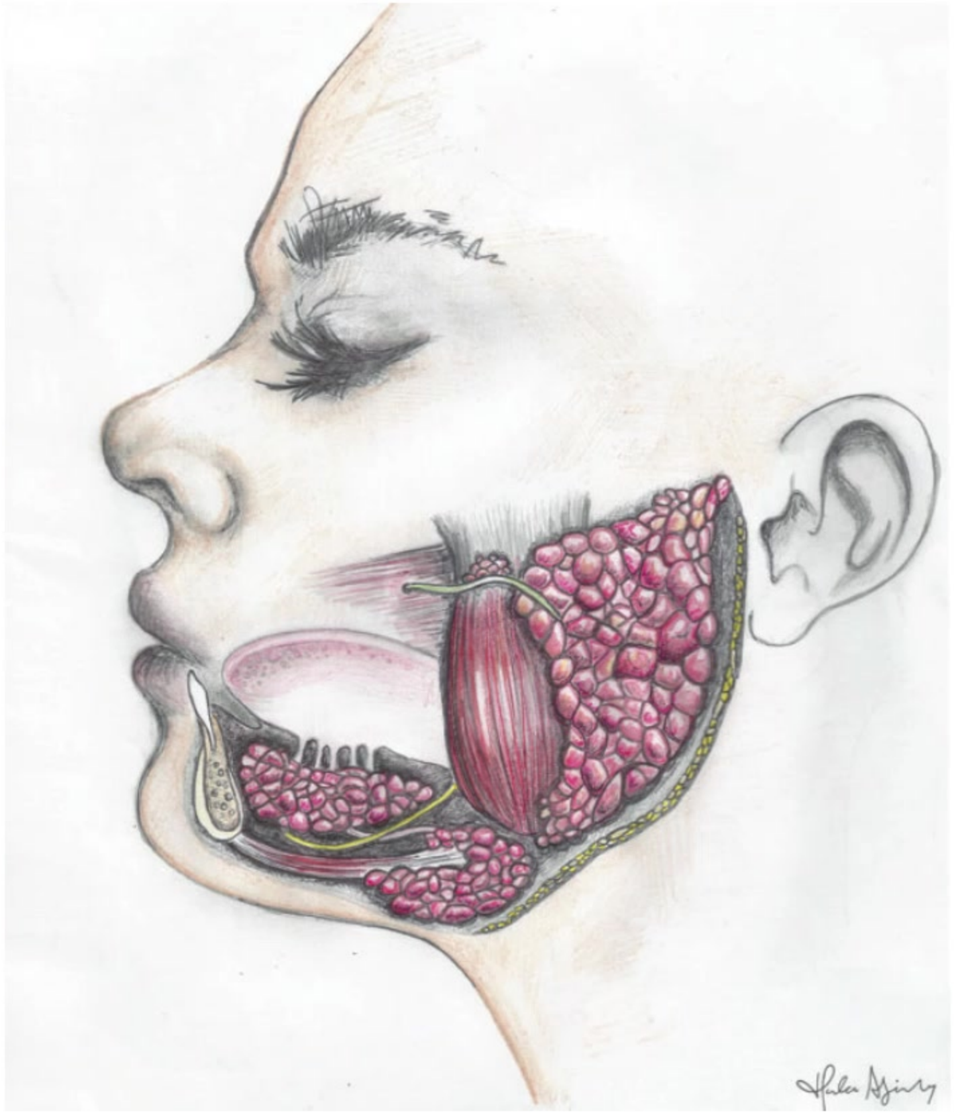
- Mucoceles
- Sialolithiasis
- Sialadentitis
- Sjogren syndrome
- Sialadenosis
- Necrotizing sialometaplasia

# Learning Outcomes

**Discuss the aetiology, pathogenesis, the clinical and histopathologic features and the diagnosis and treatment of the following salivary gland neoplasms:**

- Pleomorphic adenoma
- Warthin's tumour
- Oncocytoma
- Mucoepidermoid carcinoma
- Acinic cell carcinoma
- Adenoidcystic carcinoma
- Polymorphous low grade adenocarcinoma

**Discuss the aetiology, clinical features, diagnosis and management of dry mouth.**

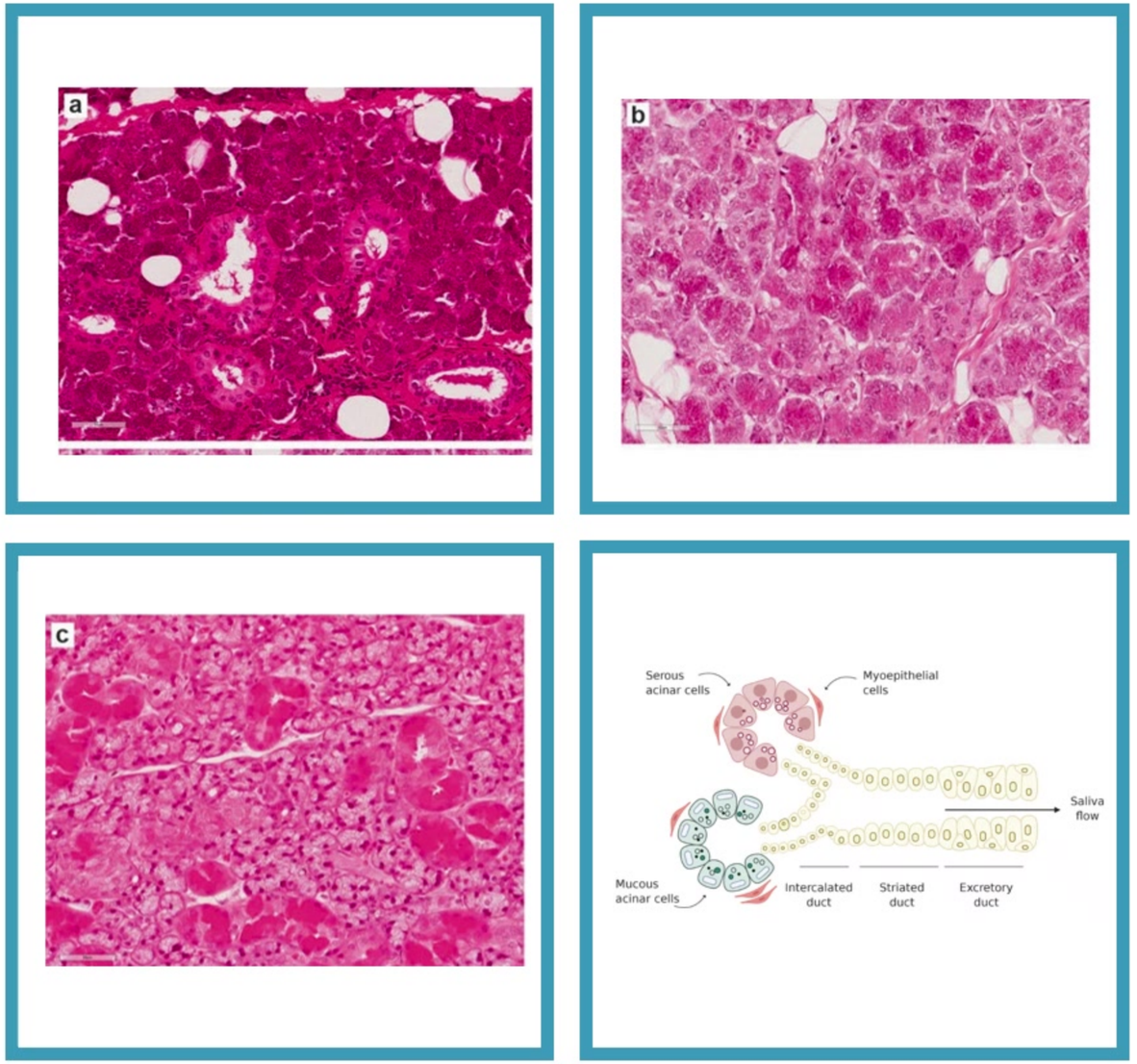


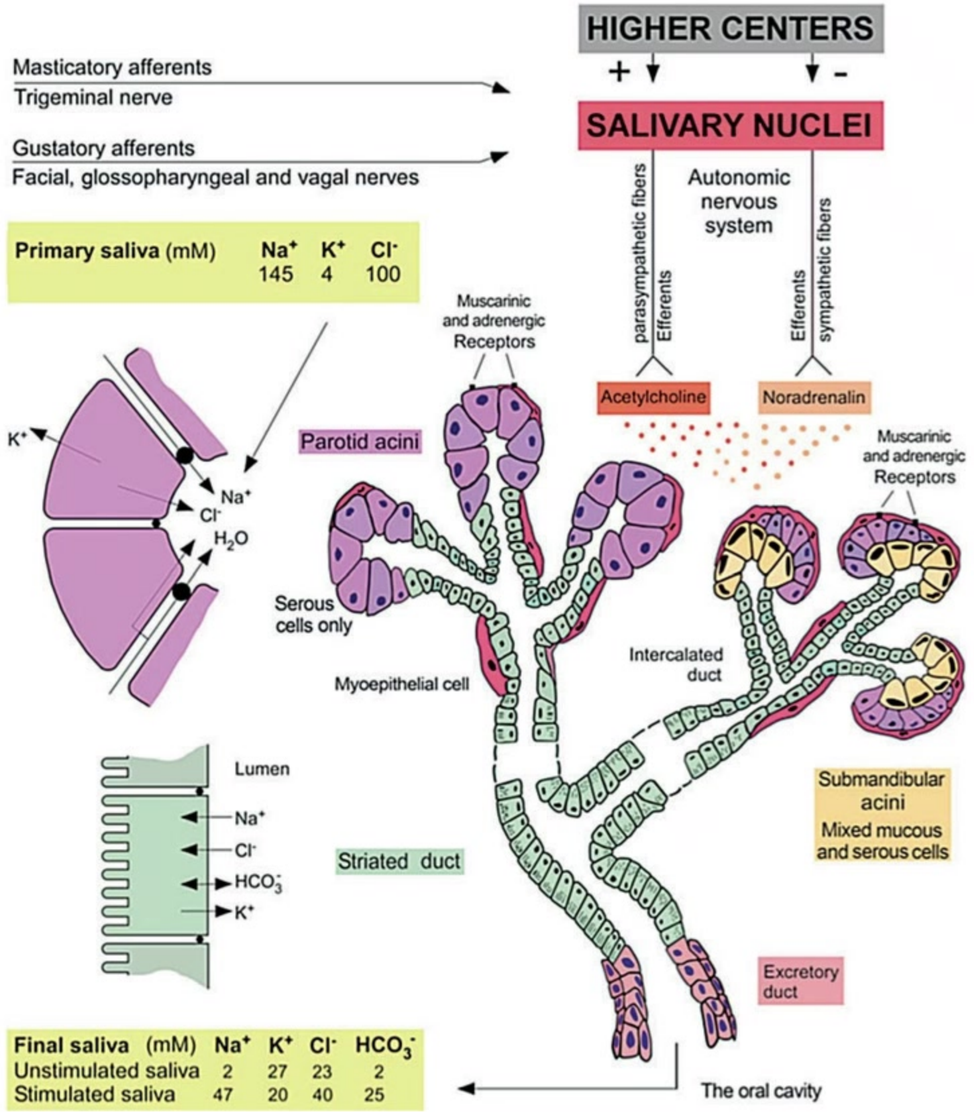
# Review of anatomy

- Three paired major salivary glands
  - Parotid
  - Submandibular
  - Sublingual
- 600 – 1000 minor salivary glands
  - Buccal, lingual, palatal, labial mucosa
  - Floor of mouth

# Review of histology

- Parotid gland:
  - Serous acini
  - Pyramidal – shaped cells with basophilic appearance
- Submandibular and Sublingual glands
  - Mixed mucous and serous acini
- Lobules of acini separated by fibrous connective tissue septa and adipose tissue
- Ductal system consists of ducts:
  - Intercalated - secretory
  - Striated - secretory
  - Interlobular – excretory
- Myoepithelial ells surround acini and intercalated ducts
- Basal cells associated with striated and excretory ducts

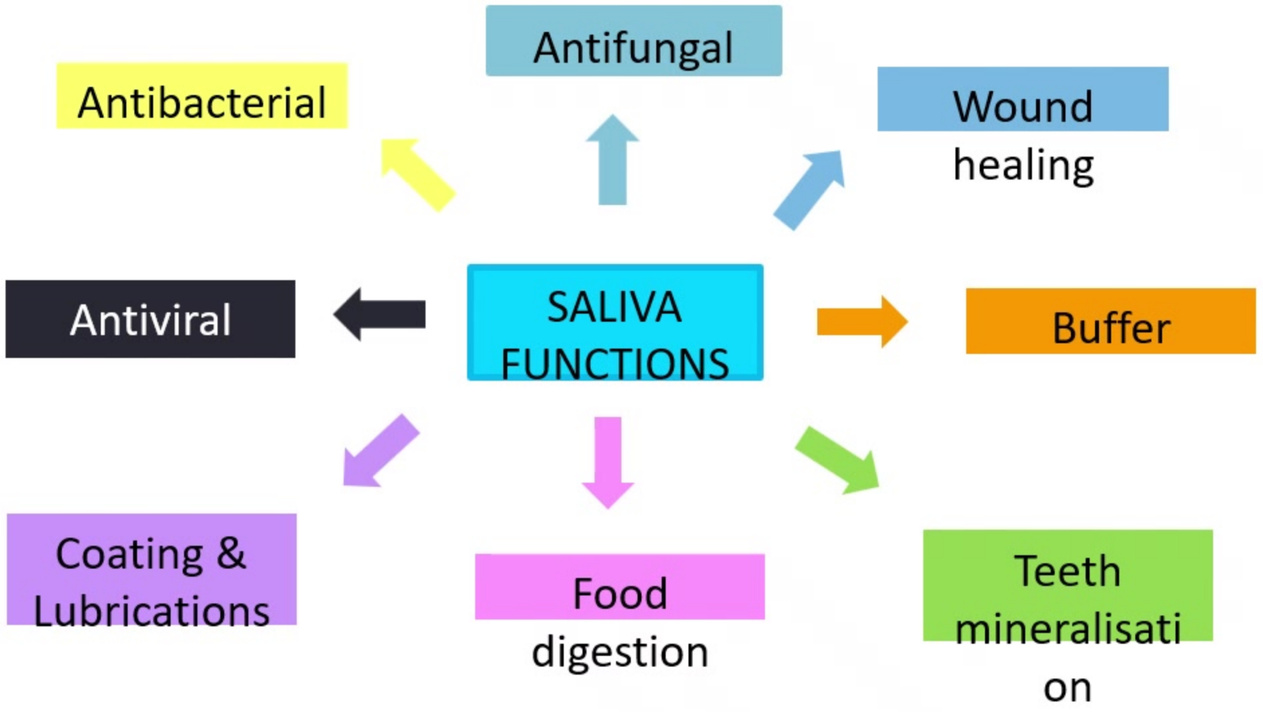





# Review of salivary gland physiology

- In health
  - Major salivary glands account for 90% of saliva production
  - Minor salivary glands account for 10% of saliva production
- Saliva flow rate has circadian variation with a peak in late afternoon
- Unstimulated whole saliva flow rate: 0.2 – 0.5 ml/min
- Stimulated whole saliva flow rate: 1.0 – 2.0 ml/min
- 60% of unstimulated whole saliva produced by submandibular glands
- Primary saliva produced by acinar cells → ion composition modified during transport through striated ducts → sodium, chloride reabsorbed → bicarbonate and potassium secreted in ductal cells → myoepithelial cells help move saliva through ducts → hypotonic saliva
- Excretion controlled by autonomic parasympathetic, and sympathetic nerves

# Gatekeeper of the oral cavity



# Salivary gland aplasia

- Congenital absence of salivary glands
- Rare
- Unilateral or bilateral
- Isolated or part of a hereditary syndrome
  - Syndromes of the ectodermal tissues
    - Ectodermal dysplasia
    - Mandibulofacial dysotosis
    - Hemifacial microsomia
- Parotid gland aplasia estimated incidence of 1: 5000 live births
  - Related to earlier morphogenesis compared to other salivary glands

| Developmental anomalies | Clinical features (head and neck) |
|---|---|
| **1. Syndromes closely related to SG aplasia/hypoplasia** | |
| Lacrimo-auriculo-dento-digital syndrome (LADD) or Levy-Hollister syndrome | Oral cavity: small and sharp lateral incisor, lateral upper incisor agenesis, and bifid uvula |
| | Lacrimal glands: aplasia/hypoplasia, duct obstruction, and absence of lacrimal punctum |
| | Other: cup-shaped ears, sensory, or mixed deafness. |
| Oculo-auriculo-vertebral spectrum (OAVS) | Oral cavity: micrognathia, macrostomia, oral facial cleft, mandibular hypoplasia/deformity, and tongue anomaly; |
| | Other: microtia, hemifacial macrosomia, facial palsy, branchial cyst, preauricular skin tag, and oral apraxia |
| Ectrodactyly ectodermal dysplasia cleft lip/palate syndrome (ECC) | Oral cavity: dental abnormalities, lip, and palate cleft Lacrimal glands: absence of lacrimal punctum Other: deformed ears, conductive hearing loss |
| **2. Syndromes that can be associated with SG aplasia/hypoplasia** | |
| Down syndrome | Oral cavity: dental agenesia, hypo/hyper/microdontia, delayed eruption, open bite, taurodontism, gingivitis/periodontitis, cheilitis-stomatitis, ogival vault, protruding tongue, and maxillary processes hypoplasia |
| | Head and neck: slanting palpebral fissures, epicanthic folds, brachycephaly, flat cranial base, and flattened nose bridge |
| Klinefelter syndrome | Oral cavity: shovel-shaped incisor, taurodontism, and delayed eruption |
| | Head and neck: brachycephaly |
| Treacher-Collins syndrome | Oral cavity: mandibular/maxillary dysostosis, cleft palate |
| **3. Developmental anomalies associated with SG aplasia/hypoplasia in non-syndromic patients** | |
| Lacrimal glands | Secretion disorders |
| Oral cavity | Hypo/oligo/anodontia, enamel hypoplasia, multiple caries, fissured tongue, lip, and palate cleft |
| Head and neck | Cranial deformity, mandibular ramus agenesia |

