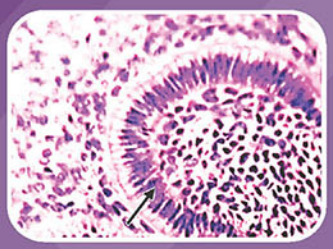
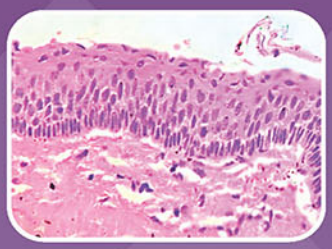
Essentials of ORAL PATHOLOGY

A Comprehensive Textbook for Students



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Highlights:

- Incorporation of WHO 2022 Classification of Cyst, Tumor & Salivary Gland Pathology
- Inclusion of Case-based Questions, Image-based Questions, Review Questions & MCQs
- Annexure—Differential Diagnosis of Important Oral Lesions
- Enhanced Pictorial Content and Infographics

5th Edition

JAYPEE

Contents

CHAPTER

4

Diseases of the Salivary Glands

CHAPTER OUTLINES

- Classification of Salivary Gland Diseases
- Developmental Anomalies of the Salivary Gland
- Reactive Lesions of the Salivary Gland
- Infective Lesions (Sialadenitis)
- Immune-mediated Disease of Salivary Gland
- Miscellaneous Disorders of Salivary Gland
- Neoplasm of the Salivary Glands
- Malignant Salivary Gland Neoplasms
- TNM Classification of Carcinomas of the Salivary Glands

Oral cavity normally has a moist environment and it is because of the continuous production and secretion of saliva in the mouth by the salivary glands. Salivary glands comprise of three paired major glands, namely, the **parotids, the submandibular and the sublingual glands**. Besides these major glands, there are numerous minor salivary glands (their number may be up to 300) present in almost every part of the oral cavity (except the gingiva), especially in the hard and soft palate, tongue, lip, and buccal mucosa. The minor glands are also found in the oropharynx, paranasal sinuses, sinonasal tracts and the upper respiratory tracts, etc. Secretion of saliva is essential for the normal health and function of the mouth; the functional unit of salivary gland is the **secretory acini, salivary ducts,** and the **myoepithelial cells**.

The secretary acini and secretary products of the salivary glands may be of three types—serous, mucous and mixed. The nature of secretion in different glands is listed below:

- **Major salivary glands:**
  - Parotid is an almost purely serous gland.
  - Submandibular is a mixed gland but predominantly serous.
  - Sublingual is also a mixed gland but predominantly mucous type.
- **The minor salivary glands may also have different characters:**
  - Minor salivary glands of the ventral tongue, palate, retromolar area are predominantly mucous in nature.
  - Minor glands of the lateral aspect of tongue, lips and buccal mucosa are seromucous type.
  - Minor glands related to the circumvallate papillae (von Ebner's glands) are serous type.

The serous acini are made up of wedge-shaped secretory glandular epithelial cells having their nuclei located at the base and the cytoplasm contains densely basophilic, PAS positive zymogen granules. The main secretion of serous acini is amylase.

The secretory cells of mucous acini also have basally placed nuclei and they have clear vacuolated cytoplasm.

The Salivary Duct System (Fig. 4.1)

Once saliva is produced by the acinar cells, it is collected in a lumen at the center of each **acinus**; from there it flows through a duct called **'intercalated duct'** (lined by a single layer of cuboidal cells with large centrally placed nuclei; these cells also have some secretory function).

At its end, the intercalated duct joins with the much larger **'striated duct'** (lined by tall columnar cells with eosinophilic cytoplasm) and this striated duct is the

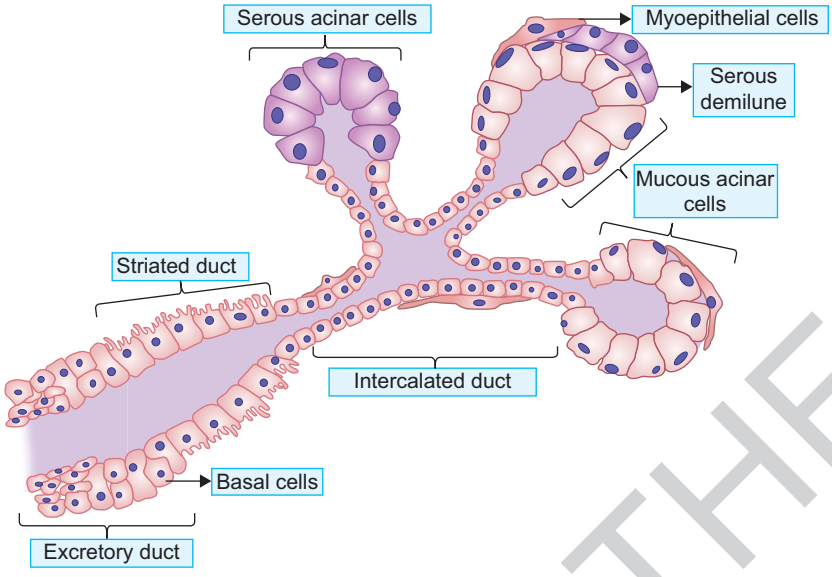

Fig. 4.1: Salivary duct system.

primary site for sodium reabsorption and potassium secretion.

Striated duct joins with the **excretory duct** (lined by pseudostratified columnar epithelial cells and few mucous cells), which finally drains into the main **collecting duct** of the salivary gland.

The **myoepithelial cells** (also called 'basket cells') form the basal cell layer of the glandular epithelium; these are stellate shaped cells with long dendritic processes that embrace the secretory acini and surround the intercalated ducts. The myoepithelial cells have contractile property (as they contain smooth muscle actin and myosin) and by their contraction they help in expelling the salivary secretions from the acini and through the intercalated duct. Myoepithelial cells can also act as epithelial progenitor cells.

Disorders of salivary gland function, which affects the composition and secretion of saliva, predisposes to many oral diseases. Salivary gland diseases are broadly divided into two categories—**non-neoplastic** disease and **neoplastic disease** (**Table 4.1**).

Non-neoplastic salivary gland diseases comprise of a heterogeneous group of entities of diverse etiopathogenic background. Most of the organic diseases of the salivary gland have a specific or nonspecific developmental, inflammatory, immunological or metabolic background.

Therefore, several special investigative procedure may be needed such as biopsy, sialometry, sialography, sialochemistry, CT scan, scintigraphy, and ultrasonography, etc., for comprehensive diagnosis of many unusual diseases. Moreover, careful examination of salivary gland tissue may be helpful in establishing the diagnosis of many systemic conditions, e.g., amyloidosis, sarcoidosis and Sjogren's syndrome, etc.

CLASSIFICATION OF SALIVARY GLAND DISEASES (TABLE 4.1 AND FLOWCHART 4.1)

TABLE 4.1: Classification of salivary gland disease.

Non-neoplastic disorders
Developmental anomalies
➢ Aplasia (agenesis) of the salivary gland
➢ Hypoplasia
➢ Aberrant salivary gland
➢ Atresia
➢ Accessory ducts
➢ Diverticuli
➢ Lingual mandibular salivary gland depression
Reactive lesions
➢ Mucus retention cyst
➢ Mucus extravasation cyst
➢ Sialolithiasis
➢ Postradiation sialadenitis
➢ Chronic sclerosing sialometaplasia
Infective lesions
➢ **Bacterial sialadenitis**
– Acute
– Chronic
– Recurrent
➢ **Viral sialadenitis**
– Mumps
– Cytomegalic inclusion disease
➢ **Immune-mediated diseases**
– Mikulicz's disease
– Sjogren's syndrome

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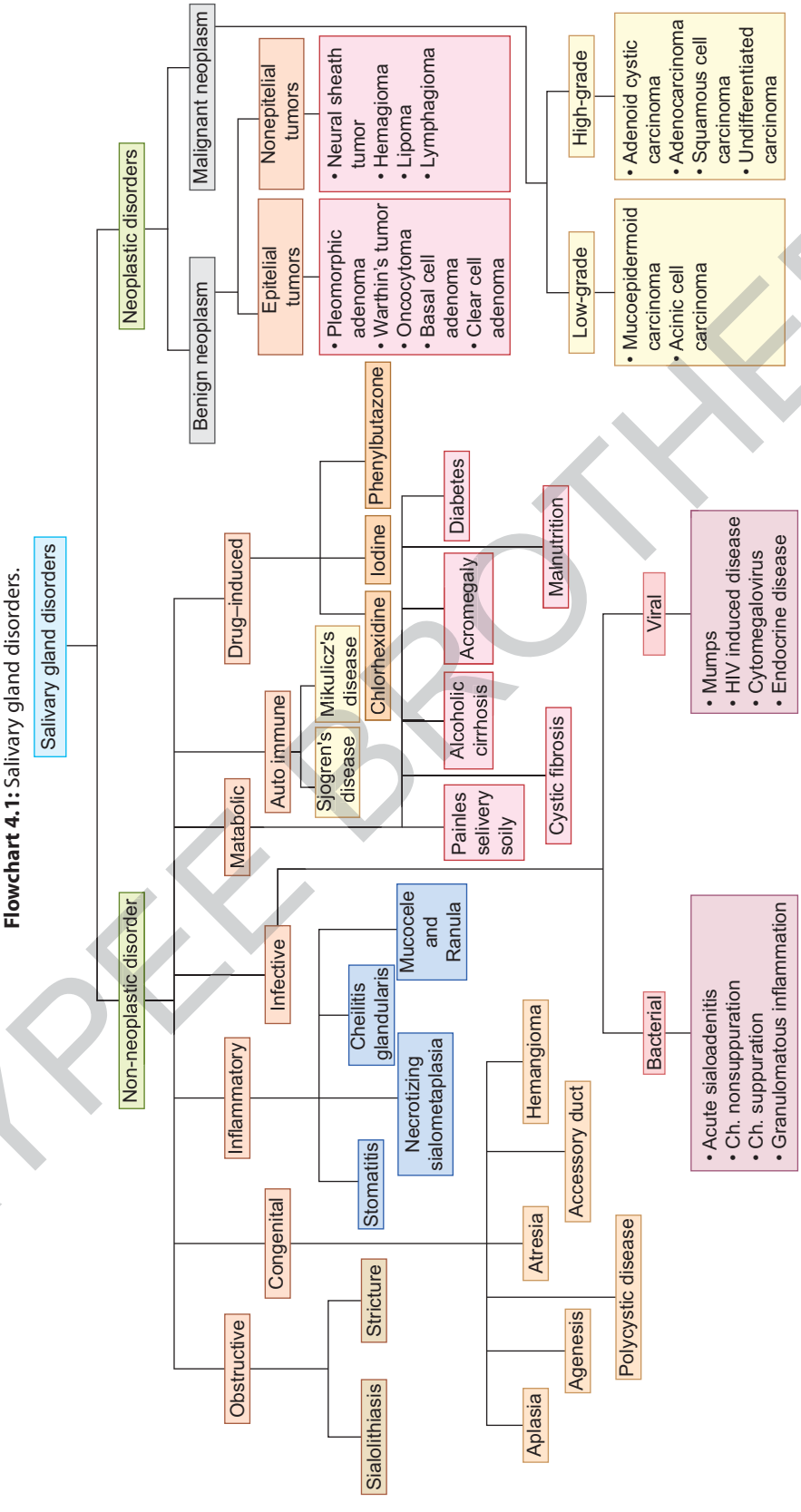


Flowchart 4.1: Salivary gland disorders.

Contd...

- **Miscellaneous diseases**
  - Heerfordt's syndrome
  - Sialosis
  - Ptyalism and aptyalism
  - HIV associated salivary gland disease

Neoplastic disorders

Classification
- Thackray and **Sobin, 1972**

Epithelial tissue neoplasms

Adenomas
- Pleomorphic adenoma (mixed tumor)
- Monomorphic adenoma
- Adenolymphoma (Warthin's tumor)
- Oxyphilic adenoma

Other types
- Mucoepidermoid tumor
- Acinic cell tumor
- Carcinomas
- Adenoid cystic carcinoma
- Adenocarcinoma
- Epidermoid carcinoma
- Undifferentiated carcinoma
- Carcinoma in pleomorphic adenoma (malignant mixed tumor)

Connective tissue neoplasms
- Fibroma
- Fibrosarcoma
- Lipoma
- Neurilemmoma
- Hemangioma
- Melanoma
- Lymphoma

The diagnosis of salivary gland diseases is often difficult and although clinical findings are of major help in many cases, it may not be sufficient to define a firm diagnosis in every single case **Flowchart 4.2.**

DEVELOPMENTAL ANOMALIES OF THE SALIVARY GLAND

Aplasia Or Agenesis of the Salivary Gland

Definition

Congenital absence of the salivary glands (both major and minor glands) due to complete failure of their development or genesis is called salivary gland aplasia.