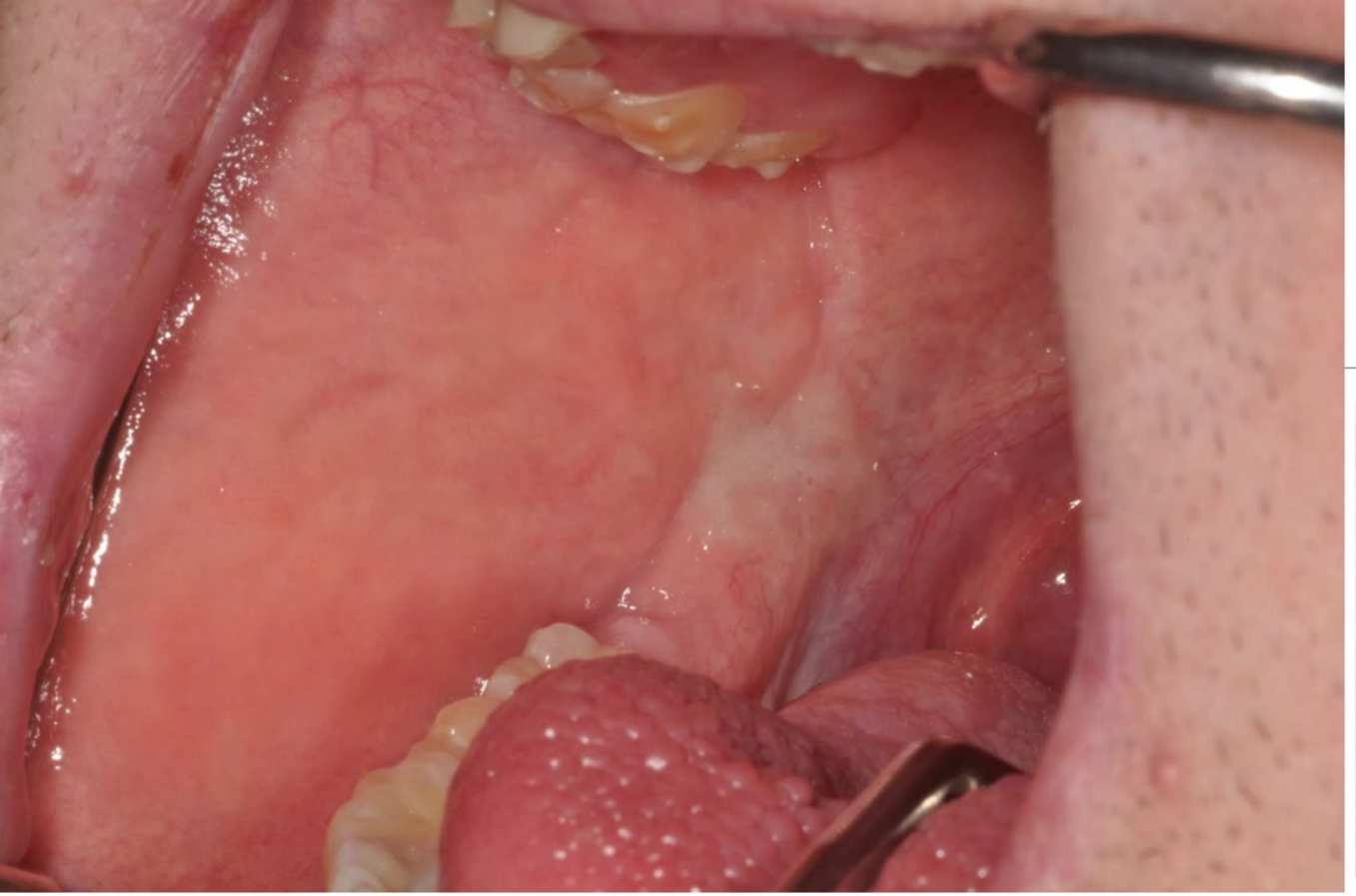
*SG, salivary gland.*

Togni Lucrezia, Mascitti Marco, Santarelli Andrea, Contaldo Maria, Romano Antonio, Serpico Rosario, Rubini Corrado, TITLE=Unusual Conditions Impairing Saliva Secretion: Developmental Anomalies of Salivary Glands , JOURNAL=Frontiers in Physiology , VOLUME=10 , YEAR=2019

# Salivary gland aplasia

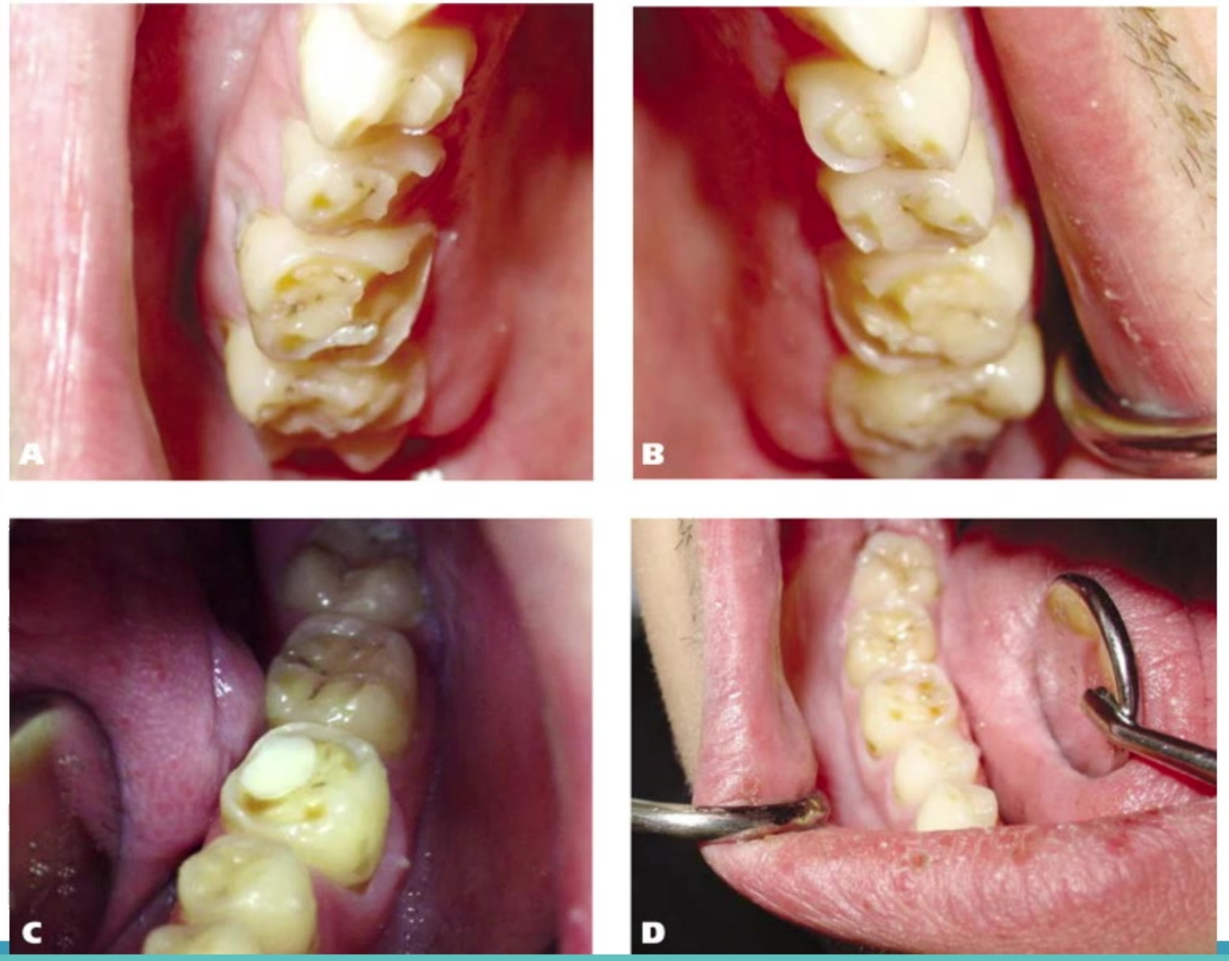
**Clinical Features**

- Dependent on number of missing salivary glands
- Variable degrees of xerostomia and oral dryness
- Some can be asymptomatic
- Erythematous oral mucosa
- Glossitis
- Cheilitis
- Chronic erythematous candidiasis
- Exfoliate lips
- Increased risk of dental caries, teeth erosion, periodontal disease
- Tongue papillary atrophy
- Oral ulcers
- Hoarseness
- Dysphagia
- Oropharyngeal symptoms
- Absence of parotid papillae or submandibular orifices
- Lack of saliva production upon palpation
- Asymmetry



Chadi, M.J., Saint Georges, G., Albert, F., Mainville, G., Nguyen, J.M. and Kauzman, A. (2017), Major salivary gland aplasia and hypoplasia in Down syndrome: review of the literature and report of a case. Clin Case Rep, 5: 939-944. https://doi.org/10.1002/ccr3.975

Louis Mandel, An unusual pattern of dental damage with salivary gland aplasia, The Journal of the American Dental Association, Volume 137, Issue 7, 2006, Pages 984-989,



# Salivary gland aplasia

**Diagnosis**

- History
- Examination findings
- Imaging
  - Ultrasonography
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)

**Management**

- Saliva substitutes
- Lifestyle changes
  - Increase water intake
  - Limit irritating foods
  - Low-sugar diet
- Regular dental examinations
- Fluoride based dental products

**2. Describe the aetiology, pathogenesis, the clinical and histopathologic features and the diagnosis and treatment of:**

- Mucoceles
- Sialolithiasis
- Sialadentitis
- Sjogren syndrome
- Sialadenosis
- Necrotizing sialometaplasia

# Mucoceles

**Introduction**

- Mucoceles are cavities filled with mucus present as benign soft tissue mass in the oral cavity (mucous extravasation cyst)
- When in the floor of mouth, they are called ranula (mucous retention cyst)

**Epidemiology**

- Very common
- Young persons are more frequently affected

# Mucoceles

**Aetiopathogenesis**

- Mucoceles are often associated with a history of trauma, resulting in the leakage of fluid from the ducts or acini into the surrounding tissue
- Mucous Retention Cysts (Ranula) are caused by obstruction of a duct rather than trauma

**Clinical Presentation**

- Mucoceles commonly present as soft, painless swellings ranging from deep blue to normal pink in colour
- Mucoceles can occur as a lump on the mucosa or vermilion of the lower lip but can present at other intraoral sites
- Duration is variable and often dependent on how much inconvenience the lesion causes

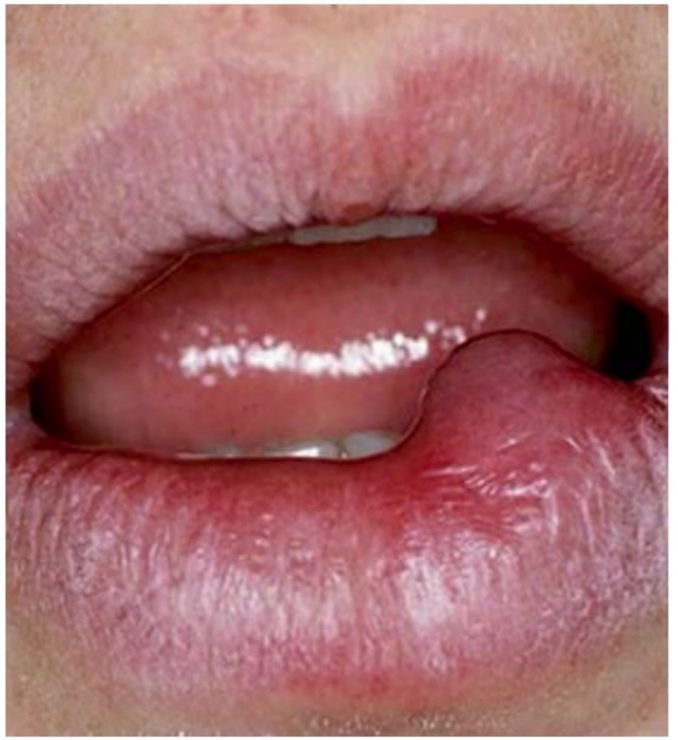
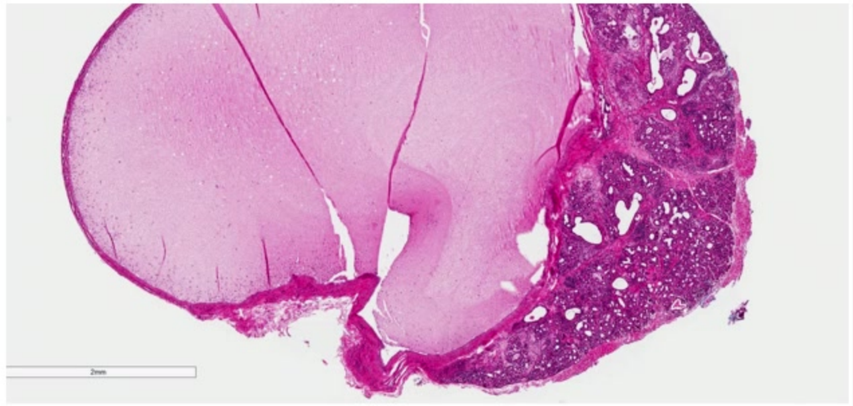
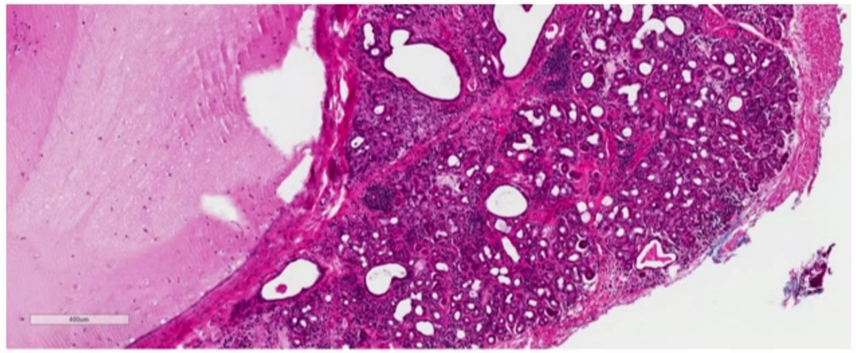


Image from Contemporary Oral Medicine 2019



Low power micrograph (H&E 1.8x) showing a fully excised mucocele with extravasated mucin and the feeding minor salivary gland.



Medium power micrograph (H&E 5x) showing obstructive changes in the minor salivary gland consistent with chronic sialoadenitis, epithelioid macrophages can be seen among the mucin.

# Mucoceles

**Histopathology**

- If removed intact
  - Pseudocyst cavity containing mucin, abundant epithelioid foamy histiocytes (muciphages), neutrophils and granulation tissue
- If removed ruptured
  - Fragments of granulation tissue containing epithelioid foamy histiocytes (muciphages) and neutrophils, may see mucinous material Removed salivary gland parenchyma showing obstructive changes
  - Acinar atrophy, ductal dilatation with periductal hyalinization, interstitial lymphoplasmacytic infiltrate and interstitial fibrosis at late stage
- May see ruptured feeding salivary duct with squamous metaplasia
- Long standing lesions organize into fibrosis resembling a fibroepithelial polyp
- No epithelial cyst lining, may see overlying surface oral mucosa with variable atrophy in superficial mucoceles

Lee N, Ng T. Mucocele. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/oralcavitymucocele.html. Accessed March 14th, 2022.

# Mucoceles

**Diagnosis**

- History
- Clinical examination
- Biopsy

**Management**

- Removal of the lesion by complete excision without rupture including removal of the associated minor salivary gland is curative.
- Damage to the adjacent gland during removal may result in a new lesion developing and the patient should be warned of this as well as possibility of sensory nerve damage.
- Cryotherapy where deliberate destruction of mucocele and underlying associated salivary gland tissue is another curative alternative, however no specimen is available for histopathologic review, so an accurate clinical diagnosis is paramount.

# Sialolithiasis

- Also known as salivary calculus or salivary stones

**Epidemiology**

- Very common disease of the salivary glands
- More than 80% of sialoliths occur in the submandibular gland or its duct, 6% occur in the parotid gland and 2% occur in the sublingual gland or minor salivary glands.
- Occur more frequently in men than women
- Peak incidence between 30 years – 60 years

# Sialolithiasis

**Aetiopathogenesis**

- Aetiology remains unknown, but there are some factors contributing to stone formation such as irregularities in the duct system, inflammation or local irritants
- It is thought that the more alkaline, viscous, mucous-rich saliva which contains a higher percentage of calcium phosphates, in addition to the long and sinuous position of Wharton's duct, contributes to stasis, making the submandibular gland more prone to the development of sialoliths than the parotid gland

**Clinical Presentation**

- Recurrent swelling and pain in the involved gland, often associated with eating due to obstructions of the draining duct may be seen, although some can be asymptomatic
- Most common cause of acute and chronic infections of salivary glands
- Can vary considerably in size, but usually less than 1cm
- Can occasionally be palpated – feel like hard small pebbles

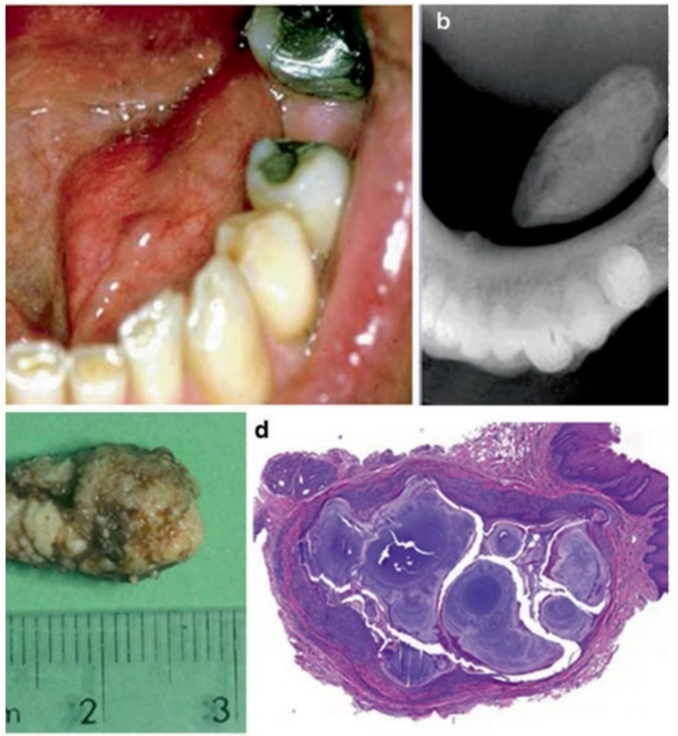
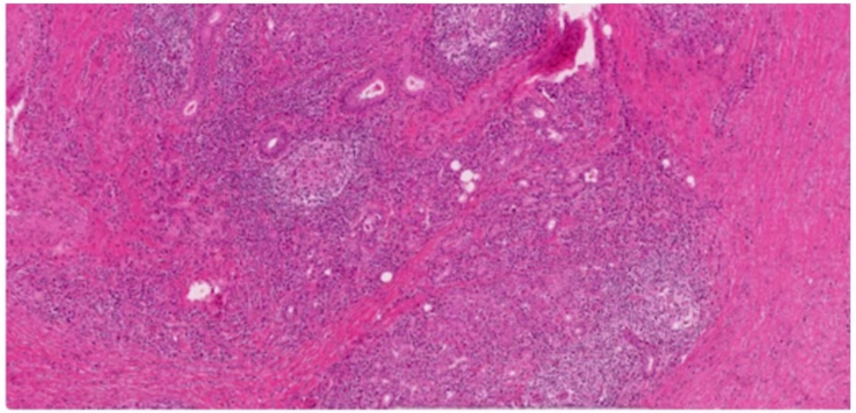
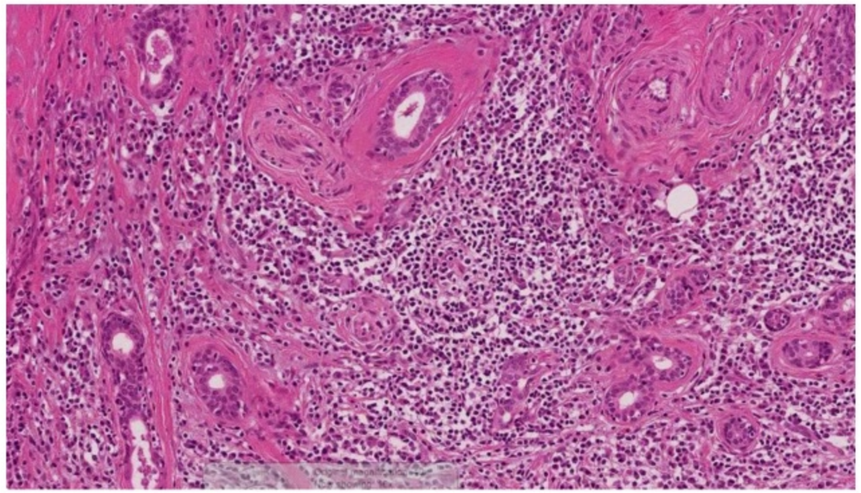



Image from Contemporary Oral Medicine 2019



40 year old man with submandibular pain; chronic inflammation is well circumscribed, lacking infiltration into the surrounding tissue (4x).



40 year old man with submandibular pain; chronic inflammation with acinar

# Sialolithiasis

**Histopathology**

- Varying degrees of acinar destruction, fibrosis and chronic inflammation, with lymphoid aggregates containing prominent germinal centers
- Ducts may undergo squamous and mucous metaplasia
- Lobular arrangement is maintained
- May see microliths

Ely KA. Chronic sialadenitis / sialolithiasis. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/salivaryglandssialolithiasis.html. Accessed March 14th, 2022.

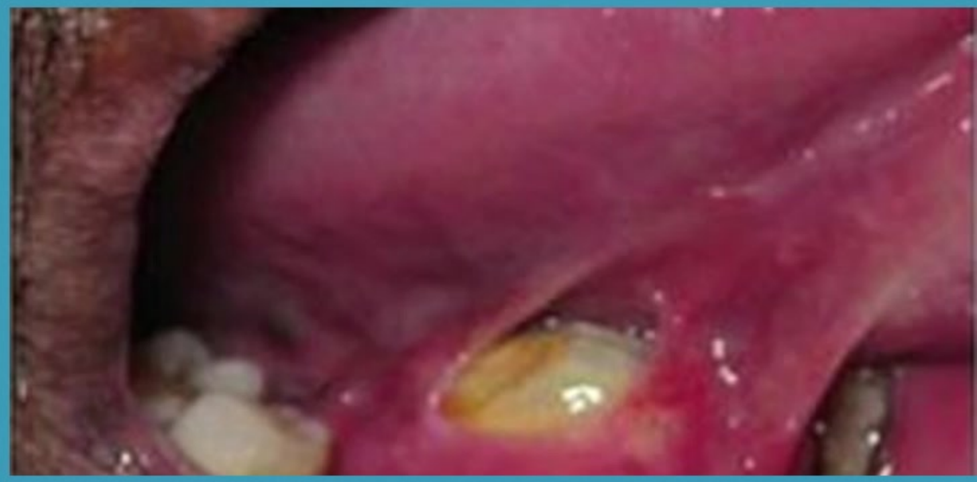
# Sialolithiasis

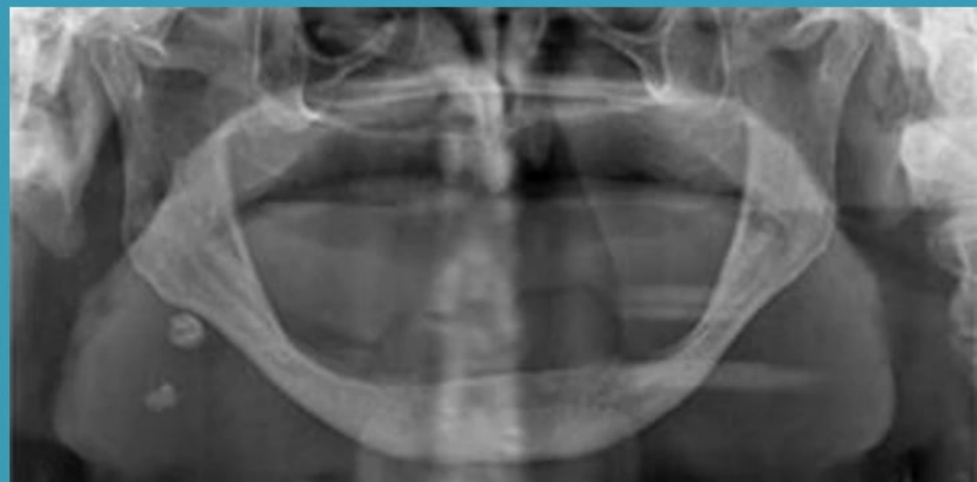
**Diagnosis**

- Clinical examination may reveal swelling and absence of saliva secretion from the gland if it is blocked
- Diagnostic imaging is used to identify presumed salivary calculi: intraoral occlusal radiograph, OPG or CBCT. However, 60-70% calcified sialoliths are not detected by conventional radiography and non-contrast computerized tomography is indicated.

**Management**

- Lesions associated with minor salivary glands can be excised with the associated gland.
- When a sialolith can be palpated in the oral cavity, the sialolith often can be removed by an intraoral or sialoendoscopic approach and the affected gland can be left in situ, otherwise the associated gland is often removed
- Salivary gland massage, irrigation, sour diet, sialologues to stimulate salivary flow in cases of small sialolith





Kraaij, S., Karagozoglu, K., Forouzanfar, T. *et al.* Salivary stones: symptoms, aetiology, biochemical composition and treatment. *Br Dent J* **217,** E23 (2014). https://doi.org/10.1038/sj.bdj.2014.1054

# Sialadenitis

**Introduction**

- Bacterial sialadenitis can be either acute or chronic.
- Often occurs in elderly patients who suffer from salivary gland hypofunction.

**Aetiopathogenesis**

- Decreased saliva flow rate is the primary predisposing factor, and this allow retrograde microbial colonization of the duct, which may result in the development of acute or chronic suppurative infection.
- It can be associated with obstruction of the salivary ducts by deposition of calculi, mucus plugs, tumour growth or by trauma.
- Staphylococcus aureus is the most common pathogen isolated from purulent sialadenitis

# Sialadenitis

**Clinical Presentation**

- Acute sialadenitis is characterized by a painful swelling of a single salivary gland, commonly the parotid gland.
- A purulent discharge may be expressed from the salivary duct orifice.
- Patient may present with redness of the overlying skin or even abscess formation within the inflamed gland tissue.
- The infection may become life-threatening in immunocompromised individuals due to sepsis.
- Chronic sialadenitis may develop following acute sialadenitis, characterized by repeated episodes of pain and inflammation.

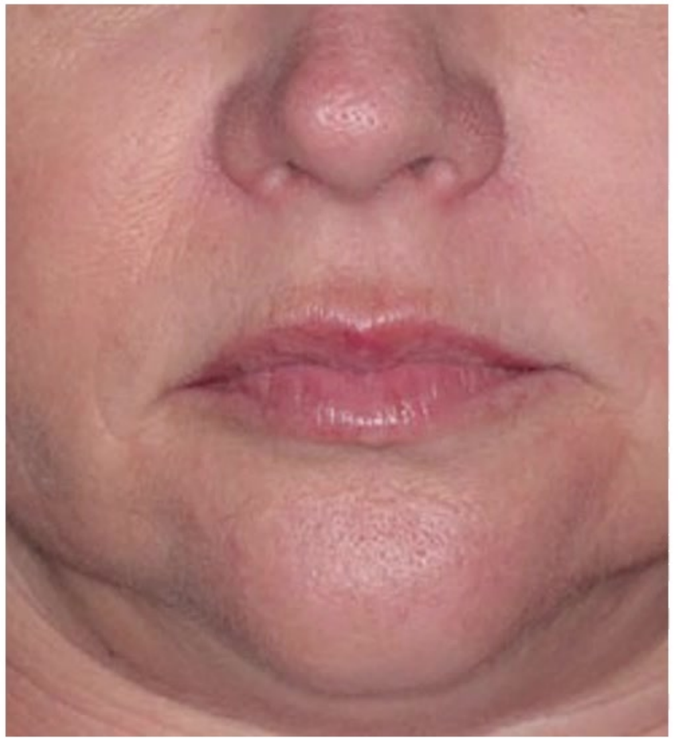


Image from Contemporary Oral Medicine 2019

# Sialadenitis

**Histopathology**

- Diagnoses of both acute suppurative and viral sialadenitis are usually reached on clinical grounds, although rarely biopsied
- Acute suppurative sialadenitis is associated with edema, hyperemia and acute inflammation
- Viral sialadenitis shows diffuse interstitial edema, intense hyperemia and a dense lymphohistiocytic infiltrate

Ely KA. Sialadenitis-infectious. PathologyOutlines.com website.
https://www.pathologyoutlines.com/topic/salivaryglandssialadenitis.html. Accessed March 14th, 2022.

# Sialadenitis

**Diagnosis**

- Diagnosis is based mainly on clinical presentation.
- Patients with chronic sialadenitis should be evaluated with imaging for underlying pathology such as a calculus or stricture.

**Management**

- Management involves treating the infection and reversing predisposing factors.
- Stimulation of salivary flow by application of warm compresses, administration of sialagogues and salivary gland massage can be employed.
- Empiric antimicrobial therapy is initially directed – often amoxycillin-clavulanate.

# Sjogren syndrome

**Introduction**

- Sjogren's Syndrome is an autoimmune systemic rheumatic disease characterized by progressive focal lymphocytic cell infiltration and destruction of exocrine glands
- It predominantly affects the salivary and lacrimal glands leading to dry eyes and subjective dry mouth

**Epidemiology**

- Commonly affects females (female: male ratio of 9:1)
- Can occur at all ages, but median age of presentation is around 50 years

**Aetiopathogenesis**

- Not completely understood but multiple environmental factors interacting with an individual's genetic susceptibility can trigger autoimmunity resulting in chronic inflammation of exocrine glands and eventual loss of physiologic function

# Sjogren syndrome

**Clinical Manifestations**

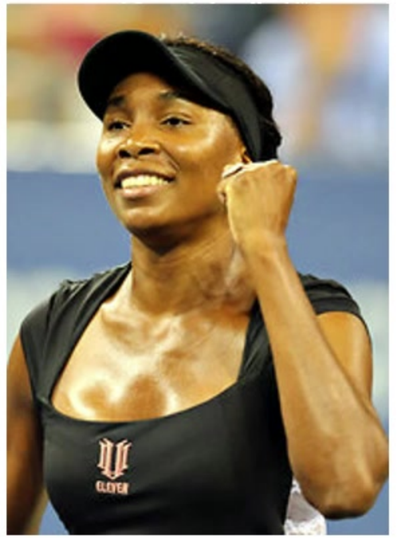
- Slowly progressing autoimmune disease
- Clinical manifestations are extremely variable
- Ranging from organ-specific disease to systemic autoimmune disease and lymphoproliferative condition

Dryness of eyes and mouth

Oral signs:
- Dry, erythematous, sticky oral mucosa
- Fissured tongue
- Accelerated dental caries, oral candidosis
- Swelling of parotid glands (1/3 of patients)

Ocular signs
- May be red in appearance
- Conjunctival inflammation

Dryness can affect nose, upper respiratory tract, oropharynx, vaginal dryness



Brito-Zeron et al. 2016

# Sjogren syndrome

**General Symptoms**

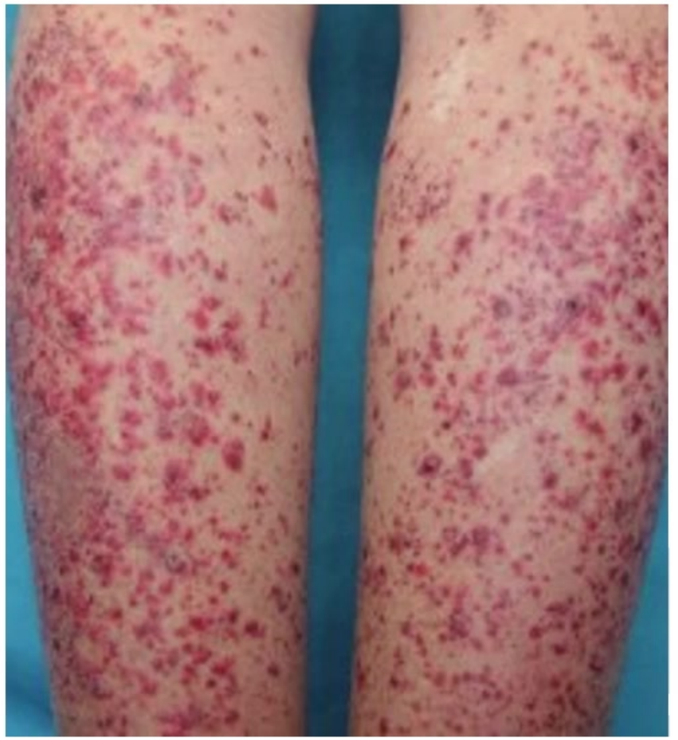
- Fatigue (80%)
- Chronic pain
- Low – grade fever (5%)
- Weight loss
- Lymphadenopathy (15%)