Clinical Features

- It is an exceptionally rare anomaly, in which either a single gland or multiple glands can be involved, both unilaterally or bilaterally. The anomaly may affect several members of the same family.
- In some patients, salivary gland aplasia may occur alone, however, in other patients this condition may be associated with other congenital facial malformations.
- Aplasia of the major salivary gland commonly produces xerostomia (dryness of mouth), due to lack of production of saliva in the oral cavity; patients often have difficulty in taking food and have increased incidence of caries and periodontal diseases, causing early tooth loss.
- Clinically, the oral mucosa appears dry, smooth, or pebbly and it shows areas of food accumulation; cracking of the lips and fissuring at the angle of mouth are common.
- Congenital aplasia of the salivary glands may be associated with hereditary ectodermal dysplasia, mandibulofacial dysostosis, congenital aplasia of the lacrimal glands and hemifacial microstomia, etc.

Treatment

Patients with congenital salivary gland aplasia will require continuous dental supervision and administration of systemic or topical fluorides to prevent dental caries.

Hypoplasia of the Salivary Glands

Relative underdevelopment of the salivary gland is known as salivary gland hypoplasia; it may occur either due to their congenital absence of the gland or due to atrophy of the gland, secondary to lack of neuromuscular stimulations or due to hereditary ectodermal dysplasia, etc.

Salivary gland hypoplasia is often associated with Melkersson-Rosenthal syndrome, which consists of cheilitis granulomatosa, facial paralysis and fissured tongue.

The clinical features of salivary gland hypoplasia are the same as seen in salivary gland aplasia but the features are comparatively less severe. It is important to note that hypertrophy of the salivary glands may occur sometimes as a congenital anomaly and it is often associated with a fibrocystic disease called mucoviscidosis.

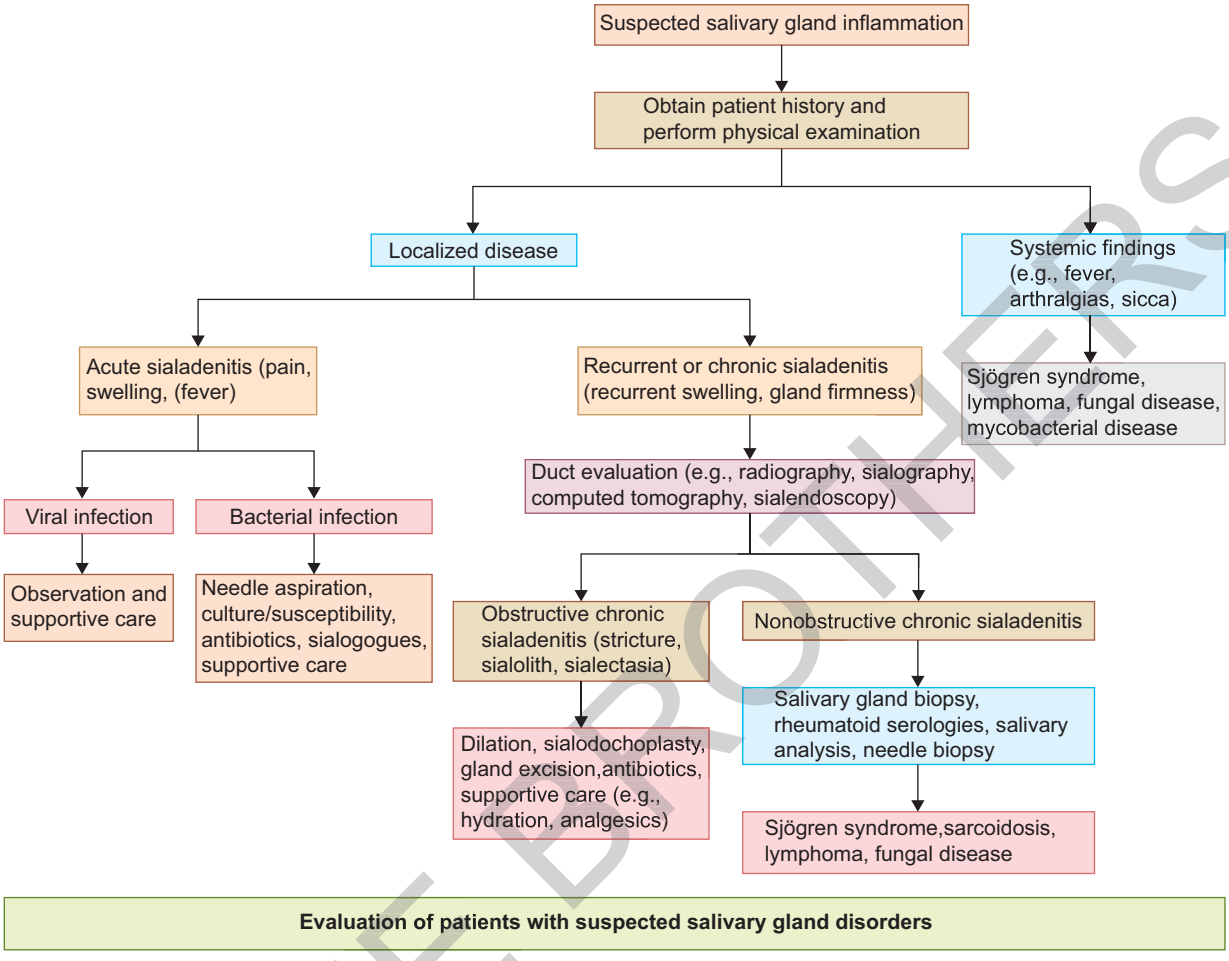
Ectopic/Heterotopic Salivary Glands (Salivary Gland Choristoma)

Definition

Presence of normal salivary gland tissue in anatomically unusual locations is known as salivary gland **ectopia** and such glands are known as ectopic salivary gland (**Table 4.2**).

Besides the major salivary gland tissues, which are having their specific locations, the minor salivary glands are distributed throughout the oral cavity, including the palate, lips, cheek, floor of the mouth, retromolar areas and tongue, etc. Therefore, it is important to know that **ectopic salivary glands are** histologically normal salivary glands, which are **found in abnormal anatomical locations.**

Flowchart 4.2: Algorithm for determining the cause of salivary gland swelling.



Common locations of ectopic salivary glands:

- Sometimes, the salivary gland tissue may be present within the **body of the mandible** and in such cases, the intraosseous gland maintains a communication with the external normal salivary gland with the help of a stalk, which has perforated through the lingual cortical plate of bone.
- Majority of the Stafne's bone cysts and the intraosseous salivary gland tissue within the body of the mandible may occur as part of the phenomenon called 'lingual mandibular salivary gland depression.'
- Ectopic salivary gland tissues may be found in the **gingiva** and where it produces a tumor-like mass, which is known as gingival salivary gland choristoma.
- Sometimes, the ectopic salivary gland tissue may occur within the **masseter muscle, upper part of the neck** in the region of branchial cleft, within **intraparotid or para-parotid lymph nodes** (Neisse Nicholson rests), **maxilla, thyroid and parathyroid, external auditory meatus and pituitary gland**, etc.
- Pathological conditions like sialolithiasis, salivary gland neoplasms and cysts, etc., which commonly affect the normal salivary glands can also involve the ectopic salivary gland tissues.
- Intraosseous ectopic salivary glands may sometimes produce diagnostic confusion during radiographic examinations and ectopic salivary glands can occur in association with other facial anomalies.

TABLE 4.2: Common locations of ectopic salivary glands.

➢ Mandibular body
➢ Gingiva
➢ Masseter muscle
➢ Intra and paraparotid lymph nodes
➢ Upper portion of neck near the branchial cleft
➢ Maxilla
➢ External ear
➢ Thyroid and parathyroid glands
➢ Pituitary gland

Sebaceous glands within normal salivary glands

Sebaceous gland tissues are normally present in the skin, although, these glands may be ectopically present within the major as well the minor salivary glands, (more in the parotids); cells at the periphery of these sebaceous glands are flat with round or oval nuclei, while the central cells have pyknotic nuclei with lipid rich vacuolated cytoplasm.

Atresia (Absence of Ducts)

Atresia of the salivary gland excretory ducts refers to the **congenital absence** or narrowing of excretory duct system.

Atresia is an extremely rare condition, which may produce severe xerostomia and it can also results in the formation of retention cyst in the salivary gland. According to some investigators, there can be another developmental defect in the excretory salivary duct system, which is characterized by absence of the duct orifices. This also can produce salivary retention cyst and xerostomia.

Accessory Ducts

Accessory salivary ducts are relatively common developmental malformations; which can occur in relation to any gland, though it is seen more often in association with the parotids. The accessory parotid ducts are usually found either above or below the normal Stensen's duct. Accessory ducts of the salivary glands most often remain undetected since their presence does not produce any clinical effect in the patient.

Diverticuli

Diverticuli refer to the small pouches or out-pocketing of the ductal system of major salivary glands and is predominantly found in relation to parotids. Diverticuli may produce recurrent swellings and acute sialadenitis due to retention of saliva in those areas where the pouches are present along the course of the duct. Diverticuli can be diagnosed by scalogram.

REACTIVE LESIONS OF THE SALIVARY GLAND

Salivary Gland Cysts

Mucous retention cyst and mucous extravasation cysts are discussed in the chapter of 'Cysts of the oral regions'.

Sialolithiasis

Definition

Sialolithiasis is a pathological condition, characterized by the presence of one or more calcified stones (sialoliths) within the salivary gland itself or within its duct.

Pathogenesis

- The exact mechanism of formation of sialolith is not known; it is generally believed that initially a small and soft nidus forms within the salivary gland or its duct, which is made up of mucin, protein, bacteria, and desquamated epithelial cells. subsequently, concentric lamellar crystallizations to occur due to the precipitation of calcium salts. A small sialolith increases in size with time, as layer after layer of salts become deposited, just like growth rings in a tree.
- Small sialoliths (microliths) can be expelled in the mouth along with the salivary secretions but those, which are not expelled, continue to enlarge until a duct or its branch is completely obstructed.
- It is important to note that the formation of sialolith is **more common in relation to the submandibular glands and its ducts** (about 70–90% cases) and the reason for this could be the following:
  - The submandibular gland ducts (Wharton's ducts) usually have **multiple sharp curvatures,** which can trap mucin plugs and cellular debris and eventually help in the formation of sialolith.
  - Saliva secreted by the submandibular gland is **more viscous** due to high mucin content and this helps in adhering more foreign particles to form cellular nidus.
  - Calcium **content of** submandibular saliva is also high.
  - The **dependent position** of the submandibular gland often **increases the risk of stasis** in the salivary flow.

Clinical Features

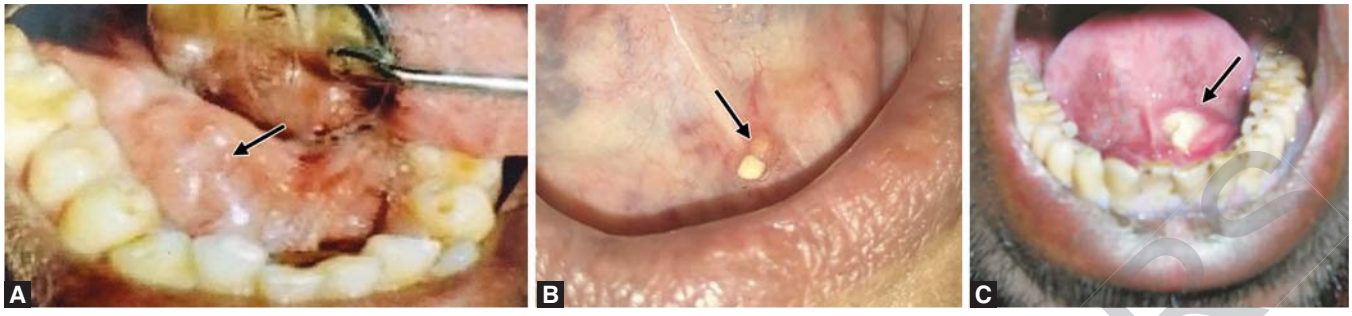
- **Age:** Sialolithiasis usually occurs among middle-aged adults however some cases are reported in children.
- **Sex:** There appears to be a slight predilection for males.
- **Sites:** Majority (70–90%) of the sialoliths form within the excretory ducts of the submandibular gland and sometimes they may occur within the body of the submandibular gland itself.

The parotid gland is the next most involved gland (about 23% cases), while the sublingual and the minor salivary glands are affected in about 4% of cases.

Sialoliths of the minor salivary glands may develop within the glands of the upper lip or buccal mucosa.

Submandibular Gland Calculi More Common Due to Following Reasons:

- *Anatomic factors*
  - The length and irregular course of Wharton's duct
  - The submandibular gland and ductal system lies in a dependent position
  - The greater size and position of the orifice
  - The orifice is much smaller than duct lumen
- *Physiochemical factors*
  - High mucin content of saliva
  - Great degree of alkalinity with high percentage of organic matter
  - Greater concentration of calcium and phosphate salts
  - Low content of carbon dioxide
  - Richness in phosphatase enzyme.



Figs. 4.2A to C: (A) Submandibular sialolith causing recurrent swelling during taking food; (B and C) sialolith in the left submandibular duct.

Points **Sialolithiasis is Responsible for—**

Reduction of salivary secretion, dry mucosa, candidiasis, dental caries, artificial saliva, systemic pilocarpine.

Clinical Presentation (Fig. 4.2)

- In many cases, sialoliths are mostly asymptomatic and are detected only during routine radiographic examination in other cases, the chief complaints are intermittent pain, discomfort, and recurrent submandibular swelling, especially during meals (because the taste and smell of the food increase the salivary secretion).
- The pain occurs due to occlusion of the salivary gland duct by the sialolith, resulting in retention of saliva in the blocked portion of the duct. The pain can be felt like a pulling, drawing or a stinging sensation in the gland.
- The pain and swelling increases when there is complete obstruction of the duct; the pain in such cases can be very severe and stabbing type.
- These symptoms are more often felt when the patient takes any sour food or in cases direct stimulation of salivary secretion is done with a lemon drop candy. The affected glands become enlarged and firm but are still movable.
- The stone or the sialolith in the submandibular gland duct can often be palpated by bimanual palpation with fingers of both hands.
- During examination, the flow and clearness of the saliva at the duct orifice should also be checked; small sialoliths may sometimes be seen, projecting from the duct orifices.
- A persistent swelling of the duct due to chronic obstruction by the sialolith eventually leads to chronic sclerosing sialadenitis.
- Sialoliths usually form unilaterally, however bilateral cases are sometimes reported.
- Multiple stones may develop within ductal branches throughout the gland and long-standing lesions may result in complete calcification of the gland.
- Involvement of the submandibular gland often produces unilateral glandular enlargement, medial to the inferior border of the mandible; the swelling is often firm and tender on palpation.
- Secondary infection in sialolithiasis causes pain, recurrent swelling and formation of sinus tracts or fistulas; ulcerations in the area may also develop in chronic cases. In chronically obstructed glands, necrosis of the gland acini and lobular fibrosis may occur, which results in complete loss of secretion from the gland.
- Parotid stone often causes firm swelling over the ramus of the mandible; the swelling also increases during meals.
- Minor salivary gland stones mostly develop in the upper lip and buccal mucosa; clinically, these lesions produce palpable, hard, movable nodule within the submucosa.
- Sialoliths do not cause xerostomia since, they involve only one or two glands.

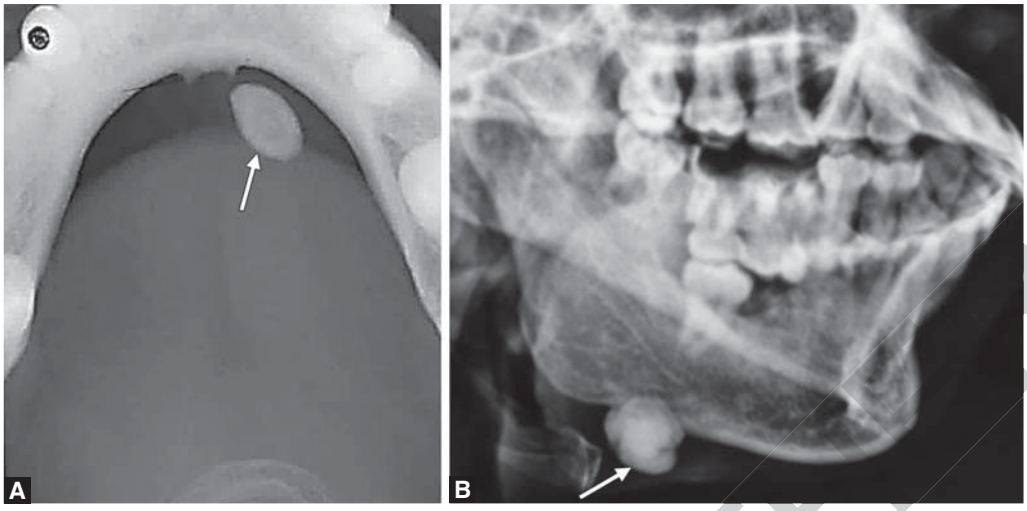
Diagnosis of Sialolithiasis

Radiography (Fig. 4.3)

- Submandibular sialoliths are easily detected by **mandibular standard occlusal radiographs**; which typically disclose the presence of calcification in the floor of the mouth.
- When a sialolith is located within the submandibular gland a **lateral jaw film** may be helpful in detecting its exact location.
- A **panoramic radiograph** usually detects parotid stones.
- If only branches of the submandibular gland duct are affected, a **posterior occlusal film, submentovertex** and sometimes a **lateral jaw film** may be required.
- Sometimes, radiographs may fail to detect a sialolith, it may be either due to superimposition of the sialolith with mandibular bone during radiography or in case, if the sialolith is not fully calcified.

Sialography

Sialography is a method, by which detection of salivary stones within the gland or its duct is done by giving a retrograde injection of a radiopaque dye within the duct system and obtaining a radiograph thereafter in order to see the size and distribution of the sialolith.



Figs. 4.3A and B: Sialolith of the Rt. submandibular gland duct; (A) mandibular standard occlusal view; (B) lateral oblique view.

Ultrasonography and CT Scan

Diagnostic sialendoscopy is another valuable tool in the evaluation and diagnosis of ductal obstructions; in this technique, a mini endoscope is inserted into the duct orifice that allows visualization of the ductal system for any stones, strictures, or adhesions, etc.

Macroscopic appearance of Sialolith

- On gross examination, sialolith appears as a round or oval, rough or smooth surfaced, solid mass of variable size.
- The stones are heavily calcified and are often multinodular, although some stones are found in small aggregates.
- The color of the stone is usually yellowish or yellowish-white.

Composition of Sialolith

Following are the general constituents of a sialolith:

- Calcium phosphate: 75%
- Calcium carbonates: 12%
- Soluble salt: 5%
- Organic matter: 5%
- Water: 3%

Histopathology (Fig. 4.4)

- Microscopically, the salivary stone is acellular and amorphous and when decalcified, it presents concentric laminations of amorphous basophilic matrix.
- The outer margin may exhibit aggregates of microbial colonies; the ductal lining surrounding the stone shows oncocytic, squamous and mucous metaplasia of varying degree.
- Because of metaplasia, the ductal lining of the gland converts into a stratified squamous epithelium, which exhibits many mucous goblet cells.

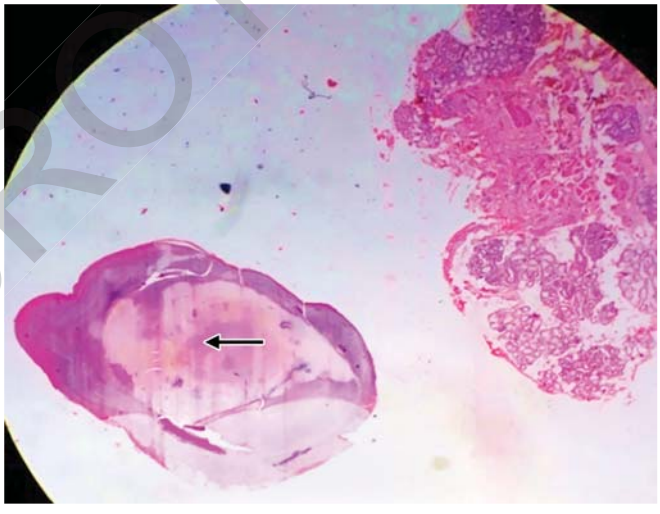


Fig. 4.4: The excised salivary gland along with the sialolith.

- The rest of the gland tissue shows varying degrees of acinar degeneration and intense mononuclear cell infiltration; the gland acini are eventually replaced by fibrous connective tissue.
- In some lesions, secondary retrograde infiltrations may occur and such lesions exhibit infiltration by neutrophils and purulent material within the ductal lumens.

Differential Diagnosis of Sialolithiasis

- Endemic parotitis
- Salivary gland neoplasm
- Mesenchymal neoplasm
- Hypervitaminosis-A
- Calcification of lymph node in chronic long-standing tuberculosis.

Ultrastructural Findings

Ultrastructural studies reveal that the microcalculi (the structural units of salivary stones) are actually formed in the acinar cells of the gland. Normally, these microcalculi are eliminated through the orifice of the duct but whenever there is secretory inactivity or disturbance, the calculi accumulate and lead to the formation of large stones.

Points **Sialolithiasis**

- Sialolithiasis is a pathological condition characterized by formation of calcified stones (sialoliths) within the salivary gland or within its duct.
- It occurs more commonly in relation to the submandibular gland and its ducts.
- The sialolith causes occlusion of the salivary gland duct resulting in retention of saliva which results in intermittent pain, discomfort and recurrent swelling of the affected gland.
- Pain and discomfort occurs especially during meals (as the taste and smell of the food increase the salivary secretion).
- Moreover, the symptoms become more severe when the patient takes any sour food or when direct stimulation of salivary secretion is done with a lemon drop candy.
- The sialolith can be palpated by bimanual palpation with finger of both hands.
- Untreated cases may cause secondary infections in the affected gland which produce pain, ulcerations, swelling and formation of sinus tracts or fistulas, etc.
- The sialolith can be easily detected by mandibular standard occlusal radiographs or by sialography.
- Structurally, the sialolith is acellular and amorphous and it contains about 75% calcium phosphate.
- Surgical removal of the stone is the treatment of choice.

Treatment

- Small stones in the distal parts of the duct can be removed through the orifice by digital manipulation only.
- Whenever, digital maneuvers fail, surgical removal of the stone is indicated; during surgery care should be taken not to push the stones into the salivary gland tissue.
- Lithotripsy sometimes can be used as a noninvasive technique for disintegrating large sialoliths (**Fig. 4.4**).
- Whenever the conditions like intraglandular stones, multiple stones in a single gland or diffuse glandular calcification, etc., occur in association with pain, indurations and chronic lack of function; removal of the stone along with the gland (sialoadenectomy) should be recommended.
- Minor salivary gland stones are treated by simple surgical excision of the stone along with the gland.

[Without treatment of sialolithiasis, recurrent retrograde infection of the gland is common].

Long standing disease with retention of secretions leads to chronic obstructive sialadenitis.

It is important to remember that stones may occur secondarily in association with neoplasms such as acinic cell carcinoma and mucoepidermoid carcinoma and other conditions such as HIV infection].

Postradiation Sialadenitis

Radiation induced sialadenitis is a **common complication of cancer radiotherapy** in the head and neck region; the salivary glands, which come within the field of radiation get damaged.

- The severity of damage of the salivary gland tissue is directly proportional to the doses of radiation used; if the dose of radiation is not very high, it may cause reversible damage to the salivary gland and therefore considerable degree of salivary function may return after several months. In the early phase of therapy, destruction of acinar cells begins and it often causes decrease in the salivary amylase enzyme along with increase in the serum amylase.
- However, in cases of very high dose of radiation, irreversible damage generally occurs in the salivary gland tissue and in such cases the gland acini are replaced by fibrous tissue with development of xerostomia. Serous acini of the salivary gland are more susceptible to radiation damage than the mucus acini.
- Once the glands are damaged, fibrosis occurs, which leads to xerostomia; this may also cause caries in the cervical portion of teeth, oral mucositis, and candidiasis, etc.
- Histologically, the affected gland shows loss of secretory granules, cloudy swelling with edema and neutrophilic infiltration followed by mononuclear cell infiltrations.

Chronic Sclerosing Sialadenitis

Definition

Chronic sclerosing sialadenitis can be defined as chronic inflammation of the salivary gland tissue resulting in degeneration and subsequent replacement of acini by fibrous tissue.