**Cutaneous features**

- Cutaneous vasculitis (10%)
- Purpura
- Cutaneous ulcers
- Annular erythema (9%)
- Abnormally dry skin (23-68%)

**Articular and Muscle Features**

- Arthralgia (60-70%)
- Non – erosive arthritis
- Subclinical synovitis (20-30%)
- Myalgias (20-40%)



# Sjogren syndrome

**Pulmonary Complications (25%)**

- Chronic obstructive lung disease
- Bronchiectasis
- Interstitial lung diseases
- Pleuritis

**Cardiovascular complications**

- Raynaud phenomenon (13% of patients)
- Pericarditis
- Pulmonary arterial hypertension
- Dysautonomia
- Cryoglobulinaemic vasculitis

**Nephro-urological complications**

- Renal tubular acidosis (9% of patients)
- Glomerulonephritis (4% of patients)
- Interstitial cystitis (in the absence of bacterial infection)
- Osteomalacia
- Recurrent renal colic due to renal stones
- Hypokalaemic paralysis

# Sjogren syndrome

**Peripheral nervous system complications (10%)**

- Mixed polyneuropathy
- Axon sensory polyneuropathy
- Axon sensorimotor polyneuropathy
- Trigeminal or other cranial neuropathies
- Demyelinating polyradiculoneuropathy
- Small-fibre neuropathy (painful paraesthesias)

- **Central nervous system complications (2%)**
  - White matter lesions (multiple sclerosis-like disease)
  - Neuromyelitis optica spectrum disorder
  - Recurrent aseptic meningitis

## Haematologic Features

- Haemolytic anaemia
- Unexplained leukopenia (lymphopenia and neutropoenia)
- Unexplained thrombocytopaenia**** (2%)
- Evans syndrome
- Unexplained monoclonal gammopathy
- Thrombotic thrombocytopaenic purpura
- B cell lymphoma**** (5%)

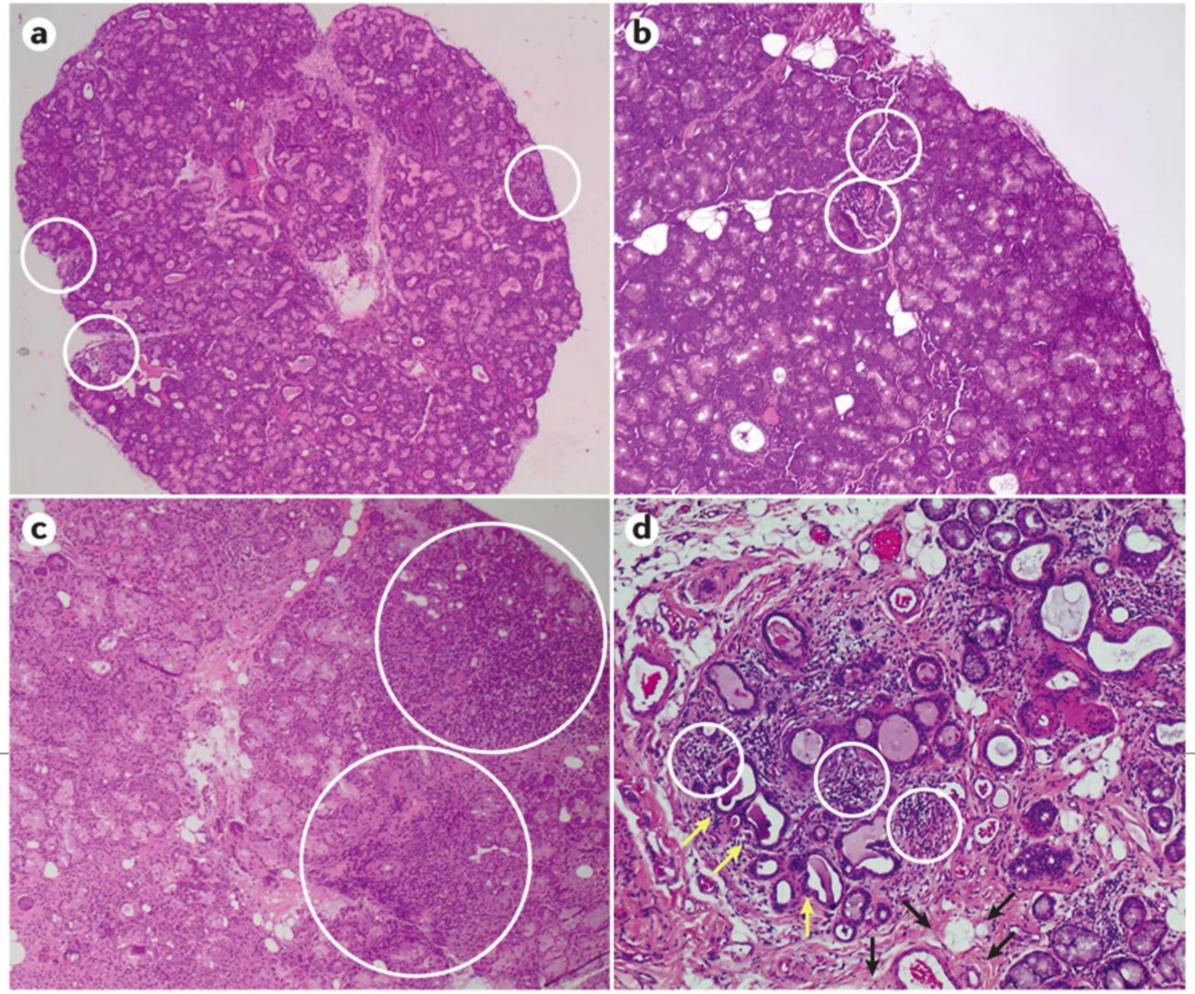
# Sjogren syndrome

**Histopathology – labial salivary gland biopsy**

- The key requirements for an accurate histological evaluation are an adequate number of glands (3–5 in total)
- Determination of an average focus score (the number of lymphocytic aggregates per 4 $mm^2$ of glandular surface analysed)
- ≥1 foci/ 4$mm^2$
- Focal lymphocytic sialadenitis is the key histopathological feature of SS

Brito-Zeron et al. 2016
Shiboski et al. 2016

**Figure 4** Histopathological features of the salivary gland in SjS scenarios




Nature Reviews | Disease Primers

Images courtesy of L. A. Hernández, Hospital Clinic, Barcelona, Spain.

Brito-Zerón, P. *et al.* (2016) Sjögren syndrom
*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.47

# Sjogren syndrome

**Table 3.** American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: The classification of primary Sjögren's syndrome applies to any individual who meets the inclusion criteria,[a] does not have any of the conditions listed as exclusion criteria,[b] and has a score of ≥4 when the weights from the 5 criteria items below are summed.

| Item | Weight/score |
|---|---|
| Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm$^2$[c] | 3 |
| Anti-SSA/Ro positive | 3 |
| Ocular Staining Score ≥5 (or van Bijsterveld score ≥4) in at least 1 eye[d, e] | 1 |
| Schirmer's test ≤5 mm/5 minutes in at least 1 eye[d] | 1 |
| Unstimulated whole saliva flow rate ≤0.1 ml/minute[d, f] | 1 |

- Diagnosis of Sjogren's Syndrome is based on both clinical presentation and laboratory investigations
- The 2016 American College of Rheumatology/European League Against Rheumatism provides a classification criterion on SS utilising a weighted sum of five items

**Management**

- 5-10% of Sjogren's syndrome patients develop mucosa-associated lymphoid issue, often in parotid glands and thus require periodic review
- Utilize products to relieve oral dryness (saliva stimulation, moisturizing agents) and reinforce caries prevention protocol

# Sialadenosis

**Introduction**

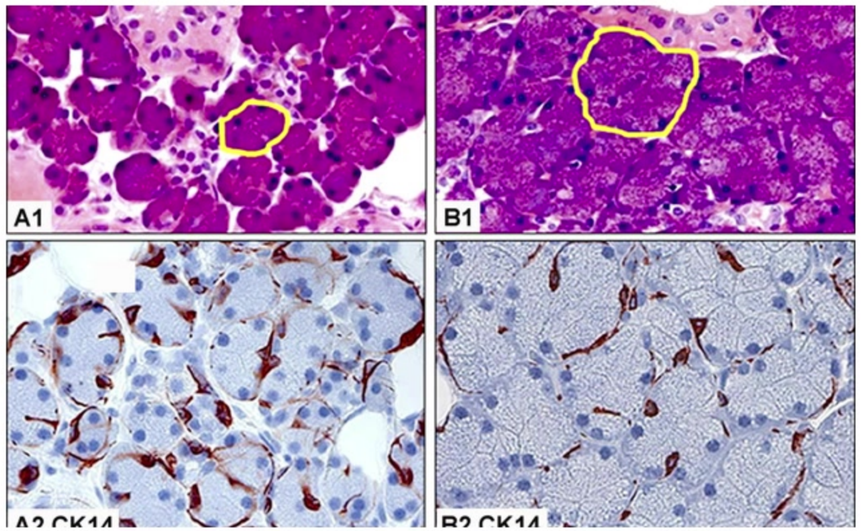
- It is an uncommon, benign, non-inflammatory, non-neoplastic, bilaterally symmetrical and painless enlargement of salivary glands.
- It is also known as sialosis.

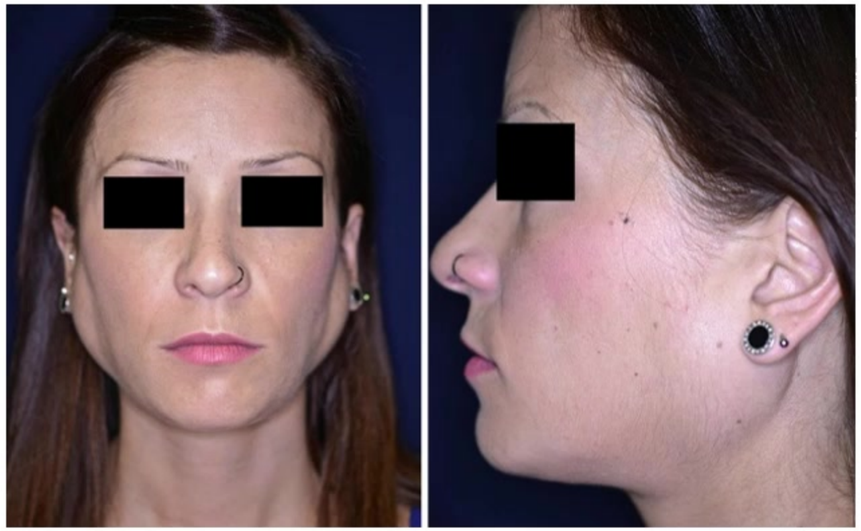
**Epidemiology**

- Usually begins between ages 20 – 60 years and may persist for more than 20 years.
- More commonly affects the parotid glands.

**Aetiopathogenesis**

- A variety of causes are recognized, most associated with autonomic neuropathy.
- This condition can be associated with endocrine disorders such as diabetes mellitus and hypothyroidism, alcohol abuse, nutritional disorders and medication induced-sialadenosis including psychotropic medications and antihypertensive drugs.



# Sialadenosis

- **Clinical Features**
- Patients present with slowly progressing bilateral swelling of parotid glands.
- They can be asymptomatic
- Rarely patients may complain of reduced salivary flow

- **Histopathology**
- Acinar enlargement
- The diameter of the acinar cell tends to increase by two to three times that of normal.
- The nuclei tend to be basally situated, and the cytoplasm tends to be packed with granules.
- There is no correlation between the specific clinical type of sialosis and the histologic appearance.
- Inflammatory cells tend to be absent.
- The long-standing nature of the underlying disease may ultimately lead to acinar atrophy and replacement with fat

# Sialadenosis

**Diagnosis**

- Diagnosis is one of exclusion, based mainly on history and clinical examination.
- Investigations may include: blood tests, ultrasound, sialography.
- Biopsy is rarely needed.

**Management**

- No treatment is available.
- If a likely cause is identified, then sialadenosis may resolve when underlying cause is managed.

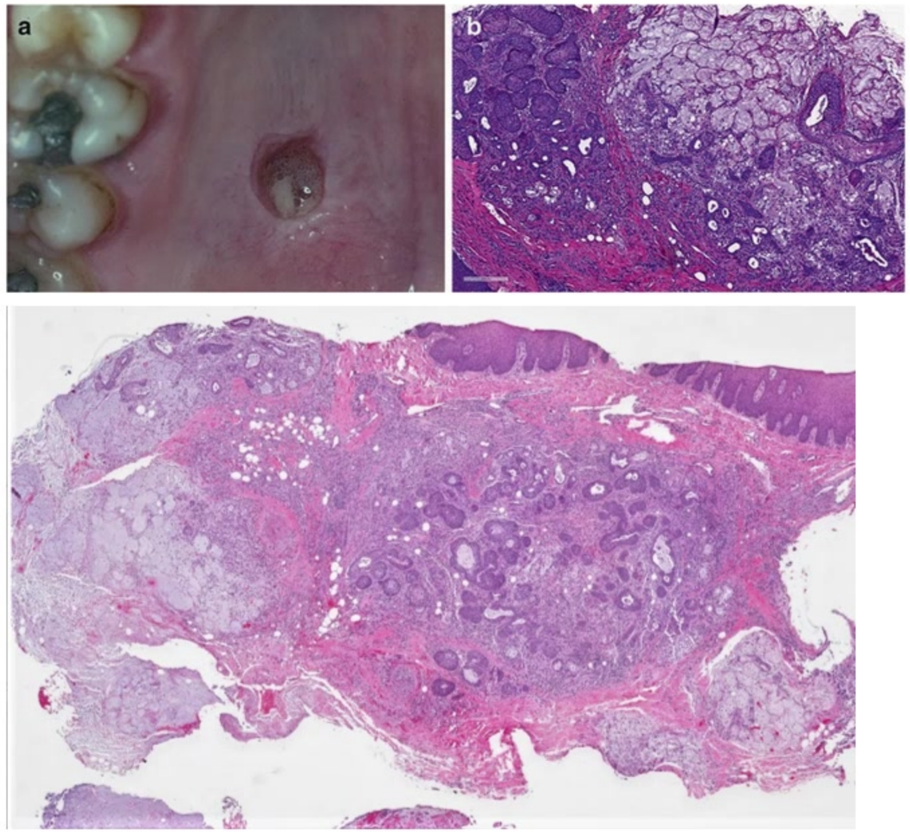
# Necrotizing sialometaplasia

- Benign, inflammatory disorder of salivary glands

**Aetiopathogenesis**

- Aetiology unknown
- Ischaemic necrosis of minor salivary gland tissue thought to be causative factor
  - Associated with smoking
  - Local trauma
  - Pressure from denture
  - Local anaesthetic injection
  - Local surgical procedures
  - Immune response to unknown allergen

# Necrotizing sialometaplasia




**Clinical Features**

- Posterior region of hard palate
- Chronic ulcer on hard palate – punched out appearance
- Can resemble malignancy

**Histopathology**

- lobular arrangements of salivary tissue with squamous cell metaplasia of ductal system centrally
- Islands of squamous cells can be close to salivary ducts with features of hyperplasia
- Necrotic acini and inflammatory cells are present at periphery
- Inflammatory infiltrate is diffuse and mixed with lymphocytes, plasma cells, neutrophils, occasional eosinophils, macrophages

Contemporary oral medicine, 2019
Tanakchi S, Aly FZ. Necrotizing sialometaplasia. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/salivaryglandsnecrotizingsialo.html. Accessed March 14th, 2022.

# Necrotizing sialometaplasia

**Diagnosis**

- Clinical examination
- Biopsy

**Management**

- Self – limiting
- Resolves in 3 – 10 weeks
- Symptomatic treatment: analgesics, 0.12% Chx
- Surgical intervention not required

# Learning Outcomes

**Discuss the aetiology, pathogenesis, the clinical and histopathologic features and the diagnosis and treatment of the following salivary gland neoplasms:**

- Pleomorphic adenoma
- Warthin's tumour
- Oncocytoma
- Mucoepidermoid carcinoma
- Acinic cell carcinoma
- Adenoidcystic carcinoma
- Polymorphous low grade adenocarcinoma

**Discuss the aetiology, clinical features, diagnosis and management of dry mouth.**

# Pleomorphic adenoma

**Introduction**

- Other names: Benign mixed tumour.
- Most common benign neoplasm of the major and minor salivary glands (account for up to 80% of benign salivary gland tumours).
- Malignant transformation may occur in long-standing lesions.

**Epidemiology**

- Wide age range – may be found in children and adults; but most common in the 3rd to 6th decades of life.
- Female predominance (2:1).

# Pleomorphic adenoma

**Aetiopathogenesis**

- Aetiology unknown.
- Incidence of pleomorphic adenomas have been reported to increase 15-20 years after exposure to radiation.