Etiology

- Autoimmune disease
- Systemic and metabolic disorders
- Direct trauma
- Infection
- Occlusion of the duct by calculi
- Compression of the gland or duct by neoplasms
- Salivary glands cysts
- Radiation therapy
- Medication and drugs.

Clinical Features

- The affected salivary gland can be either the major glands or the minor glands and there may be presence of sialolith in the gland or there can be mucous extravasations within the gland tissue.
- The affected gland is often enlarged either due to retention of saliva in the duct or due to inflammatory change.
- The enlarged gland is freely movable and firm in consistency; the firmness increases with time due to more and more fibrosis.

Histopathology

- There will be progressive destruction of the salivary gland acinar cells because of both apoptosis and necrosis.
- There is chronic inflammatory cell infiltration in the gland comprising of lymphocytes and plasma cells.
- Once the acini are lost, the gland parenchyma undergoes progressive sclerosis or fibrosis, although, the ductal tissue remains unaffected.
- Sometimes, there can be retrograde bacterial infection within the remaining duct tissue.

Treatment

- Removal of causative factors, maintenance of oral hygiene and use of artificial saliva to counter the dryness of mouth.
- If the gland is partially destroyed, administration of pilocarpine may stimulate salivary flow; electro stimulatory devices can be effective in stimulating the salivary flow.
- Sialoadenectomy is to be done, in cases the gland parenchyma is completely destroyed.

Necrotizing Sialometaplasia

Definition

Necrotizing sialometaplasia is a benign, self-limiting, reactive inflammatory condition of the salivary gland of unknown etiology; it is characterized by necrosis of minor salivary glands of the palate along with the surface epithelium and the underlying connective tissue. The lesions are self-healing, necrotizing, and variably ulcerative; clinicopathologically these lesions may resemble malignant lesions like squamous cell carcinoma or mucoepidermoid carcinoma.

Predisposing Factors

Ischemic damage to the salivary gland tissue due to obstruction in the vessels supplying them is the most likely cause of this disease; the factors responsible for such obstructions include the following:

- Traumatic injury
- Injection of local anesthetics
- Odontogenic infections
- Smoking and alcohol consumption
- Radiotherapy
- Intubation
- Ill-fitting dentures

Pathogenesis

Many investigators believe that necrotizing sialometaplasia occurs due to infarction of the tissue, although the underlying cause of the infarction is unknown. Moreover, it is not due to the systemic microvascular occlusion or any thromboembolic disease. Some people have reported about initiation of the disease following a local palatal anesthetic injection. It is also associated with long-term intubation complicated by herpetic infection of the trachea, fellatio, Buerger's disease, Raynaud's phenomenon, sickle cell disease and chronic vomiting, etc.

The disease progresses in five stages:

1. Infraction (death of tissue due to lack of blood supply)
2. Sequestration (gradual detachment or separation of tissue)
3. Ulceration
4. Reparation (tissue repair)
5. Healing.

Clinical Features

- **Age:** The disease often occurs in adults and the mean age is about 47 years, although this disease affects women at a much younger age.
- **Sex:** It occurs in males more often than the females with a ratio of 2:1.
- **Site:** Mostly the palate is affected at the region of the junction between hard and soft palate. In some rare cases, the disease can occur in other gland bearing oral mucosal sites such as the lower lip, retromolar pad, tongue and buccal mucosa, etc. Parotid gland is occasionally affected.

Clinical Presentation (Fig. 4.5)

- Necrotizing sialometaplasia initially presents one or two nonulcerated submucosal swellings on the palate with pain and paresthesia; although, many patients can be completely asymptomatic.
- Later, one or two **deep-seated, crater-like or punched-out ulcers** characteristically develop over the hard or the soft palate; which resemble malignant process; although these ulcers do not have any raised or rolled borders.
- Majority of the ulcers measure about 2–3 cm in diameter, which occur unilaterally, sometimes bilaterally; few ulcers may occur in the midline of the palate.
- At the base of the ulcer, there is presence of few grey, granular lobules, representing the necrosed minor salivary glands.

Fig. 4.5: Necrotizing sialometaplasia.

- In fully developed lesions, patients may complain of numbness or burning type of pain in the palate or many patients have a feeling as if 'a part of the palate is falling out', which occurs due to erosion of the palatal bone with perforation.
- Biopsy is mandatory to rule out malignancy; lesions heal spontaneously within 1–3 months.

Histopathology (Fig. 4.6)

The histologic features of necrotizing sialometaplasia are characteristic and highly specific:

- The base of the ulcer shows absence of epithelium, which is replaced by necrotic debris and eosinophilic fibrinous materials.
- The minor salivary gland tissues, which are present below the necrotic debris, exhibit features of **coagulation necrosis.**
- The salivary **acinar cells show absence of nuclei**, these cells are distended and often appear pale and basophilic.
- The cytoplasmic borders of the necrotic acinar cells remain intact and despite the cell damage, the lobular architecture of the salivary gland is also maintained.
- In the zone of necrosis, accumulated mucin is often seen and also there is presence of numerous scattered neutrophils and foamy histiocytes.
- The salivary ductal and acinar cells show **squamous metaplasia** with loss of normal acinar morphology and the metaplastic foci often appear as round or oval epithelial islands; which therefore raises the suspicion of malignancy such as mucoepidermoid carcinoma (due to presence of entrapped mucous cells within the squamous islands) or squamous cell carcinoma (due to the presence of many squamous islands in the lesion), although, no cellular atypia is evident in the lesion, indicating the nonmalignant nature of the disease.
- Pseudoepitheliomatous hyperplasia of the overlying surface epithelium may be seen in some cases and occasionally, mucin pooling within the areas of necrosis and granulation tissue may be seen.

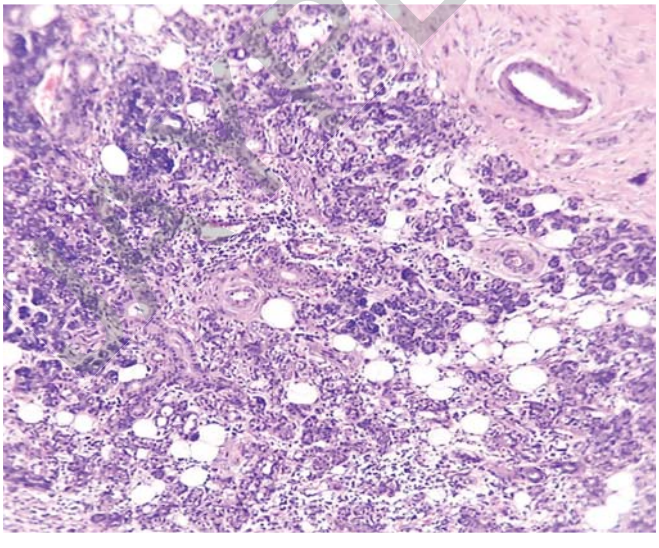


Fig. 4.6: Photomicrograph of necrotizing sialometaplasia.

Immunohistochemistry

In necrotizing sialometaplasia, detection of myoepithelial cells present around the squamous islands by positive immune staining with calponin and smooth muscle actin can distinguish it from squamous cell carcinoma.

Differential Diagnosis of Necrotizing Sialometaplasia

- Mucoepidermoid carcinoma
- Squamous cell carcinoma
- Subacute necrotizing sialadenitis (it has many similar features but squamous metaplasia is absent)
- Adenocarcinoma
- Tuberculous ulcer
- Syphilitic ulcer
- Traumatic ulcer
- Chemical burns

Treatment

Once the diagnosis is confirmed, no treatment is required and the lesion heals spontaneously in about 1–3 months' time.

INFECTIVE LESIONS (SIALADENITIS)

Bacterial Sialadenitis

Acute Bacterial Sialadenitis

Acute bacterial sialadenitis is an uncommon disease, which frequently affects the parotid gland. Therefore, the disease can be synonymous to "acute parotitis or acute suppurative parotitis". In some cases, the condition can affect the submandibular salivary gland also.

Causative Organisms

Acute parotitis is mostly caused by *Streptococcus pyogenes* and *Staphylococcus aureus*; less commonly *Hemophilus* and *Bacteroides* groups may be involved.

Route of Spread of Infection

In case of acute parotitis, the infection is usually of ascending type and the bacteria reach the gland via the Stensen's duct.

Predisposing Factors

- Previous major surgery (especially abdominal surgery)
- Debilitated and dehydrated patients
- Diabetes, malignancy, prematurely born infants
- Sjogren's syndrome, sialolithiasis
- Immunocompromised patients and use of drugs, which cause reduced salivary secretions.

Clinical Features (Fig. 4.7)

- Sudden onset of painful swelling in the preauricular region; the parotid gland may be involved either unilaterally or bilaterally.
- The constitutional symptoms like fever, malaise and redness of the skin overlying the parotid are often present.
- Many patients complain of trismus and difficulty in swallowing. Intraorally, the parotid papilla is often inflamed and there may be discharge of pus or exudates from the duct opening.
- In some cases, acute parotitis may occur because of acute exacerbation of the pre-existing chronic sialadenitis.

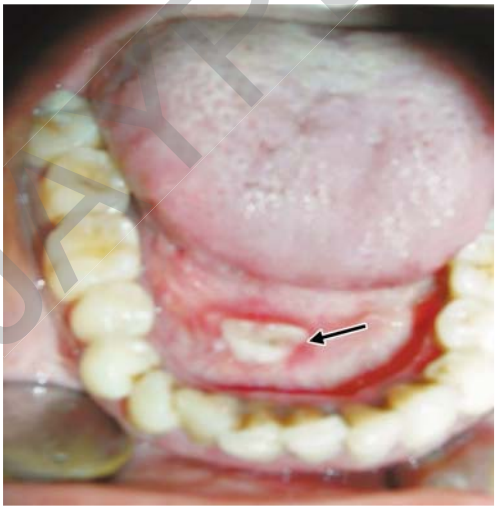


Fig. 4.7: Sialadenitis.

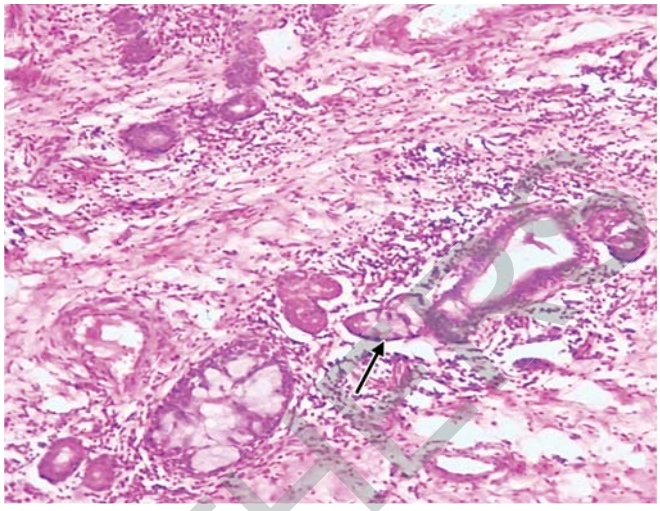


Fig. 4.8: Photomicrograph of acute bacterial sialadenitis.

Histopathology (Fig. 4.8)

The histopathology of acute bacterial sialadenitis reveals interstitial neutrophilic infiltration, acinar destruction, and abscess formation, sometimes with gland enlargement and dilated ducts. The lobular architecture is typically maintained or slightly expanded, and necrotic tissue within the abscesses is common.

Investigation

Bacterial culture from saliva or from parotid secretions.

Treatment

Drainage and antibiotic therapy, management of pre-existing systemic diseases is essential.

Chronic Bacterial Sialadenitis

Definition

Chronic bacterial sialadenitis is a nonspecific inflammatory disease of the salivary gland, secondary to duct obstruction or low-grade sustained ascending infection.

Clinical features

- The condition occurs both in adults and children; the parotid gland is more frequently affected, mostly unilaterally.
- Recurrent tendered swelling of the affected gland with inflammation of the duct orifice; in cases of acute exacerbations, there can be purulent discharge from the duct opening.
- The condition is often associated with decreased salivary flow.

Investigation

- Sialography
- Radiography

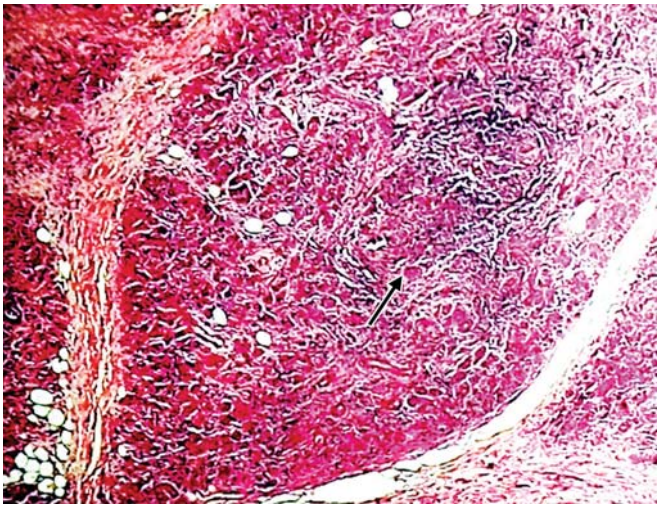


Fig. 4.9: Photomicrograph of chronic sialadenitis.

- Bacterial culture from saliva or secretion of the gland
- Biopsy.

Histopathology (Figs. 4.9)

- Acinar atrophy of the salivary gland with subsequent fibrosis; dilatations of the ductal system with hyperplasia of the ductal epithelium.
- Periductal fibrosis with chronic inflammatory cell infiltration.

Recurrent Parotitis

Recurrent parotitis is a rare condition, which affects both children and adults.

Predisposing factors

- Salivary gland calculi.
- Stricture of the ducts.
- Abnormally low secretion of saliva due to any cause.
- Congenital absence of the duct system.
- Immunosuppression.

Clinical features

- The condition may occur either unilaterally or bilaterally and there is recurrent painful swelling of the affected gland.
- Discharge of pus from the duct orifice is common; some conditions resolve spontaneously.

Viral Sialadenitis

Mumps (Endemic Parotitis)

Mumps is an acute contagious infection of the salivary glands caused by the paramyxovirus.

- It mostly occurs in children between the age of 5 and 18 years and it often spreads as minor epidemic.
- Parotid gland is mostly affected; however, submandibular gland is also involved on few occasions.
- The virus is transmitted by direct contact with infected saliva or by airborne droplets from infected people; incubation period is about 2–3 weeks.
- Infected parotid glands produce acute pain with rapid, often bilateral swelling; recurrent exudation from the duct orifice is often seen.
- Sometimes, other internal organs may be affected by the disease, which include, testes, central nervous system (CNS), ovaries and pancreas, etc.

Details of the disease is discussed in the chapter 8 "Bacterial, Viral and Fungal Diseases".

Cytomegalic Inclusion Disease

Cytomegalic inclusion disease of salivary gland is a common infective disease caused by cytomegalovirus or the human herpes virus 5 (HHV 5) and among the salivary glands, parotid is most frequently affected.

Most of these infections by the virus, affecting the salivary glands are asymptomatic; histologically the infected salivary gland tissue exhibits the presence of large, doubly contoured, **"owl-eye"** shaped inclusion bodies within the nucleus or cytoplasm of the ductal epithelial cells.

Disseminated form of the infection may also affect other vital organs, e.g., kidney, liver, spleen, lungs and brain, etc.

(For detailed description of the disease kindly see the chapter 8 "Bacterial, Viral and Fungal Diseases").

IMMUNE-MEDIATED DISEASE OF SALIVARY GLAND

Mikulicz Disease

Definition

Mikulicz disease is a **progressive, autoimmune disease of the salivary gland** characterized by replacement of gland acini by dense infiltrates of T-lymphocytes, along with squamous metaplasia of the ductal epithelium.

It is a localized benign lymphoepithelial lesion, which frequently involves the parotid and lacrimal glands. According to many investigators, the disease is closely related to Sjogren's syndrome.

Etiology

The exact etiology of the disease is not known; some scientists believe that genetic abnormality or defective cell-mediated immunity probably causes the disease.

Clinical Features

- **Age:** Middle-aged or elderly adults.
- **Sex:** Male predilection.
- **Site:** Parotid, submandibular and lacrimal glands.

Presentation

- Mikulicz disease clinically presents **unilateral or bilateral, diffuse swelling** of the infected glands; the swelling is soft, movable, and painless that often measures about few centimeters in diameter.
- The onset of the disease is often marked by fever, upper respiratory tract infection and any other oral or orofacial infections; most patients have severe xerostomia.
- Sometimes, Mikulicz disease can be a manifestation of Sjogren's syndrome or AIDS.
- Moreover, Mikulicz disease should not be confused with Mikulicz syndrome, which refers to parotid and lacrimal gland enlargements accompanied by the enlargement of lymph nodes; Mikulicz syndrome may represent some generalized specific diseases, e.g., lymphomas or tuberculosis, etc.

Histopathology

- Histologically, Mikulicz disease is characterized by replacement of the salivary gland acini by benign infiltration of lymphocytes with squamous metaplasia of the ductal epithelium.
- Several myoepithelial islands are seen in the infected parotid tissue, which are produced by extensive proliferation of the ductal lining of those parts of the gland that are not destroyed by the disease.
- The proliferating of the ductal epithelial cells may obliterate the lumen of these ducts and in advanced lesions, some eosinophilic hyaline materials are seen within the epithelial islands.

Differential Diagnosis of Mikulicz disease

- Sjogren's syndrome
- Chronic sialadenitis
- Warthin's tumor
- Uveoparotitis
- Malignant lymphoma
- Disseminated tuberculosis
- Metastatic carcinoma of the salivary gland

Points **Mikulicz's Disease**

- Mikulicz's disease or localized benign lymphoepithelial lesion is a progressive autoimmune disease of the salivary gland.
- The disease starts with fever, upper respiratory tract infection and any other oral or orofacial infections, etc.
- Clinically, the disease presents unilateral or bilateral, diffuse, soft, painless swelling of the involved glands with xerostomia.
- It is histologically characterized by replacement of gland acini by dense infiltrates of T-lymphocytes along with squamous metaplasia of the ductal epithelium.
- Treatment is done by steroids.

Treatment

Moderate doses of steroid (20–30 mg prednisolone daily) may help to control the disease.

Sjogren's Syndrome

Definition

Sjogren's syndrome is a multisystem immune-mediated chronic inflammatory disease, characterized by lymphocytic infiltration and acinar destruction of salivary and lacrimal glands. It is one of the **most common autoimmune disorders** together with rheumatoid arthritis and systemic lupus erythematosus (SLE) and shows marked predilection for women.

Pathogenesis

Although, exact etiopathogenesis of Sjogren's syndrome is not known, it is strongly believed that the disease is of **autoimmune nature.** Rheumatoid factors, which are associated with many autoimmune disorders, are frequently present in Sjogren's syndrome; moreover, presence of serum antinuclear antibodies (ANA), e.g., **anti-Sjogren's syndrome-A (anti-SS-A)** and **anti-Sjogren's syndrome-B (anti-SS-B)** also further reiterate the autoimmune origin of this disease. Viruses such as Epstein-Barr virus (EBV) or human T-cell lymphotropic virus, may play a pathogenetic role in Sjogren syndrome.

Clinical Features

- **Incidence rate:** Sjogren's syndrome occurs in 0.5–1% of the population.
- **Age:** Middle aged adults are affected (peak age of incidence from 4 to 6th decade of life).
- **Sex:** Strong predilection for females (M:F ratio is about 20:80)
- **Site:** The disease mainly affects salivary and lacrimal glands; parotid is most frequently affected followed by submandibular gland. Minor salivary glands are affected but they are always asymptomatic.

Sjogren's syndrome is generally classified into two groups (**Table 4.3**):

Clinical Presentation (Fig. 4.10)

- The most common symptoms of Sjogren's syndrome are xerostomia, xerophthalmia and arthralgia (pain in the joints).
- The primary Sjogren's syndromes produce more severe oral and ocular changes than the secondary Sjogren's syndromes (**Table 4.4**).
- Severe tiredness and fatigue are important associated features of the disease with depression in few cases; most of patients usually sleep for about 10–15 hours in a day.

TABLE 4.3: Types of Sjogren's syndrome

Primary Sjogren's Syndrome (SICCA Complex)
➢ When the disease affects only salivary and lacrimal glands, without other co-existing systemic autoimmune diseases, it is called primary Sjogren's syndrome. ➢ Primary Sjogren's syndrome is also referred to as 'sicca **syndrome**' or 'keratoconjunctivitis sicca', which produces the principal features of dry mouth (xerostomia) due to involvement of salivary glands and dry eyes (xerophthalmia) due to involvement of lacrimal glands.
Secondary Sjogren's Syndrome
Secondary Sjogren's syndrome characteristically have xerostomia, xerophthalmia and some associated autoimmune connective tissue disorders including rheumatoid arthritis, SLE, progressive systemic sclerosis, etc. The other associated diseases could be primary biliary cirrhosis, periarteritis nodosa, polymyositis, dermatomyositis or macroglobulinemia, etc.

- Keratoconjunctivitis sicca is an extremely important manifestation of Sjogren's syndrome [sicca means 'dry'], which manifests as dryness of the eyes with conjunctivitis (occurs due to decreased secretion from the lacrimal glands). The dry eyes cause a gritty, burning sensation in the eyes and patients often feel as if there is a foreign body inside the eye, causing blurred vision and itching pain in the eye.
- In case of Sjogren's syndrome, parotid glands are persistently enlarged, often bilaterally and the swelling is usually painless.
- Xerostomia or the dryness of mouth is another important feature of this syndrome, which causes soreness of mouth with difficulty in eating, swallowing, and talking, etc.

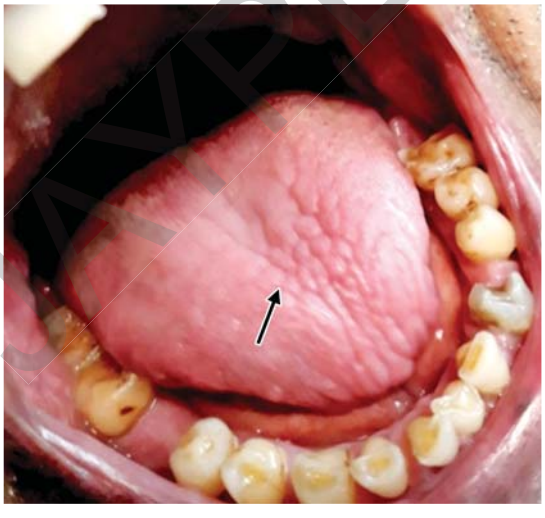


Fig. 4.10: Sjogren's syndrome showing dry mouth and 'cobble stone' appearance of tongue.

TABLE 4.4: List of general signs and symptoms in Sjogren's syndrome.

Eye	➢ Conjunctivitis ➢ Dry eyes ➢ Corneal ulceration
Oral	➢ Xerostomia ➢ Burning mouth ➢ High caries index ➢ Oral ulcerations ➢ Difficulty in chewing and speech ➢ Disturbed taste sensations ➢ Candidiasis
Neurological (central)	➢ Poor concentration ➢ Brain fog
Neurological (peripheral)	➢ Neuropathy (numbness and tingling of extremities)
Skin	➢ Dry skin, vasculitis ➢ Raynaud's phenomenon
Digestive system	➢ Stomach upset ➢ Gastroparesis ➢ Autoimmune pancreatitis
Throat	➢ Dyspahgia ➢ Heartburn ➢ Reflux esophagitis
Respiratory	➢ Recurrent bronchitis ➢ Pneumonia
Muscle and joints	➢ Arthritis ➢ Muscle pain
Sino nasal system	➢ Dry nose ➢ Epistaxis ➢ Sinusitis
Hepatic system	➢ Disturbed liver function ➢ Autoimmune hepatitis ➢ Biliary cirrhosis
Genital	Dryness of genital mucosa

- Oral mucosa appears red, dry, tendered, smooth and glazed; often there is a 'parchment-like' **appearance** of the mucosa. Besides oral mucosa, patients may have dryness of the nasal, pharyngeal and laryngeal mucosa.
- About 88% cases exhibit decreased salivary flow of the submandibular and sublingual glands and parotid salivary flow decreases in about 55% cases.
- The saliva appears frothy and there can be altered taste sensation and associated oral candidiasis; few patients develop angular cheilitis and most patients feel difficulty in wearing denture due to persistent dryness of mouth.
- Xerostomia and recurrent candidiasis mostly affect the tongue; the dorsum of tongue reveals red and atrophic