**Clinical Presentation**

- Slow-growing, painless submucosal mass. The tumour may remain undiagnosed for years.
- May be fixed or mobile.
- Signs and symptoms depend on site of involvement. It may also present with pain, facial nerve palsy, skin fixation and epistaxis.
- In the major salivary glands, the most common site of occurrence is the superficial lobe of the parotid gland. Less commonly, it can occur in the submandibular and sublingual salivary glands.
- In minor salivary glands, the most common sites of occurrence are the palate and upper lip; but can occur at any oral site as well as the nose, paranasal sinuses and larynx.
- Rapid enlargement of a tumour nodule should raise suspicion of malignant transformation.

# Pleomorphic adenoma

**Histopathology**

- Bosselated outer surface, often with tongue-like protrusions (pseudopods)
- Typically has 3 components:
  - Epithelial (ductal) component forming the inner layer of cysts and tubules
  - Myoepithelial cells as the outer layer of cysts and tubules and scattered within the myxoid stroma
    - Cytology of myoepithelial cells can be plasmacytoid, spindled, epithelioid, clear or stellate shaped
  - Stromal component is typically myxoid, chondroid or myxochondroid
    - It can also be hyalinized or fibrotic
- Metaplastic changes may be seen, e.g. adipose metaplasia, osseous metaplasia, squamous metaplasia (sometimes with keratinization), sebaceous metaplasia and mucinous metaplasia
- Intravascular permeation has been reported in a small percentage of cases and does not increase the risk of recurrence or distant metastasis

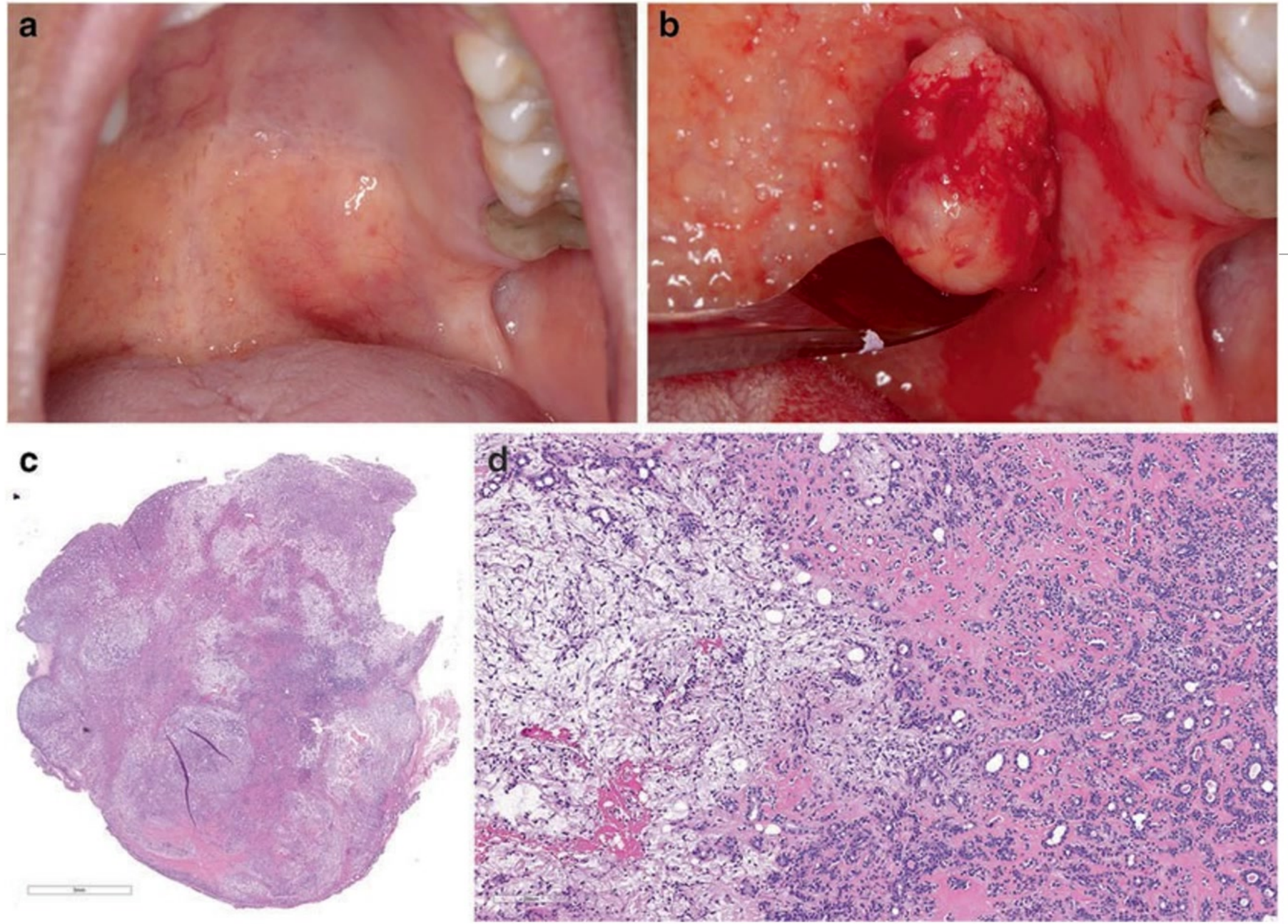



Image from Contemporary oral medicine, 2019

# Pleomorphic adenoma

**Diagnosis**

- History.
- Clinical examination.
- Investigations may include:
  - Imaging – e.g. ultrasound, CT, MRI.
  - Biopsy
    - Small incisional biopsies or fine needle aspirates can complicate diagnosis as they may not be representative of the entire lesion.

**Management**

- Excision of the tumour with clear margins.
- Prognosis is excellent after surgical resection in most cases.
- Recurrence is related to many factors, including incomplete encapsulation, extracapsular tumour extension, and intraoperative tumour rupture and spillage.
- Malignant transformation into Carcinoma ex pleomorphic adenoma occurs in up to 7% of cases.

# Warthin’s tumour

**Introduction**

- Other names: Adenolymphoma, papillary cystadenoma lymphomatosum, cystadenolymphoma.
- Warthin tumour is a benign salivary gland tumour composed of oncocytic epithelial cells lining ductal, papillary and cystic structures in a lymphoid stroma.
- It is the second most common salivary gland neoplasm.
- Malignant transformation has been reported.

**Epidemiology**

- Accounts for up to 15% of all salivary gland tumours.
- Most commonly diagnosed in the 6th to 7th decade of life.
- Slight male predominance.

# Warthin's tumour

**Aetiopathogenesis**

- Smoking
  - Reported since 1980's
  - Numerous studies have noted associations
  - Demonstrate that smoking habit has 4 – 8-fold greater risk of developing WT than non-smokers
  - Kotwall C. 1992
    - Case-control study  between 1980 – 1989
    - WT (28) V PA (69)
    - Defined positive smoking hx as 10 pack-year
    - 8 times risk of developing WT than non-smokers

# Warthin's tumour

**Aetiopathogenesis**

- Autoimmune diseases
  - Gallo et al. 1997 : retrospective analysis of 140 WT patients c.f 380 patients with PA over 25-year period
    - WT patients had higher incidence of autoimmune disorders (23% v 3%; $p<0.001$)
    - Significant smoking hx (87% v 38%; $p<0.001$)
    - Support hypothesis of immune pathogenesis of WT
    - Possible role of smoking facilitating immune reactions

# Warthin’s tumour

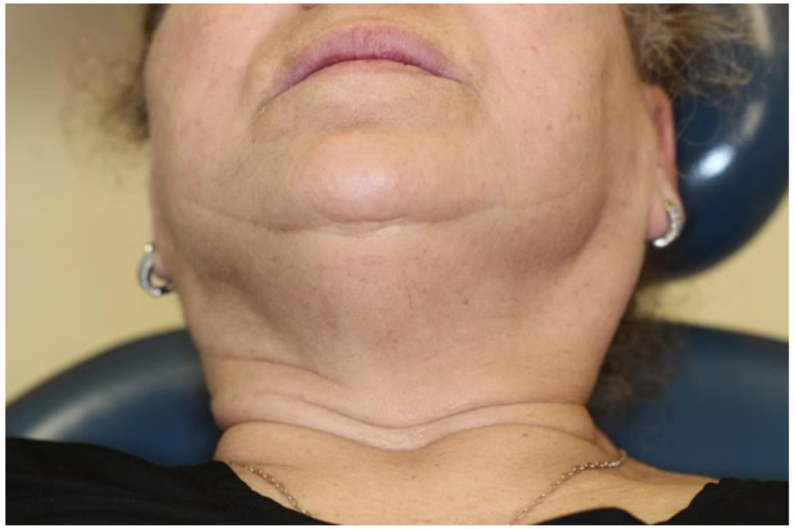
**Aetiopathogenesis**

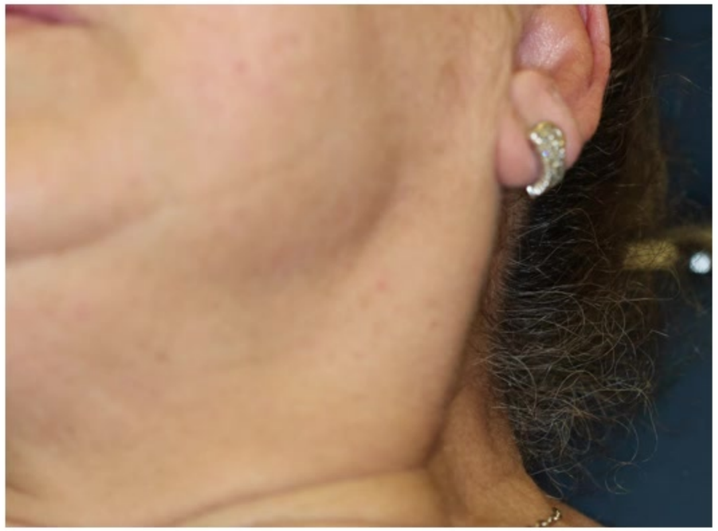
- EBV infection
  - Santucci et al. 1993:
    - First reported detection of EBV genome in Warthin’s tumour
    - Frequently noted in neoplastic cells of multiple/bilateral Warthin's tumour (86.7%)
    - Occasionally noted in solitary Warthin’s tumour (16.7%)
    - Suggested strong association between EBV infection of cells and development of multiple/bilateral lesions

# Warthin's tumour

**Pathogenesis**

- Controversial and not completely understood
  - neoplastic process vs metaplastic with secondary lymphoid reaction
- Accepted theory:
  - Neoplasm arising from heterotopic salivary ducts
  - Present within pre-existing intra-parotid or para-parotid lymphoid tissue
  - Supported by IHC
    - luminal and basal epithelial cells of Warthin's tumour similar to striated duct cells and basal cells of excretory duct of salivary gland
    - Ellis & Auclair 1996
- Nitrous Oxide associated with development of WT
  - role in pathogenesis in Warthin's yet to be established

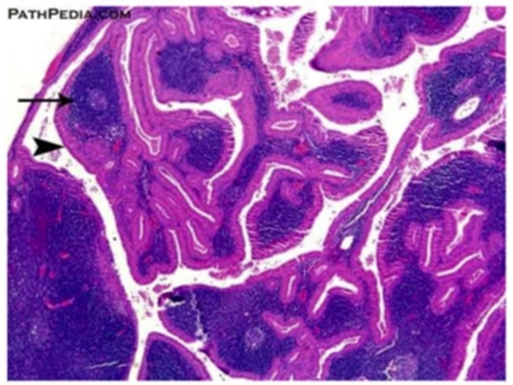




# Warthin’s tumour

**Clinical Presentation**

- Painless, discrete, slow-growing lump.
- Almost exclusively involves the parotid glands, and often presents as a mass/swelling in the upper neck or angle of the mandible.
- There may be multifocal lesions.
- Unilateral or bilateral involvement.
- May present with facial nerve palsy if there is facial nerve involvement.

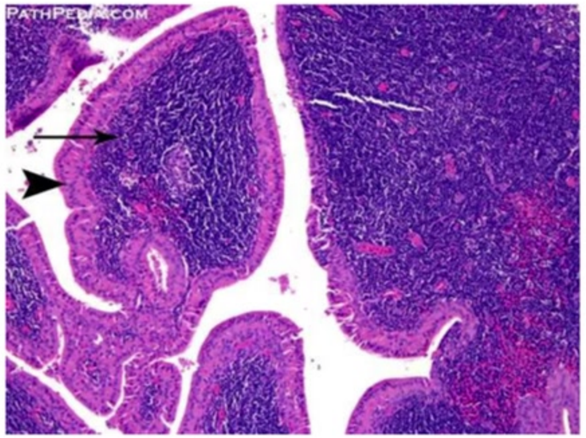



# Warthin’s tumour

Histopathology

- Papillary – cystic structures
- Lined by oncocytic epithelial cells
- Lymphoid stroma with germinal centres
- Epithelial component:
  - inner columnar
  - outer cuboidal cells
- Granulomatous reaction with Langham's type giant cells may occur

WHO 4th editon ; Images from: pathpedia.com/warthins



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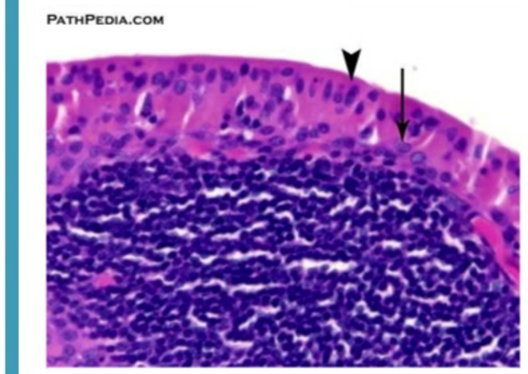


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WHO 4th editon ; Images from: pathpedia.com/warthins

# Warthin's Tumour

**Diagnosis**

*NCCN Guidelines; Guidelines for diagnosis and management of salivary gland tumours; AHNS; 2019*

- Clinical Evaluation
  - History and physical examination including H+N examination
  - Known risk factors for salivary gland tumours?
    - Smoking history
- Role of Imaging
  - Imaging of clinically benign, superficial parotid tumours is unclear
  - Warthin's tumour appear hypermetabolic on PET scan

# Warthin's tumour

**Management**

- Surgical management – complete excision + adequate margin
  - Superficial parotidectomy
    - Facial nerve damage
    - Freys syndrome
    - haematoma
- Low recurrence rate
- Malignant transformation rare (0.3%)
  - Few reported cases
- Conservative management
  - Observation – controversial

# Oncocytoma

**Introduction**

- Other names: Oncocytic adenoma, oxyphilic adenoma.
- Oncocytoma is an uncommon benign salivary gland neoplasm predominantly composed of large eosinophilic epithelial cells called oncocytes.

**Epidemiology**

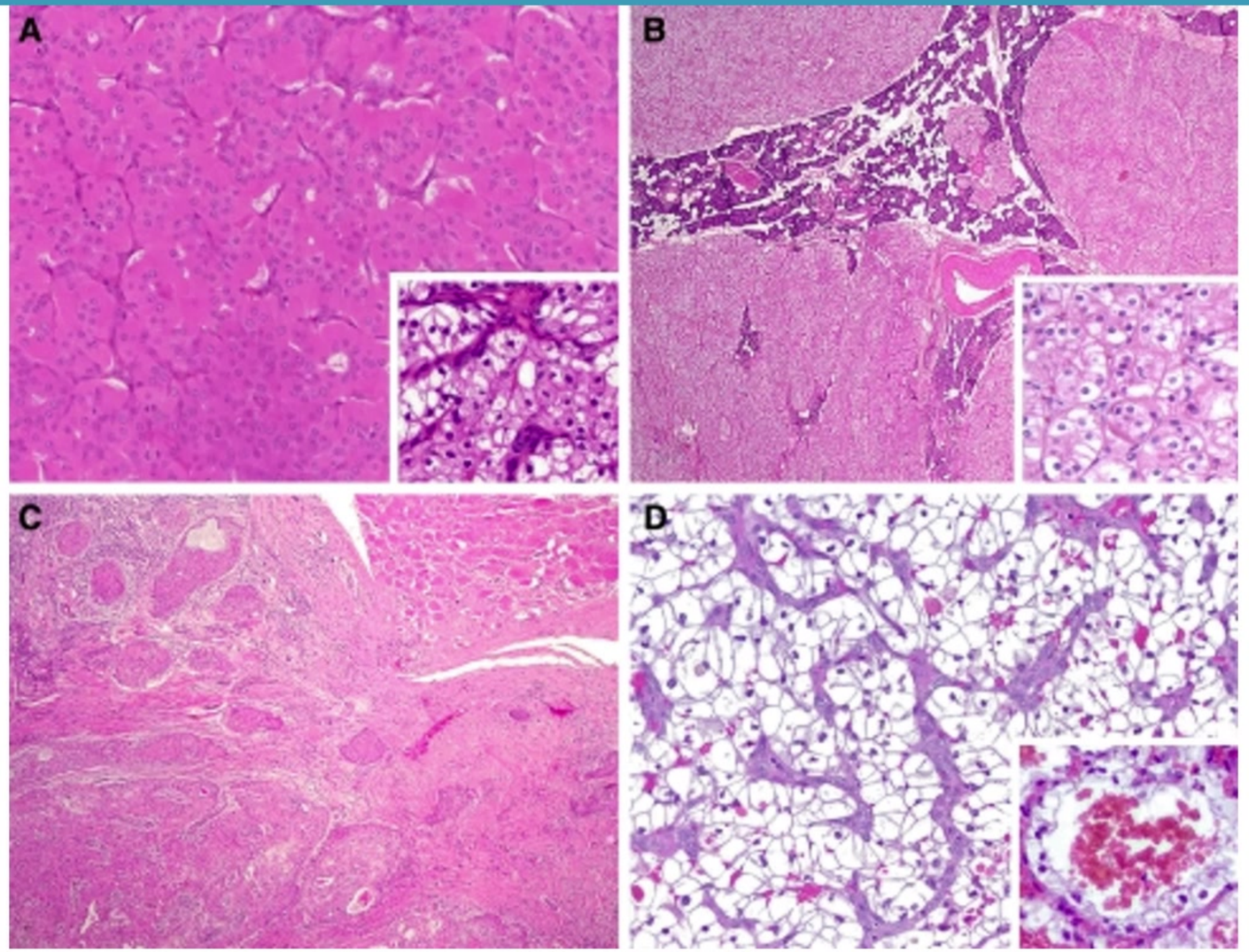
- Uncommon (up to 2% of all salivary gland neoplasms).
- Most common in 6th to 8th decades of life.
- No gender predilection.