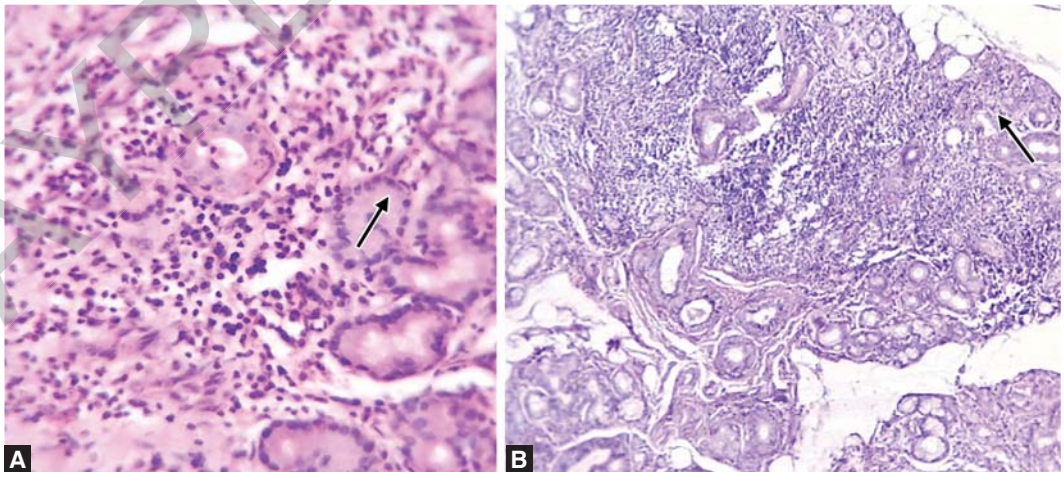
mucosa with varying degrees of fissuring and lobulations on the surface ('cobble-stone' appearance).
- There is often secondary acute bacterial sialadenitis characterized by fever and purulent discharge from the duct orifice. Moreover, development of rapidly progressive dental caries (typically in the cervical areas of teeth) is also common.
- In Sjogren's syndrome, the parotid swelling is painless; however, in suppurative parotitis, the swelling of the gland is painful and affected gland is hot on palpation, tendered and the overlying skin appears red and inflamed.
- Although parotid gland is predominantly affected, sometimes submandibular or minor glands can also be affected; enlargement of lacrimal glands is rare.
- Sjogren's syndrome is associated with an increased risk of development of extra-salivary malignant lymphoma.
- Causes of Xerostomia are given in **Table 4.5**.

Histopathology (Fig. 4.11)

Histologically, Sjogren's syndrome reveals the following features
- Initially, there is mild infiltration of lymphocytes in the intralobular ducts of the involved salivary gland; gradually the lymphocytic infiltration becomes more intense, causing destruction of gland parenchyma with atrophy of the gland acini along with proliferation of the ductal epithelial cells.
- The hyperplasia of the ductal epithelium eventually obliterates the ductal lumen and this leads to the formation of discrete islands of epithelial tissue, which are known as the myoepithelial islands.
- In the fully developed lesions, the entire glandular tissue is replaced by multiple myoepithelial islands, which are surrounded by proliferating lymphoid tissue; moreover, lymphoid follicles with germinal center formation may be noted in areas of dense lymphocytic infiltrations.
- The lobular architecture and the capsule of the major glands remain unchanged.

TABLE 4.5: Causes of Xerostomia.

Temporary causes	➢ Playing or outdoor activity for long time on a hot day ➢ Psychological disorders, e.g., anxiety and depression ➢ Consumption of alcohol, smoking ➢ Sialadenitis ➢ Medications like-atropine, antihistaminic, bronchodilators, diuretics and antidepressants ➢ Impaired fluid intake in the body or increased fluid loss ➢ Dehydration due to diarrhea/vomiting and hemorrhage
Permanent causes	➢ Aplasia of the salivary glands in hereditary ectodermal dysplasia ➢ Artesia (missing ducts) of salivary glands ➢ Radiotherapy in the head/neck region with permanent destruction of salivary gland ➢ Sjogren's syndrome ➢ Diabetes mellitus and diabetes insipidus ➢ Vitamin deficiency (A and B complex) ➢ Sarcoidosis, HIV-associated salivary gland disease, amyloidosis ➢ Pernicious and Iron deficiency anemia ➢ Graft versus host reaction ➢ Parkinson's disease ➢ Defective secretomotor stimulations and ageing



Figs. 4.11A and B: (A) Photomicrograph of Sjogren's syndrome showing damage to salivary gland tissue with metaplasia of ductal epithelium; (B) salivary gland tissue replaced by inflammatory cells.

Investigations in Sjogren's Syndrome

- **Biopsy:** Labial salivary gland biopsy is a helpful investigative method in establishing the diagnosis of Sjogren's syndrome.
- **Sialography:** In Sjogren's syndrome, sialography often produces a **'snow-storm'** or **'cherry tree in blossom'** like appearance.
- **Scintigraphy:** Salivary scintiscanning using [Tc-Pertechnetate] reveals reduced uptake of the isotope in Sjogren's syndrome. Although, the normal salivary gland tissue usually shows an increased uptake of the said isotope.
- **Staining:** The keratoconjunctivitis sicca is characterized by corneal keratotic lesions, which stain pink when "rose Bengal" dye is used. [Rose Bengal is a sodium salt containing stain, which is commonly used in eye drops to stain damaged conjunctival and corneal cells.]
- **Schirmer test:** The reduced lacrimal flow rate in Sjogren's syndrome is measured by this test; a strip of filter paper is placed in between the eye and the eyelid to determine the degree of tearing, which should be measured in millimeter. When the flow is reduced to less than 5 mm in a 5 minutes of sample period, the patient should be considered positive for Sjogren's syndrome.

Points **Sjogren's Syndrome**

- Sjogren's syndrome is a multisystem immune-mediated chronic inflammatory disease of the salivary and lacrimal glands which predominantly affects women.
- The disease occurs in two forms-primary and secondary:
  1. When the disease affects only salivary and lacrimal glands without other coexisting systemic autoimmune diseases, it is called primary Sjogren's syndrome.
  2. Secondary Sjogren's syndrome affects salivary and lacrimal glands and it is also characteristically associated with autoimmune connective tissue disease, usually the rheumatoid arthritis.
- Although, exact etiopathogenesis of Sjogren's syndrome is not known, it is strongly believed that the disease is an autoimmune disorder.
- Primary Sjogren's syndrome is also referred to as "sicca syndrome" in which dry mouth (xerostomia) and dry eyes (xerophthalmia or keratoconjunctivitis sicca) are the principal features.
- Severe tiredness and fatigue are the important features of the disease with depression.
- Secondary Sjogren's syndrome has all the above features and in addition has Rheumatic arthritis and SLE, etc., the former disease causes severe joint pain.
- Histologically the disease is characterized by lymphocytic infiltration and acinar destruction of salivary and lacrimal glands

Specific Laboratory Tests

- Raised ESR
- Diminished total salivary flow rate
- Hypergamaglobulinemia-elevated β_2 microglobulin
- Positive serologic test for rheumatoid factors.
- Immunohistochemistry detects the presence of antinuclear antibodies ANA (anti-SS-A and anti-SS-B) in the serum of large number of patients.

Points **San Diego Criteria for Sjogren's Syndrome**

Primary Sjogren syndrome
- Symptoms and objectives signs of ocular dryness
  - Schirmer's test less than 8 mm wetting per 5 minutes
  - Positive Rose Bengal staining of cornea or conjunctiva to Demonstrate keratoconjunctivitis sicca.
- Symptoms and objectives signs of dry mouth
  - Decreased parotid flow rate using Lashley cups or other methods
  - Abnormal findings from biopsy of minor salivary gland
- Serologic evidence of a systemic autoimmunity
  - Antinuclear antibody (ANA) titer >1:320

Treatment

- Use of artificial saliva
- Use of systemic steroids
- Antibiotic eye drops
- Antifungal drugs to treat secondary candidiasis
- Maintenance of oral hygiene, avoidance of sweets and fluoride applications to control caries.

Prognosis

Patients with Sjogren syndrome have a lifetime risk for lymphoma of 5–15%; prognostic risk factors for lymphoma development include persistent parotid gland enlargement, lymphadenopathy, splenomegaly, neutropenia, low C_4 complement levels, cryoglobulinemia, and palpable purpura. The detection of immunoglobulin gene rearrangements in labial salivary gland biopsies may prove to be a useful marker for predicting the development of lymphoma.

MISCELLANEOUS DISORDERS OF SALIVARY GLAND

Heerfordt's Syndrome

The Heerfordt's syndrome or uveoparotitis is a rare syndrome and is characterized by swelling of the parotid gland, fever and paralysis of the facial nerve.

Sialosis

Definition

Sialosis or sialadenosis is a condition characterized by **bilateral, recurrent, noninflammatory, nonneoplastic enlargement** of the salivary glands.

Etiology

- Disturbance in the neurosecretory control
- Hormonal disturbance such as thyroid insufficiency
- Administration of certain sympathomimetic drugs
- Malnutrition, liver cirrhosis/chronic alcoholism, pregnancy
- Mucoviscidosis (a genetic disease, causing increased viscosity of mucous)
- Diabetes mellitus, Bulimia (an eating disorder, in which patient eats unusually large volumes of food)
- Idiopathic

Clinical Features

- It frequently affects the parotid and occasionally the submandibular salivary gland.
- The swelling may cause little pain and discomfort; however, in some cases, the condition may produce severe pain in the affected glands.

Histopathology

- Hypertrophy of the serous acinar cells, which may be up to twice the normal size.
- The cytoplasm may be packed with secretory granules with edema of the interstitial connective tissue.
- Lipomatosis may occur in the gland.

Treatment

No treatment is generally required, except eliminating the causative systematic factors. In case the severe pain in the affected gland cannot be controlled, surgical excision of the gland may be necessary.

Ptyalism (Excessive Salivation)

Definition

Ptyalism is an abnormal condition characterized by **increased secretion of saliva** in the mouth.

Etiology of Ptyalism (Hypersecretion of Saliva)

- Metal poisoning, abnormal neurosecretory stimulation, ANUG, general stomatitis.
- Aphthous ulcer, psychological stress, major surgery in the mouth.
- Improper swallowing of food due to any cause, wearing of new dentures.
- Idiopathic.

Aptyalism (Xerostomia/Dry Mouth)

Aptyalism is the pathological condition characterized by a decrease or complete cessation of secretion of saliva, causing dryness of mouth. Causes of Xerostomia given in **Table 4.5** and indication given in **Table 4.6**.

TABLE 4.6: Common medications causing Xerostomia.

➢ Anticholinergics	➢ Atropine ➢ Scopolamine
➢ Antihistaminic	➢ Diphenhydramine ➢ Chlorpheniramine
➢ Antipsychotic drugs	➢ Phenothiazine derivatives ➢ Haloperidol
➢ Antihypertensives	➢ Reserpine ➢ Methyldopa ➢ Chlorthiazide ➢ Furosemide ➢ Calcium channel blockers
➢ Antidepressants	➢ Amitriptalyne

Clinical Features of Xerostomia

1. General symptoms

- Soreness, burning or pain sensations in the mouth
- Difficulty in taking foods (especially dry and crispy foods, e.g., cereals and crackers) as it causes irritation and burning sensation.

2. Problems in oral mucosa

- Erythematous changes in the oral mucosa
- Cracking, fissuring and occasional ulceration of mucosa
- Candidiasis
- Red spots over the mucosal surfaces of tongue, hard and soft palate.

3. Tongue problems

- Due to dry sticky oral mucosa, tongue always sticks to the palate
- Atrophy of the tongue papilla with cracking, fissuring and occasional ulceration of the surface.

4. Symptoms in lips

- *'Lipstick sign'* is positive for women (lipstick always sticks to the upper front teeth)
- Inflammation and fissuring of the lips (chelitis).

5. Throat problems

- Constant sore throat and there is difficulty in swallowing.
- Hoarseness of voice and speech difficulty.

6. Change in saliva and salivary gland

- Parotid swelling with sialadenitis
- Little or no pool of saliva in the floor of the mouth
- Whatever saliva is present it looks stringy, ropy or foamy.

7. Tooth and gum problems

- Increase in the incidence of dental caries due to lack of protective action of saliva.
- Increased incidences of periodontal disease with gum bleeding.
- Early tooth loss in adults
- Difficulty in wearing artificial prosthesis.

8. Miscellaneous problems

- Taste disorder (dysgeusia) and burning tongue (glossodynia)
- Increased need to drink water especially at night
- Difficulty in maintaining proper oral hygiene and persistent halitosis
- Dry nasal passage.

Diagnosis of Xerostomia

- Patients history and clinical features in the mouth are important.
- **Sialometry:** Evaluates the salivary flow rate; the normal resting or unstimulated salivary flow rate is about—0.3 to 0.5 mL/minute, while the stimulated salivary flow rate is about 1–2 mL/minute; values below 0.1 mL/minute are considered xerostomia.
- **Sialography:** Imaging techniques to detect stones or other mass inside the gland.
- **Salivary scintigraphy:** Helps in assessing salivary gland function.
- **Biopsy:** Helps to detect cellular changes in the gland.

Treatment

- Removal of local or systemic causes, frequent sipping of sugarless fluids, chewing xylitol containing gums.
- Regular use of artificial saliva (carboxymethyl cellulose containing saliva)
- Antifungal drugs to treat candidiasis, administration of pilocarpine and use of transmucosal neurostimulatory devices to stimulate the salivary secretion.
- Avoidance of antihistaminic and decongestant drugs.

NEOPLASM OF THE SALIVARY GLANDS

The salivary gland neoplasms are relatively uncommon entities and they comprise about 3% of all neoplastic disorders of the human body. These neoplasms may be derived from salivary epithelium (parenchymal) or the supportive connective tissues stroma (mesenchymal)

The epithelial tissue neoplasms are more prevalent among adults whereas the mesenchymal tissue neoplasms are more often encountered among children.

The overall incidence rate of salivary gland neoplasms among general population is about 1–3% per 100,000 people. However, the people of Inuit and parts of Scotland exhibit a slight to tenfold increase in the prevalence rate of these lesions **WHO histologic classification of Tumors of the Salivary Glands—2005 and 2022 given in Tables 4.7–4.8** respectively.

About 70% of the neoplasms are derived from the major glands and the rests are developing from the minor glands. Among the major gland neoplasms 90% occur in the parotid gland and about 10% occur in the submandibular gland, however the sublingual gland lesions are exceptionally rare.

The basic unit of a salivary gland is made up of four types of cells in two groups-luminal cells (comprising of acinar and ductal epithelial cells) and abluminal cells (comprising of myoepithelial and basal cells) (**Table 4.9**)

More than 50% of minor salivary gland neoplasms occur in the palate, about 20% lesions develop in the upper lip, lower lip lesions are rare. Malignant variety of salivary gland neoplasms occur far more frequently in relation to the minor glands. Relative frequency of benign and malignant tumors in different salivary glands given in **Table 4.10**

On rare occasion, salivary gland neoplasms may occur as central jaw lesions (mainly in relation to mandible) and in such cases, the neoplasms can be derived from either the ectopic entrapped salivary glands or from mucous metaplasia in the lining of the odontogenic jaw cyst.

Pleomorphic Adenoma

Definition

Pleomorphic adenoma, also known as 'benign **mixed tumor'** is the most common neoplasm of the salivary glands, is defined as "a tumor of variable capsulation characterized microscopically by architectural rather than cellular pleomorphism. Epithelial and modified myoepithelial elements intermingle most commonly with tissue of mucoid, myxoid or chondroid appearances". The basic unit of a salivary gland is made up of four types of cells in two groups—luminal cells (comprising of acinar and ductal epithelial cells) and abluminal cells (comprising of myoepithelial and basal cells). In pleomorphic adenoma the neoplastic ductal epithelial cells and the modified myoepithelial elements intermingle typically with mucoid (resembling mucin), myxoid or chondroid like mesenchymal tissues.

Origin

According to the multicellular theory, these tumors originate from intercalated duct cells and myoepithelial

TABLE 4.7: WHO histologic classification of Tumors of the Salivary Glands—2005.

➢ Malignant epithelial tumors	➢ Benign epithelial tumors
➢ Acinic cell carcinoma	➢ Pleomorphic adenoma
➢ Mucoepidermoid carcinoma	➢ Myoepithelioma
➢ Adenoid cystic carcinoma	➢ Basal cell adenoma
➢ Polymorphous adenocarcinoma	➢ Warthin's tumor
➢ Epithelial-myoepithelial carcinoma	➢ Oncocytoma
➢ Clear cell carcinoma, not otherwise specified	➢ Canalicular adenoma
➢ Basal cell adenocarcinoma	➢ Sebaceous adenoma
➢ Sebaceous carcinoma	➢ Lymphadenoma
➢ Sebaceous lymph adenocarcinoma	➢ Sebaceous nonsebaceous ductal papillomas
➢ Cystadenocarcinoma	➢ Inverted ductal papilloma
➢ Low-grade cribriform cystadenocarcinoma (LGCCC)	➢ Intraductal papilloma
➢ Mucinous adenocarcinoma	➢ Sialadenoma papilliferum
➢ Oncocytic carcinoma	➢ Cystadenoma
➢ Salivary duct carcinoma	➢ Soft tissue tumors
➢ Adenocarcinoma, not otherwise specified	➢ Hemangioma
➢ Myoepithelial carcinoma	➢ Hematolymphoid tumors
➢ Carcinoma ex pleomorphic adenoma	➢ Hodgkin's lymphoma
➢ Carcinosarcoma	➢ Diffuse large B-cell lymphoma
➢ Metastasizing pleomorphic adenoma	➢ Extranodal marginal zone-B cell lymphoma
➢ Squamous cell carcinoma	➢ Secondary tumors
➢ Small cell carcinoma	
➢ Large cell carcinoma	
➢ Lymphoepithelial carcinoma	
➢ Sialoblastoma	

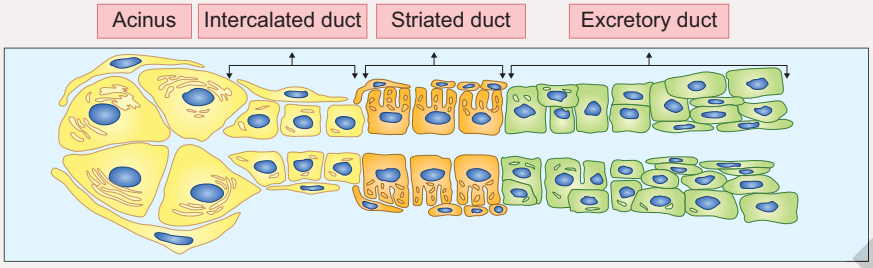
TABLE 4.8: WHO classification of Salivary Gland tumors 2022.

Carcinomas/Malignant epithelial tumors	*Adenomas/Benign epithelial tumors*
➢ Adenoid cystic carcinoma	➢ Pleomorphic adenoma (mixed tumor)
➢ Polymorphous adenocarcinoma	➢ Myoepithelioma
➢ Basal cell adenocarcinoma	➢ Basal cell adenoma
➢ Intraductal carcinoma	➢ Warthin's tumor
➢ Sebaceous adenocarcinoma	➢ Oncocytoma
➢ Mucinous adenocarcinoma	➢ Sebaceous adenoma
➢ Sclerosing microcystic adenocarcinoma	➢ Ductal papilloma
➢ Microsecretory carcinoma	➢ Sialadenoma papilliferum
➢ Salivary carcinoma, NOS and emerging entities	➢ Cystadenoma
➢ Epithelial-myoepithelial carcinoma	➢ Lymphadenoma
➢ Myoepithelial carcinoma	➢ Canalicular adenoma
➢ Squamous cell carcinoma	➢ Sclerosing polycystic adenoma
➢ Salivary duct carcinoma	➢ Keratocystoma
➢ Carcinosarcoma	➢ Intercalated duct adenoma
➢ Lymphoepithelial carcinoma	➢ Striated duct adenoma
➢ Sialoblastoma	
➢ Secretory carcinoma	
➢ Mucoepidermoid carcinoma	
➢ Acinic cell carcinoma	
➢ Carcinoma ex pleomorphic adenoma	
➢ Hyalinizing clear cell carcinoma	

cells of the salivary glands. There is molecular evidence using Human androgen receptor gene (HUMARA) that the epithelial and stromal cells in pleomorphic adenoma arise from the same origin (**Table 4.10**).

Hubner and his associates have postulated that the myoepithelial cell is responsible for the morphologic diversity of the tumor, including the production of the fibrous, mucinous, chondroid and osseous areas.

TABLE 4.9: Tumors developing from different parts of the salivary duct.



Acinus	*Intercalated duct*	*Striated duct*	*Excretory duct*
Acinic cell carcinoma	➢ Adenoid cystic carcinoma ➢ Pleomorphic adenoma ➢ Epithelial-myoepithelial ➢ Carcinoma ➢ Myoepithelioma (from myoepithelial cells on the outer surface of the duct)	➢ Warthin's tumor ➢ Oncocytoma ➢ Polymorphous adenocarcinoma	➢ Mucoepidermoid tumor ➢ Salivary duct carcinoma ➢ Squamous cell carcinoma ➢ Adenocarcinoma

TABLE 4.10: Relative frequency of benign and malignant tumors in different salivary glands.

Gland type	*Overall incidence of tumors*	*Benign tumors*	*Malignant tumors*
Parotid gland	Above 80%	80%	20%
Submandibular gland	Only 15%	50%	50%
Sublingual and minor glands	Only 5%	30%	70%

Regezi and Batsakis postulates that the intercalated duct reserve cell can differentiate into ductal and myoepithelial cells and the latter, in turn, can undergo mesenchymal metaplasia, since they inherently have smooth muscle like properties.

Another researcher (Dardick) stated that, neoplastically altered epithelial cell with the potential for multidirectional differentiation might be histogenetically responsible for pleomorphic adenoma. pleomorphic adenoma gene (PLAG1) has been mapped to chromosome 8q12 might be another theory of tumorogenesis, but not confirmed yet.

Clinical Features (Fig. 4.12)

- **Age:** Pleomorphic adenomas can occur at any age but they develop more frequently in the 5–6th decade of life (mean age of occurrence is 46 years), 10% cases occur in children.
- **Sex:** More common among females than males (60:40).
- **Site:** It accounts for 60–70% of all neoplasms of the parotid 40–60% of submandibular and 40–70% neoplasms of the minor salivary glands (majority of them occur in the palate). It is exceptionally rare in sublingual glands. Minor gland neoplasms may also occur in upper lip (25%) and cheek (10%) and 10% minor gland tumors may occur in nasal cavity, paranasal sinuses and larynx, etc.

Parotid tumors usually arise within the superficial lobe, especially its lower pole, but 10% may occur in the deep lobe or from an accessory parotid gland.

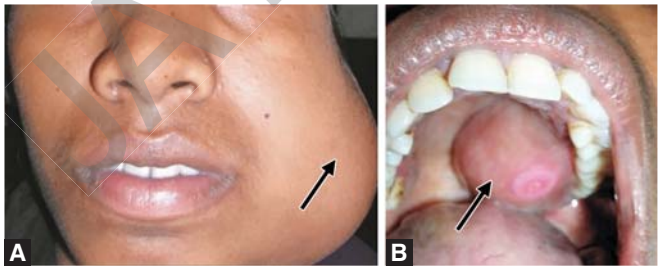
Pleomorphic adenomas may also arise from the heterotopic salivary gland tissue in cervical lymph node; soft tissue of the neck, upper and lower limbs, axilla, and trunk; mandible; lung; breast, lacrimal gland, ear and mediastinum, etc.

Fig. 4.12: Pleomorphic adenoma of the parotid gland.

Pleomorphic adenomas are the most common salivary tumors showing synchronous (co-existing) or metachronous (occurring subsequently) association with other salivary neoplasms, especially with Warthin's tumors, in the same or other glands.

Clinical Presentation (Fig. 4.13)

- Pleomorphic adenoma usually produces a **slow growing, painless, well-delineated, nodular exophytic growth** of the affected salivary gland (**Fig. 4.13A**).
- These lesions take several years to grow to a size of 1 inch in diameter.
- The neoplasm is usually **solitary** but sometimes there can be multiple lesions (multinodular) especially in case of recurrent lesions.
- The surface of the lesion is mostly nonulcerated, smooth, and lobulated, and generally there is no pain.
- Anesthesia or paresthesia of the facial nerve in benign pleomorphic adenomas is rare.
- The neoplasm is usually **soft or rubbery** in consistency and since it is **not fixed** to the overlying or the underlying tissues the tumor is always freely movable. However, the larger tumors are relatively less movable as compared to the smaller lesions.
- Some lesions can be present for many years and **assume massive size;** and the overlying skin or mucosa is generally intact.
- The parotid gland lesions are usually superficial and often arise in the superficial lobe as a small mass overlying the angle of mandible or anterior to the external ear.
- Neoplasms arising from the deep lobe of parotid may not always be detected as a facial mass, since these may protrude in to the lateral wall of the oropharynx.
- Sometimes the lesion can be multinodular and they can assume an enormous size, especially the longstanding lesions.
- The minor gland neoplasms in the oral cavity frequently exhibit slow growing, painless firm, swelling with a **smooth surface. These are mostly seen at the junction of the hard and soft palate unilaterally (Fig. 4.13B).**
- The palatal neoplasms are usually firm in consistency and are less movable due to the tough nature of the palatal mucosa, these lesions sometimes exhibit surface ulceration especially when traumatized.
- Large intraoral lesions are often associated with disturbance in speech and mastication, etc.
- In the buccal mucosa or the lip pleomorphic adenoma presents small, painless, well-defined, movable nodular lesion with intact overlying mucosa.
- Pain in the minor salivary gland tumors indicate infection or infraction within the lesion; palatal lesions sometimes extend into the maxillary antrum and such lesions produce clouding of the antrum in radiographs (**Fig. 4.14**)



Figs. 4.13A and B: (A) Pleomorphic adenoma of the parotid gland; (B) pleomorphic adenoma of minor salivary glands of palate.