# Oncocytoma

**Histopathology**

- Eosinophilic or clear cell (glycogen) with sheets, trabeculae, acini or follicular patterns of monotonous large polygonal cells with well defined cell borders, deeply eosinophilic, granular cytoplasm, small round nuclei
- Vascular stroma, may have clear cell change, background of oncocytic nodular hyperplasia, psammoma bodies, tyrosine rich crystals
- No mitotic figures, no elastosis

Head Neck Pathol. 2007 Dec; 1(2): 123–131.




(**a**) Typical oncocytoma composed of nests and trabeculae of granular eosinophilic cells with scattered lumina and separated by a delicate vascular stroma. Many examples demonstrated clear cells and about one-fourth had a prominent RCC-like vascular stroma (inset). (**b**) Typical case of oncocytosis with multiple unencapsulated nodules of oncocytes growing in a lobular configuration. Like this example, one-third of the cases demonstrated a predominance of clears cells (inset). (**c**) Oncocytic carcinomas typically demonstrated bland oncocytic cytology, however, unequivocal invasion was identified in all cases and features of other salivary gland carcinomas with oncocytic cytoplasm were not present. (**d**) Metastatic conventional (clear cell) RCC with characteristic prominent vascular stroma. Nearly two-thirds of cases were composed of clear cells but over one-third were of oncocytic type. Blood lakes (inset) were found in half of the metastatic RCC and were specific for RCC as none of the primary salivary gland tumors had them

# Oncocytoma

**Diagnosis**

- History.
- Clinical examination.
- Investigations may include:
  - Imaging – e.g. ultrasound, CT, MRI.
  - Cytology.
  - Technetium 99-m pertechnetate scintigraphy – Oncocytomas present as hot lesions.

**Management**

- Surgical excision.
- Recurrences are rare, though additional oncocytomas may arise in the residual salivary gland.

# Mucoepidermoid carcinoma

**Introduction**

- Other names: Mucoepidermoid tumour.
- Mucoepidermoid carcinoma (MEC) is a salivary gland malignancy composed of mucinous, intermediate (clear-cell) and squamoid/epidermoid tumour cells forming cystic and solid patterns.
- It is the most common malignant salivary gland tumour in children and young adults.

**Epidemiology**

- Wide age range, with peak incidence in the second decade of life.

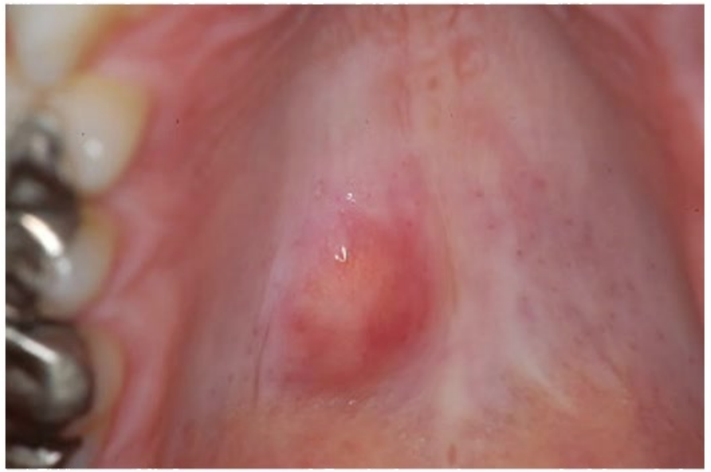
**Aetiopathogenesis**

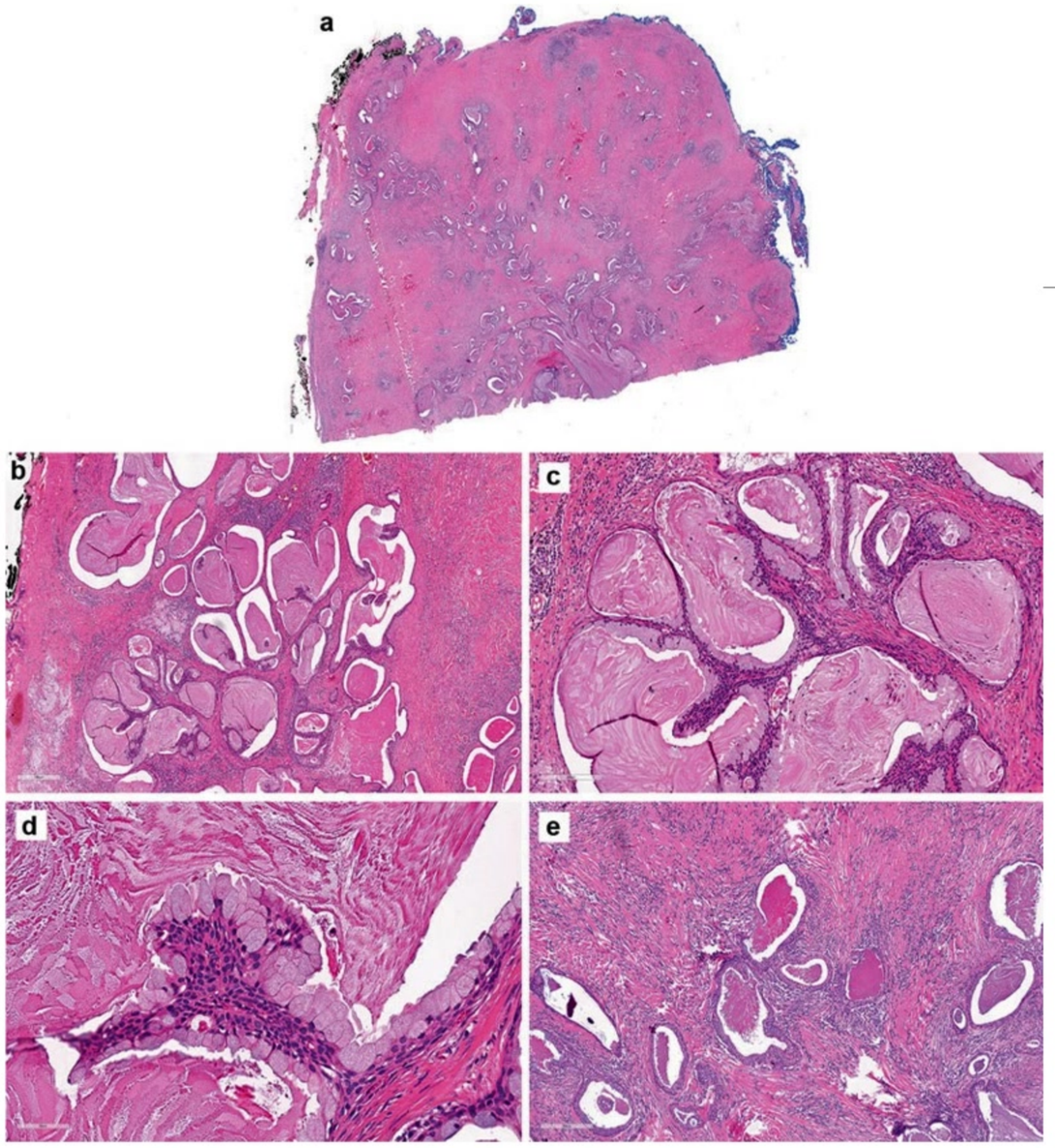
- MECs may develop secondary to radiation or chemotherapy during childhood (median latency period of 8 years).

# Mucoepidermoid carcinoma

**Clinical Presentation**

- Clinical presentation varies depending on tumour site, size and grade.
  - Generally presents as a slow-growing mass.
  - Cystic intraoral MEC can resemble a mucocoele.
  - Mucinous MEC may fluctuate in size due to cyst rupture.
- Most commonly occurs in the parotid gland, followed by the palate, submandibular gland, and other intraoral minor salivary glands. Rarely, they can present as primary intraosseous (central) MECs.






Mucoepidermoid carcinoma. Sections show parotid parenchyma with a mucoepidermoid carcinoma, occupying predominantly the inferior half of the gland (a).

The tumor is composed of numerous mucin-filled cysts of varying shape and size and cribriform structures set within dense desmoplastic stroma (b).

The cystic spaces are lined by a combination of mucocytes, intermediate cells, and epidermoid cells (c).

The mucous cells contain pale cytoplasm and peripherally displaced nuclei. The epi-dermoid cells are polygonal with central, mildly pleomorphic nuclei and abundant cytoplasm, but no defi-nite keratinization (d).

In the surrounding stroma, there is extensive sclerosis and a prominent peritumoral inflammatory infiltrate composed of lymphocytes and plasma cells, with small lymphoid aggregates containing reactive germinal centers (e)

# Mucoepidermoid carcinoma

**Diagnosis**

- History.
- Clinical examination.
- Investigations may include:
  - Imaging – e.g. ultrasound, CT, MRI.
  - Cytology.
  - Biopsy.

**Management**

- Surgical excision with clear margins.
- Radiotherapy may be appropriate for local control in some cases.
- Low- and intermediate-grade MECs are generally less aggressive.
- 10-year survival rates range from 90% (low-grade MEC), 70% (intermediate-grade MEC) and 25% (high-grade MEC).

# Acinic cell carcinoma

**Introduction**

- Other names: Acinic cell adenocarcinoma, acinar cell carcinoma.
- Acinic cell carcinoma is a malignant salivary gland neoplasm composed of cancer cells with acinar features.
- Second most common salivary gland malignancy in children.

**Epidemiology**

- Occurs over a wide age range (including children), but most are found in patients aged 50 years and above.
- Female predominance (1.5:1).

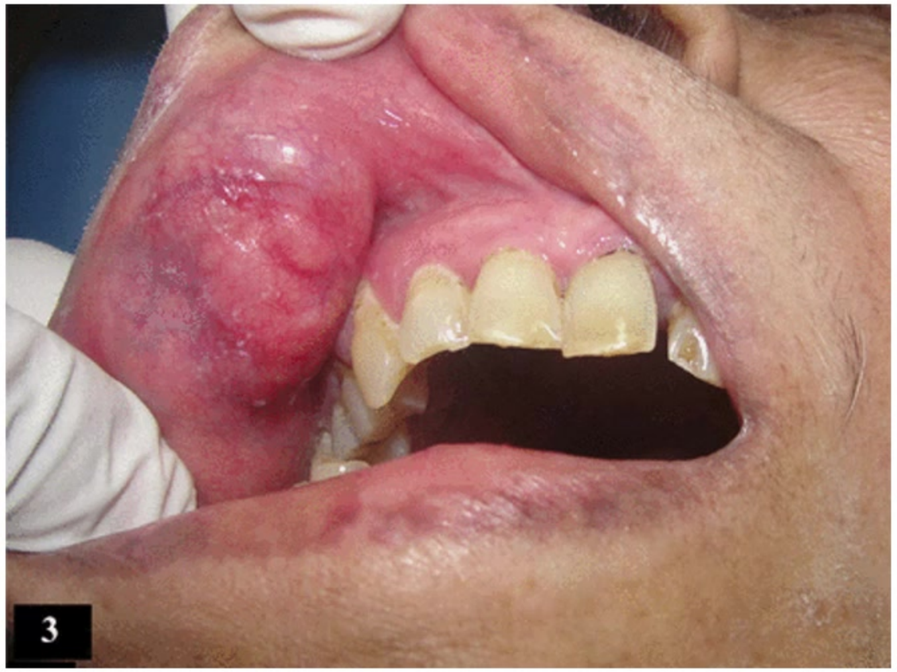
**Aetiopathogenesis**

- Aetiology unknown.
- Risk factors include previous radiation exposure.

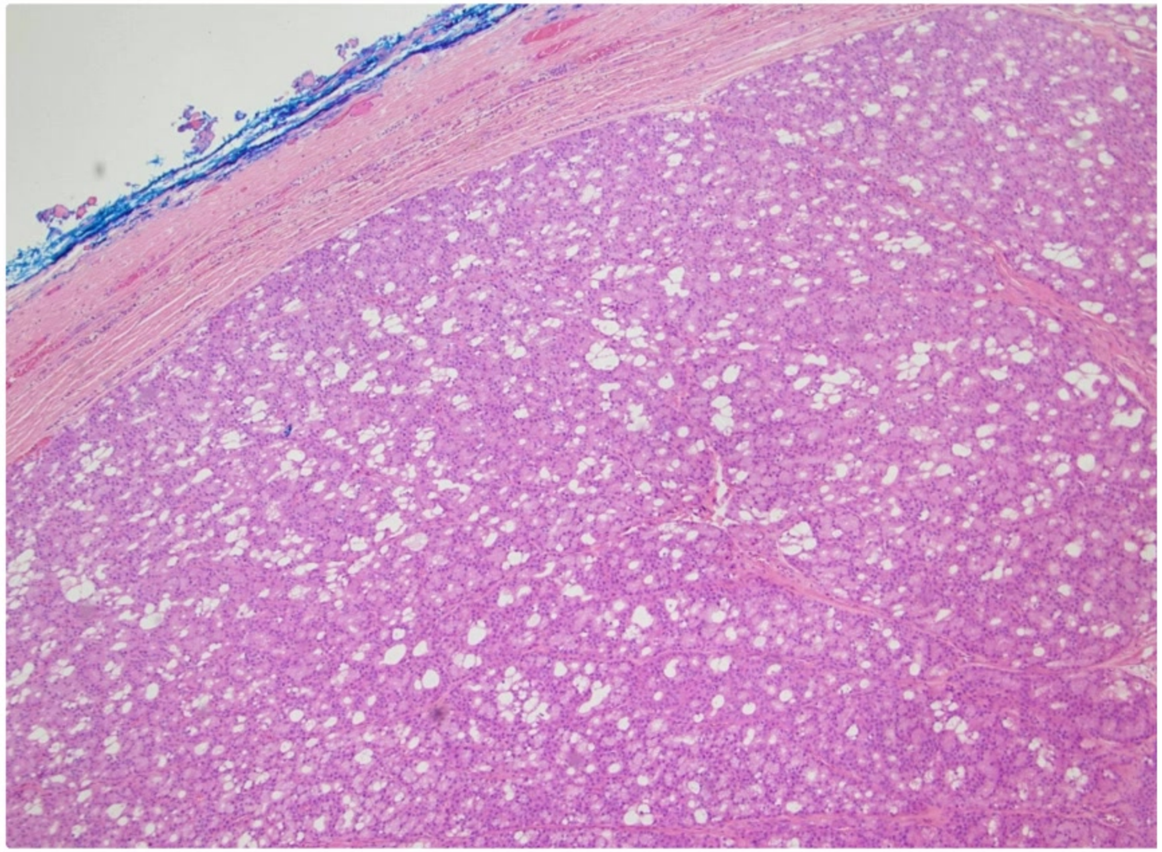
# Acinic cell carcinoma

**Clinical Presentation**

- Slow-growing, solitary, unfixed masses.
- Over 90% occur in the parotid glands. They can also occur in the intraoral minor salivary glands.
- Some may be multinodular and/or fixed to the skin.
- Pain may be a symptom in a third of patients.
- Facial paralysis may develop if there is neural involvement.




Bavle RM, Makarla S, Nadaf A, *et al*
Solid blue dot tumour: minor salivary gland acinic cell carcinoma
*Case Reports* 2014;**2014:**bcr2013200885.



Parotid gland excision, acinic cell carcinoma. Well circumscribed tumor with microcystic to solid growth pattern (H&E).

# Acinic cell carcinoma

**Histopathology**

- Multiple cell types are noted
  - Cell types include serous acinar, intercalated ductal, vacuolated, nonspecific glandular and clear cells
- Acinar cells are large and polyhedral, with basophilic granular cytoplasm and eccentric nuclei
  - Cytoplasmic diastase resistant positive periodic acid-Schiff (PAS) reaction may be focal
- Variety of morphologic patterns, including solid, microcystic, papillary cystic and follicular
- Prominent lymphoid infiltrate may be present (tumour associated lymphoid proliferation varies from randomly scattered, patchy collections of lymphocytes to diffuse, dense infiltrates with well formed follicles throughout the tumour)
- Mitosis, necrosis and significant pleomorphism usually absent

Lahouti AH, Rao RA. Acinic cell carcinoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/salivaryglandsaciniccell.html. Accessed March 15th, 2022.

# Acinic cell carcinoma

**Diagnosis**

- History.
- Clinical examination.
- Investigations may include:
  - Imaging – e.g. ultrasound, CT, MRI.
  - Cytology.
  - Biopsy – wide variation in histomorphology.

**Management**

- Surgical excision.
- Radiotherapy may be indicated in some cases.
- Recurrence rates of up to 35% have been reported.
- The tumour can metastasise to regional lymph nodes and the lungs.
- Good survival rate of approximately 90% over 10 years.

# Adenoidcystic carcinoma

**Introduction**

- Adenoid cystic carcinoma (ACC) is a slow-growing but relentless salivary gland malignancy.
- Composed of epithelial and myoepithelial neoplastic cells that form various patterns (manifest as a variety of tubular and cribriform structures with variably solid components).
- Accounts for < 10% of all salivary gland neoplasms.

**Epidemiology**

- Annual incidence: 2 cases per 100 000 population.
- Median age: 57 years.
- Female predominance (1.5:1).
- No ethnic predilection.

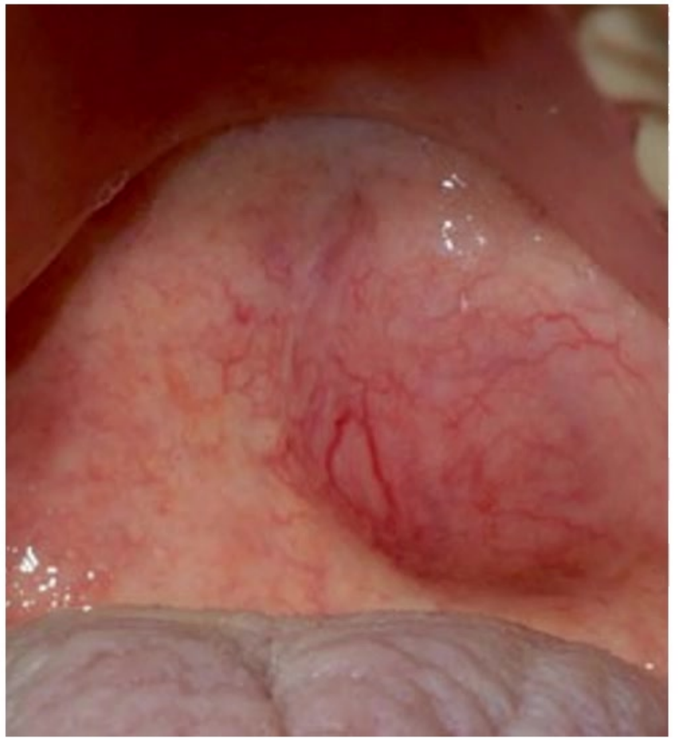
# Adenoidcystic carcinoma

**Aetiopathogenesis**

- Aetiology unknown.

**Clinical Presentation**

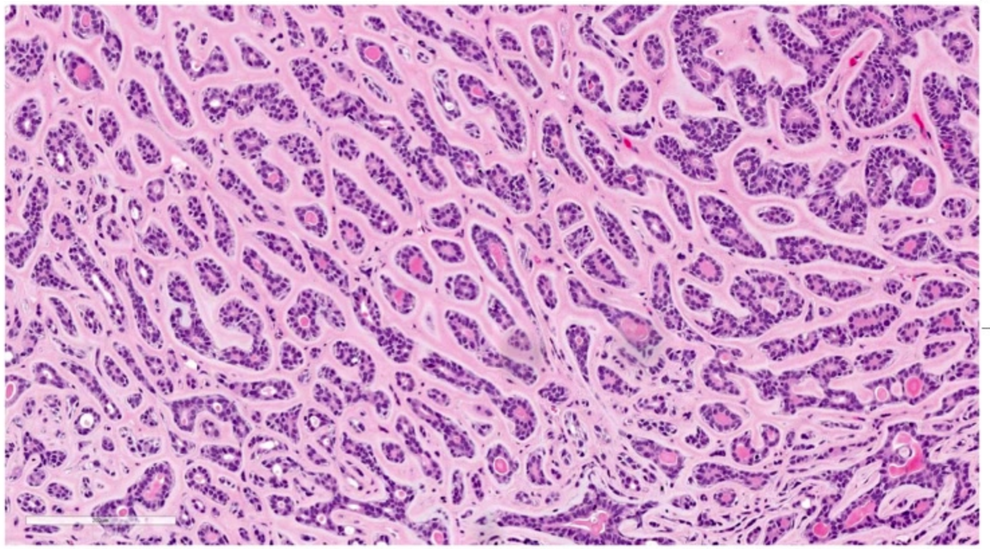
- Mass/swelling.
- Perineural invasion – neurological signs or symptoms such as numbness, paraesthesia, pain or facial/tongue weakness may be present.
- Occurs most frequently in the major salivary glands; however over 30% of cases occur in minor glands of the oral cavity, sinonasal tract or other sites.
- Lymph node involvement is uncommon.
- Distant metastasis reported in over 50% of cases (lungs, bone, liver, brain).



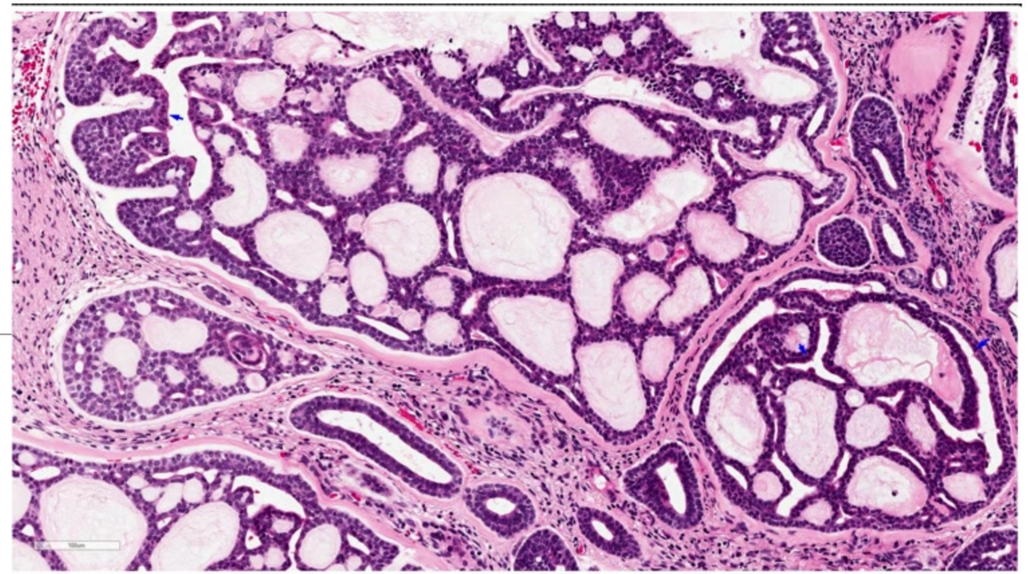
# Adenoidcystic carcinoma

**Histopathology**

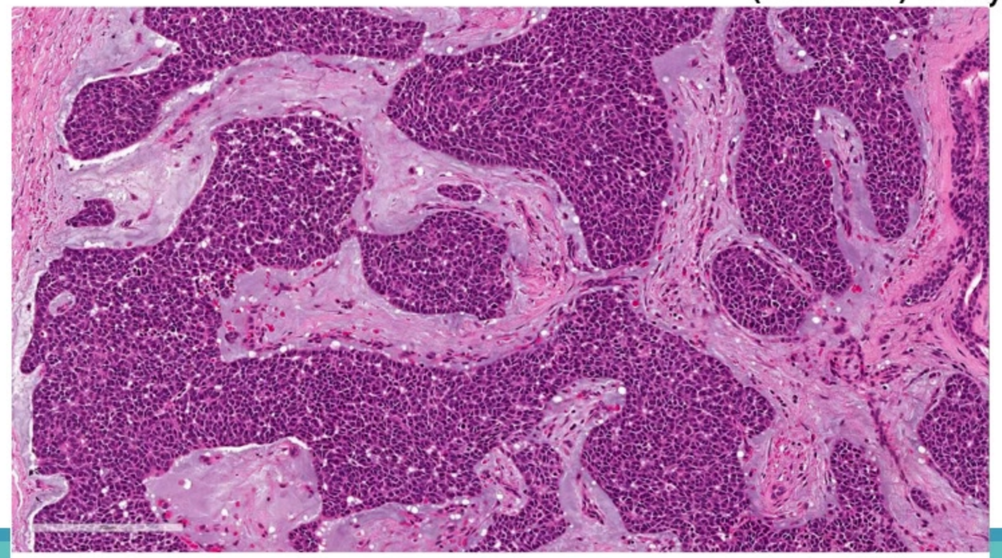
- Biphasic salivary gland tumor, composed of ductal and myoepithelial cells
- Myoepithelial cells have dark angulated nuclei and scanty cytoplasm, giving a basaloid appearance
- Tubular, cribriform and solid architecture
- Tubular pattern contains simple tubules composed of inner ductal and outer myoepithelial cells
- Cribriform pattern is composed of predominantly myoepithelial cells with myxoid or hyalinized globules
- Scattered ductal elements may be seen within the cribriform area
- Solid pattern is solid nests composed of sheets of basaloid cells
- Perineural invasion is frequent
- High grade transformation can be seen in a small number of cases, defined as comedo type tumor necrosis, frequent mitoses (often > 10 per 10 high power fields) and marked nuclear atypia; high grade transformation is associated with high risk of lymph node metastasis, distant metastasis and disease related death



Tubular pattern is composed of inner ductal and outer myoepithelial cells. The ductal cells are cuboidal with eosinophilic cytoplasm. The myoepithelial cells are angulated and basaloid.



Cribriform pattern is composed predominantly of myoepithelial cells admixed with hyalinized or myxoid globules. Scattered ductal elements (arrows) may also been present.



Tumor cells forming solid sheets and nests.

Xu B. Adenoid cystic carcinoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/salivaryglandsadenoidcystic.html. Accessed March 15th, 2022.

# Adenoidcystic carcinoma

**Diagnosis**

- History.
- Clinical examination.
- Investigations may include:
  - Imaging – e.g. ultrasound, CT, MRI.
  - Cytology.
  - Biopsy.

**Management**

- Surgery – wide excision with clear margins.
- Radiotherapy can help to improve local control in microscopic residual disease.
- Local recurrence rate highly variable.
- In recurrent or metastatic disease, treatment success with radiotherapy +/- chemotherapy is limited.
- 10-year survival rate is 50-70%.

# Polymorphous low grade adenocarcinoma

**Introduction**

- Other names: Polymorphous low-grade adenocarcinoma, terminal duct carcinoma, lobular carcinoma, cribriform adenocarcinoma of tongue/minor salivary glands.
- Polymorphous adenocarcinoma (PAC) is a malignant salivary gland tumour characterised by cytological uniformity, histomorphological diversity, and an infiltrative growth pattern.
- It is the second most common intraoral malignant salivary gland neoplasm.

**Epidemiology**

- Wide age range from young adult to elderly, but most commonly diagnosed in patients over 50 years of age.
- Female predominance (2:1).

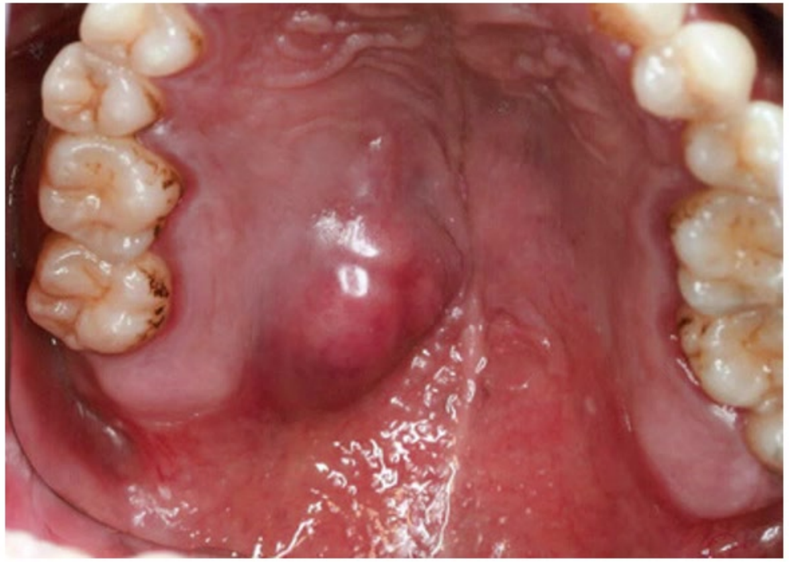
**Aetiopathogenesis**

- Aetiology unknown.

# Polymorphous low grade adenocarcinoma

**Clinical Presentation**

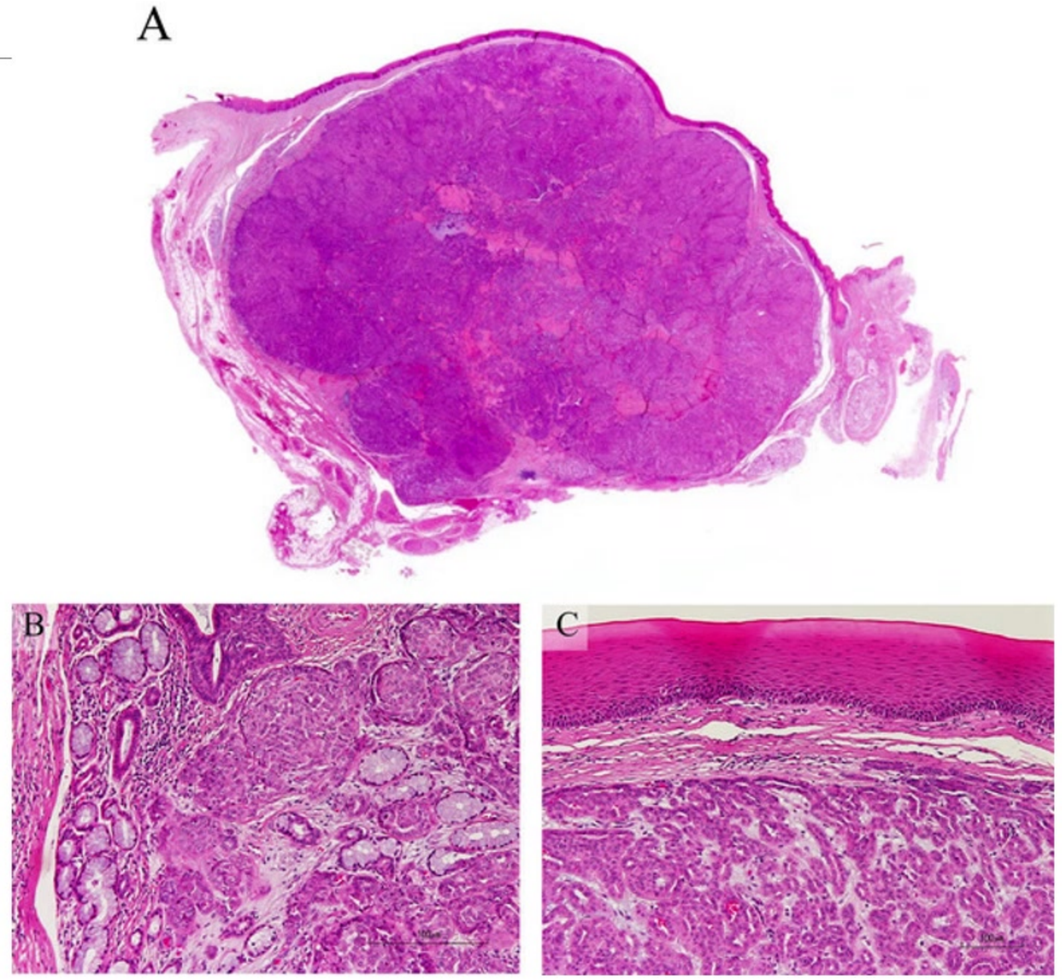
- Painless mass of variable duration (weeks to years).
- There may be clinical signs of bleeding, telangiectasia and ulceration of the overlying mucosa.
- Most common site of involvement is the palate (hard palate > soft palate), followed by lips, buccal mucosa, alveolar mucosa and other intraoral sites. Other less common sites include the major salivary and lacrimal glands, nasopharynx and nasal cavity.
- Aggressive clinical behaviour.
- May invade adjacent soft tissue and infiltrate adjacent bone. There is often perineural involvement.
- Nodal metastasis in up to 15% of cases



# Polymorphous low grade adenocarcinoma

**Histopathology**

- Cytologic uniformity: the tumor is composed entirely of one type of tumor cells characterized by monotonous pale nuclei with marked chromatin clearing resembling that of papillary thyroid carcinoma
- Architectural diversity: showing highly variable architectural patterns of different proportions, including single filing arrangement, trabecular, tubular, reticular, papillary, solid and cribriform pattern
- Targetoid arrangement and streaming of tumor cells and nests around nerves and vessels are common




Head Neck Pathol. 2019 Jun; 13(2): 131–139.

# Polymorphous low grade adenocarcinoma

**Diagnosis**

- History.
- Clinical examination.
- Investigations may include:
  - Imaging – e.g. ultrasound, CT, MRI.
  - Cytology.
  - Biopsy
    - Diagnostic difficulties, especially with small biopsy samples.
    - PAC neoplastic cells may appear deceptively bland.

**Management**

- Surgical excision with clear margins.
- Radiotherapy may also be appropriate in some cases.
- Overall survival is generally good.
- Local recurrence rates of up to 33% are reported, and about half occur within 5 years of initial diagnosis.

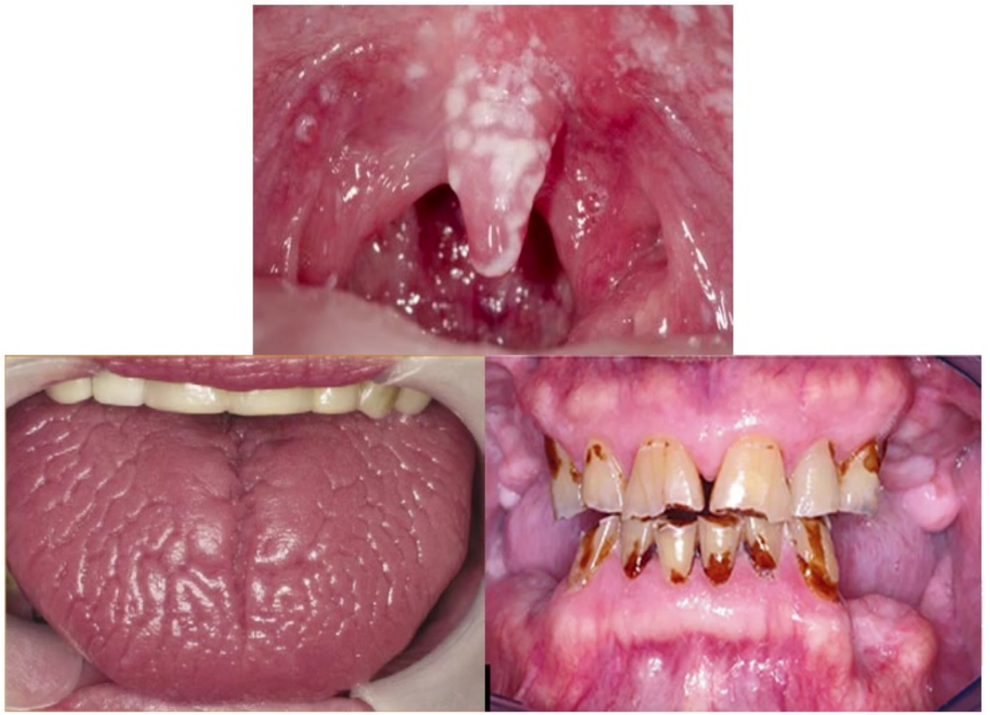
**Discuss the aetiology, clinical features, diagnosis and management of dry mouth.**

# Xerostomia vs Salivary gland hypofunction

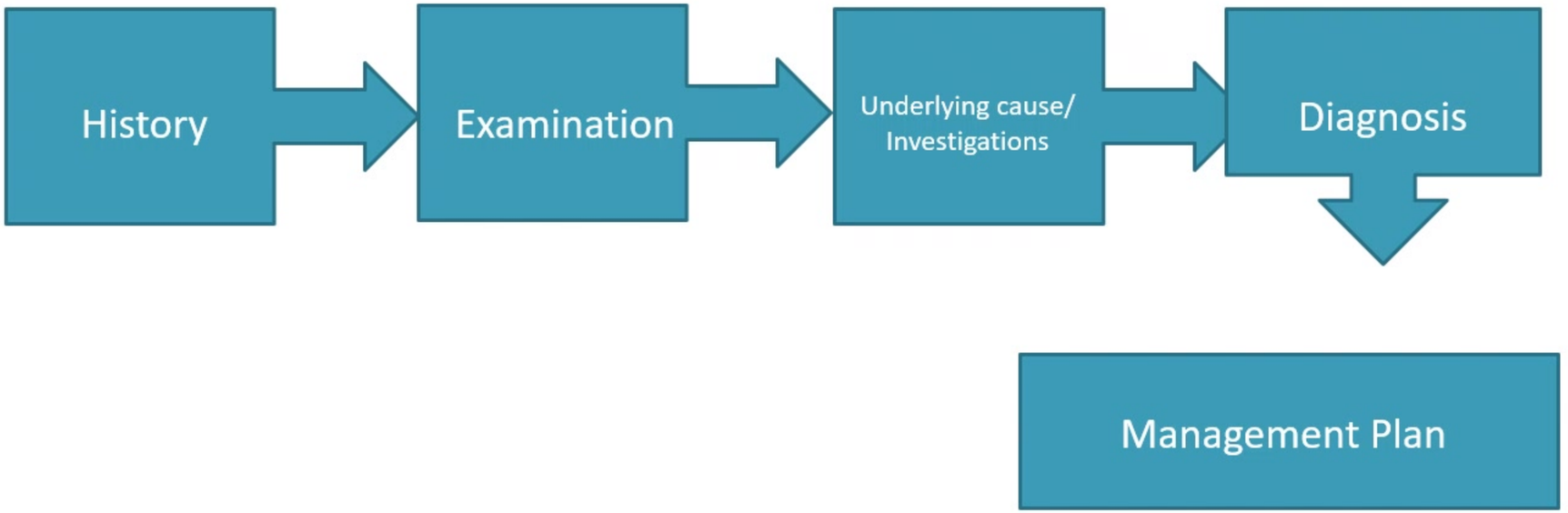
- Salivary gland hypofunction: decreased saliva flow rate
- Hyposalivation: pathological low saliva flow rate
  - Unstimulated whole saliva flow rate ≤ 0.1ml/min
  - Stimulated whole saliva flow rate ≤ 0.5-0.7 ml/min
- Xerostomia: subjective feeling of oral dryness

# Why should dentists care about a dry mouth?

- Negative impact on quality of life
  - Functional limitation
  - Physical pain
  - Physical disability
  - Psychological discomfort
- Taste changes
- Difficulty chewing
- Difficulty swallowing
- Dental diseases



# An approach to the patient with dry mouth

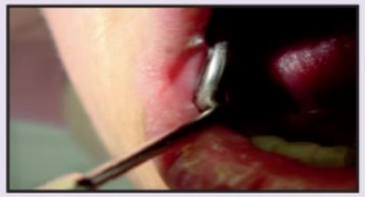
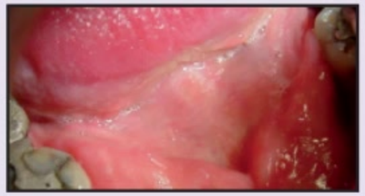


# History

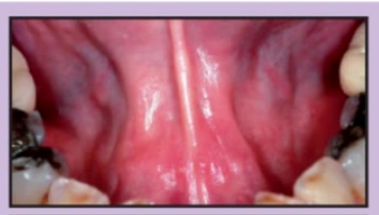
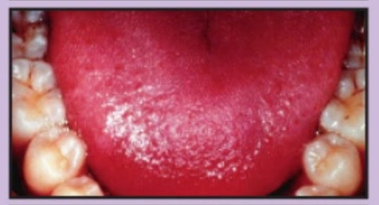
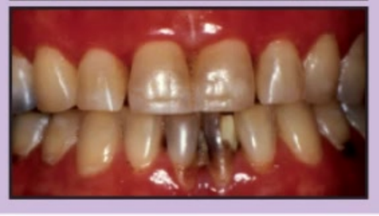
- Subjective symptoms
  - Complain of xerostomia throughout their oral cavity or localised to a part of their oral cavity
  - Carry bottles of water or other fluids
  - Glass of water beside bed
  - Change in saliva consistency
- Assessment of xerostomia – Fox et al. 1987
  - Does the amount of saliva in your mouth seem to be too little, too much, or do you not notice it?
  - Do you have any difficulty in swallowing?
  - Does your mouth feel dry when eating a meal?
  - Do you sip liquids to aid in swallowing dry food?
- Medical history & Medications
- Behaviours
  - Water intake?
  - Caffeine intake?
  - Alcohol/smoking

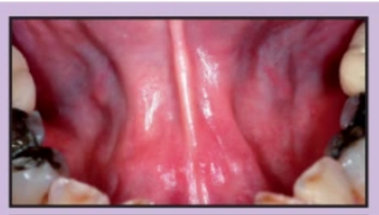
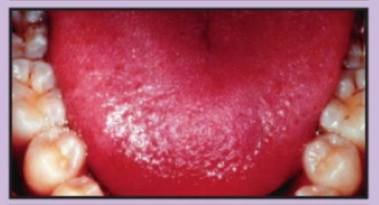
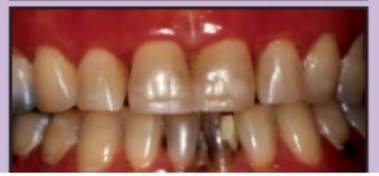
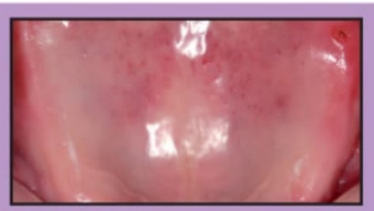
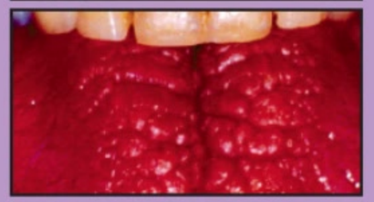
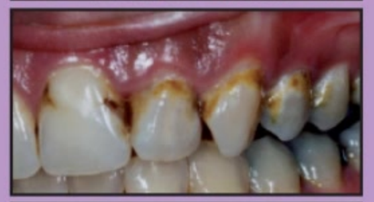
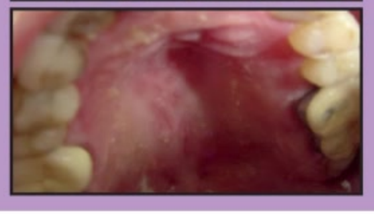
# Examination

The Challacombe Scale of clinical oral dryness

| | | |
|---|---|---|
| 1 |  | Mirror sticks to buccal mucosa |
| 2 |  | Mirror sticks to tongue |
| 3 |  | Saliva frothy |

An additive score of 1 - 3 indicates mild dryness. May not need treatment or management. Sugar-free chewing gum for 15 mins, twice daily and attention to hydration is needed. Many drugs will cause mild dryness. Routine checkup monitoring required.

| | | | |
|---|---|---|---|
| 4 |  | No saliva pooling in floor of mouth | An additive score of 4 - 6 indicates moderate dryness. Sugar-free chewing gum or simple sialogogues may be required. Needs to be investigated further if reasons for dryness are not clear. Saliva substitutes and topical fluoride may be helpful. Monitor at regular intervals especially for early decay and symptom change. |
| 5 |  | Tongue shows generalised shortened papillae (mild depapillation) | |
| 6 |  | Altered gingival architecture (ie. smooth) | |

| | | |
|---|---|---|
| 4 |  | No saliva pooling in floor of mouth |
| 5 |  | Tongue shows generalised shortened papillae (mild depapillation) |
| 6 |  | Altered gingival architecture (ie. smooth) |
| 7 |  | Glassy appearance of oral mucosa, especially palate |
| 8 |  | Tongue lobulated / fissured |
| 9 |  | Cervical caries (more than two teeth) |
| 10 |  | Debris on palate or sticking to teeth |

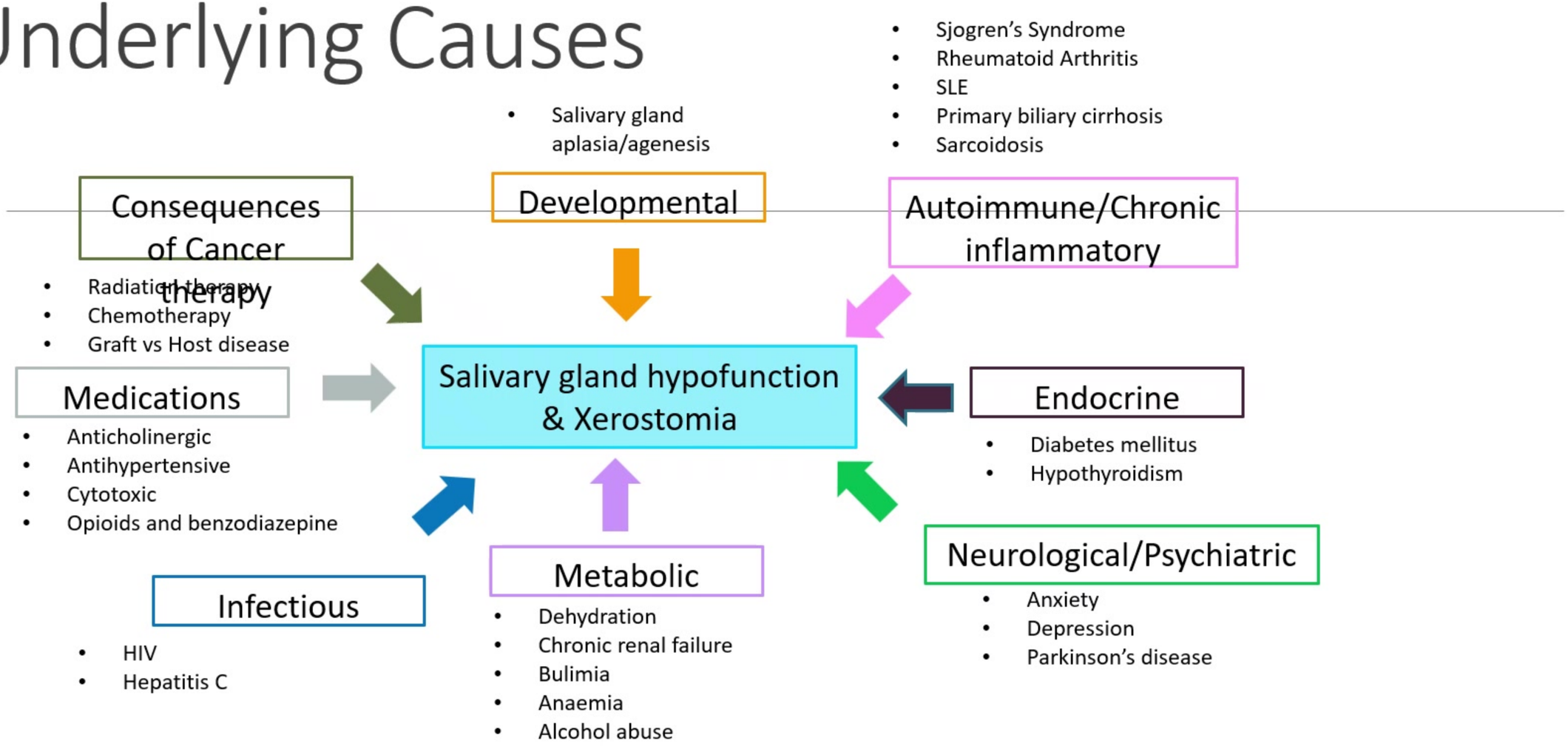
An additive score of 4 - 6 indicates moderate dryness. Sugar-free chewing gum or simple sialogogues may be required. Needs to be investigated further if reasons for dryness are not clear. Saliva substitutes and topical fluoride may be helpful. Monitor at regular intervals especially for early decay and symptom change.

An additive score of 7 - 10 indicates severe dryness. Saliva substitutes and topical fluoride usually needed. Cause of hyposalivation needs to be ascertained and Sjögrens Syndrome excluded. Refer for investigation and diagnosis. Patients then need to be monitored for changing symptoms and signs, with possible further specialist input if worsening.

# Underlying Causes

Salivary gland hypofunction
& Xerostomia

# Underlying Causes



# Investigations

- Unstimulated or stimulated whole saliva test
- Serology : SS-A, SS-B, ds-DNA, fasting glucose/HBA1C, Thyroid function test
- Ultrasound
- CT/MRI imaging
- Salivary gland biopsy
- Ophthalmology – Schirmer’s test

# Management

Salivary Stimulation

- Chewing gum – sugar free, caries prevention
- Pharmacology
  - Pilocarpine
- Electro-stimulating devices
  - Saliwell device
  - Augments salivary reflex, stimulate motor neural pathways of submandibular and sublingual salivary glands

# Management

Managing oral mucosa and dental complications

- Antifungal therapy
- Reduce exposure to irritants: alcohol, smoking, hot or spicy food
- Ensure adequate fit of denture
- Caries prevention protocol
  - Oral hygiene
  - Fluoride use
  - Dietary modifications


# You survived!

Questions

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