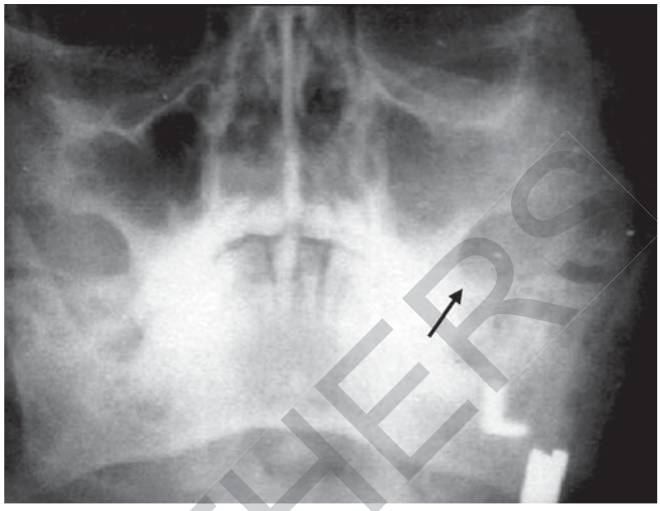
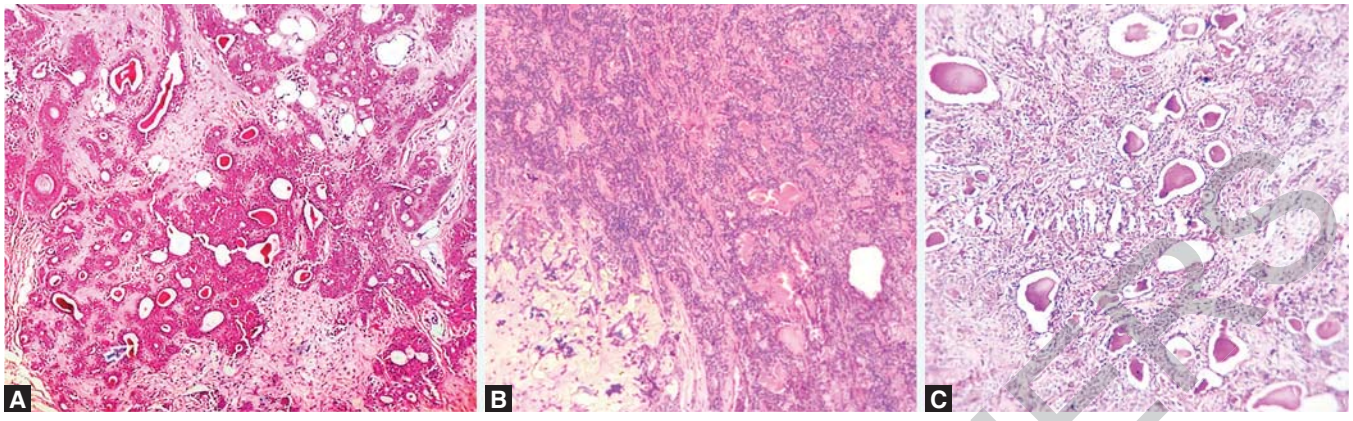


Fig. 4.14: Pleomorphic adenoma of the palate extending into the maxillary antrum.

Macroscopic Findings

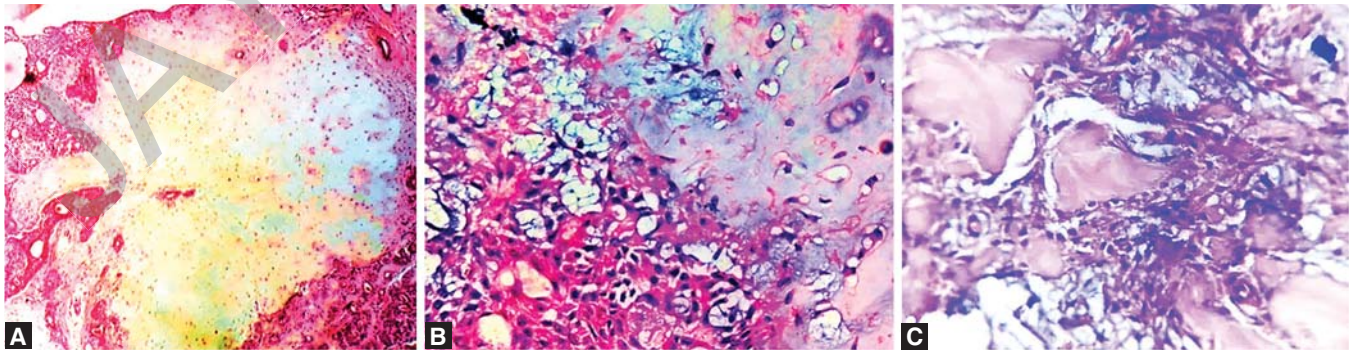
- Macroscopically, pleomorphic adenoma appears as a **well-circumscribed, lobulated, globular mass,** which is surrounded by a **capsule** of variable thickness or completeness.
- On palpation, these lesions feel like rubbery, resilient masses with bosselated surface; the consistency varies between hard to firm, and some tumors can be soft and fluctuant as well.
- The cut surface shows a **variegated appearance** with presence of few hemorrhagic or **cystic areas, the color lesion can be gray-blue or pale yellow.** The tumor sometimes causes compression of the surrounding capsule and isolated nodules of the neoplasm may sometimes be seen within or even outside the capsule.



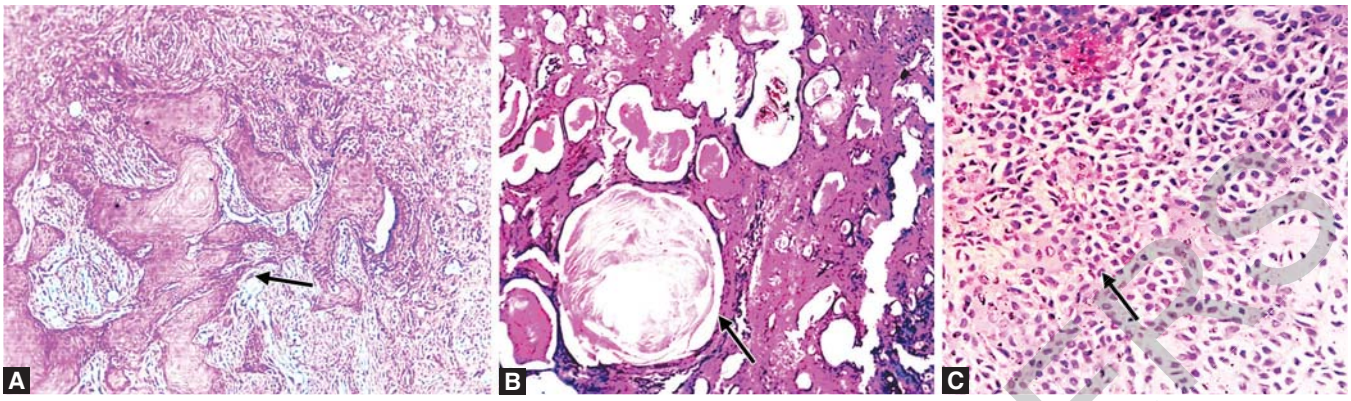
Figs. 4.15A to C: (A and B) Photomicrograph of pleomorphic adenoma showing ductal proliferation with stroma; (C) pleomorphic adenoma high-power.

Histopathology (Figs. 4.15 and 14.16)

- The microscopic appearance of pleomorphic adenoma is highly variable because of the diverse (pleomorphic) nature of the epithelial, modified myoepithelial cells, and the mesenchymal or stromal components of the neoplasm.
- The neoplastic epithelial cells are cuboidal, basaloid, or squamous type and they have tendency to form **duct-like** structures and because of that within the tumor, several duct-like structures are of varying size, shape, number are found. Besides the duct-like structures, the neoplastic epithelial cells may also appear in diffuse **sheets or cords or clusters, etc**.
- Histologically, each duct-like structure exhibits an **inner row of cuboidal or columnar cells** and an **outer row of spindle-shaped** myoepithelial cells. At the center of each duct-like structure, there is often presence of either clear or brightly eosinophilic, PAS-positive material (epithelial **mucin).**
- The myoepithelial cells of the tumor often appear spindle shaped, few cells can be plasmacytoid or clear type; they gradually merge into the surrounding connective tissue stroma. Sometimes these myoepithelial cells may be morphologically similar to the ductal epithelial cells of the tumor, although they do not form ducts. Mixed population of epithelial and myoepithelial cells can be present in solid sheets within the tumor and since they do not form any ducts, these are called 'nonductal cells.
- When the spindle shaped myoepithelial cells constitute the bulk of the neoplastic tissue, the pleomorphic adenoma assumes a 'fibroma-like' appearance and whenever such cells are arranged in palisading growth pattern, the tumor exhibits a schwannoma-like appearance (**Table 4.10**).
- Neoplastic myoepithelial cells sometimes proliferate to form a thick, ill-defined sheath around the salivary gland ducts or in other cases these cells become swollen or hydropic to, appear cartilage-like cells (chondroid change).
- **Squamous metaplasia** is a common finding in pleomorphic adenoma, which may progress to keratin pearls formation by these metaplastic epithelial cells, keratin formation can be observed in both ductal and nonductal epithelial cells (**Fig. 4.17**).
- The connective tissue or the stromal component is often made up of loose, chondromyxoid, hyalinized stroma, which often characteristically exhibits metaplastic changes that results in the formation of **mucoid, myxoid, chondroid and even osseous tissues.** The mitotic activity is rare in the tumor cells.



Figs. 4.16A to C: (A) Photomicrograph of the stromal tissue of pleomorphic adenoma showing myxoid area; (B) myxochondroid area; (C), mucoid stroma (resembling mucous).



Figs. 4.17A to C: (A and B) Photomicrograph of pleomorphic adenoma showing squamous metaplasia of ductal epithelial cells with keratin formation; (C) proliferation of nonductal tumor cells in sheets.

- Such diverse variety of mesenchymal tissues is formed within the tumor due to the pluripotential nature of the myoepithelial cells.
- The fibrous in nature of the stroma is often consisting of either delicate network or of dense bundles of collagen fibers, which may undergo hyalinization to form a structureless, homogeneous material.

In myxoid areas, strands or clumps of epithelial cells are seen widely separated and surrounded by mucoid material. Foote and Frazell (1954) categorized the tumor, based on its histology (**Fig. 4.18**).

- Sometimes fibromyxoid appearance of the stroma is seen with abundant elastic tissues.
- The chondroid areas of the stroma exhibit isolated, rounded epithelial cells lying in lacunae within the mucoid material and osseous tissue may also form due to osseous metaplasia in the stroma.
- The mucoid materials in myxochondroid areas are composed of glycosaminoglycans and consist mainly of chondroitin sulphates.
- Fat cells are frequently seen in the stroma of pleomorphic adenoma, particularly in minor glands; tumors that have a lipomatous stromal component of 90% or more have been called 'lipomatous' pleomorphic adenoma.
- The presence of capsule is also not a consistent finding in pleomorphic adenoma, it can be thick or thin or even absent at places and sometimes extra capsular stellate cell nests are found. Pleomorphic adenomas of the minor glands do not have capsule.
- Histologically, benign lesions may sometimes cause metastasis and such lesions are known as "metastasizing benign pleomorphic adenomas".
- Malignant transformations can occur (less than 1% cases), usually in neoplasms, which have been present from many years.

Points **Pleomorphic Adenoma**

- Pleomorphic adenoma or benign mixed tumor is the most common neoplasm of the salivary glands.

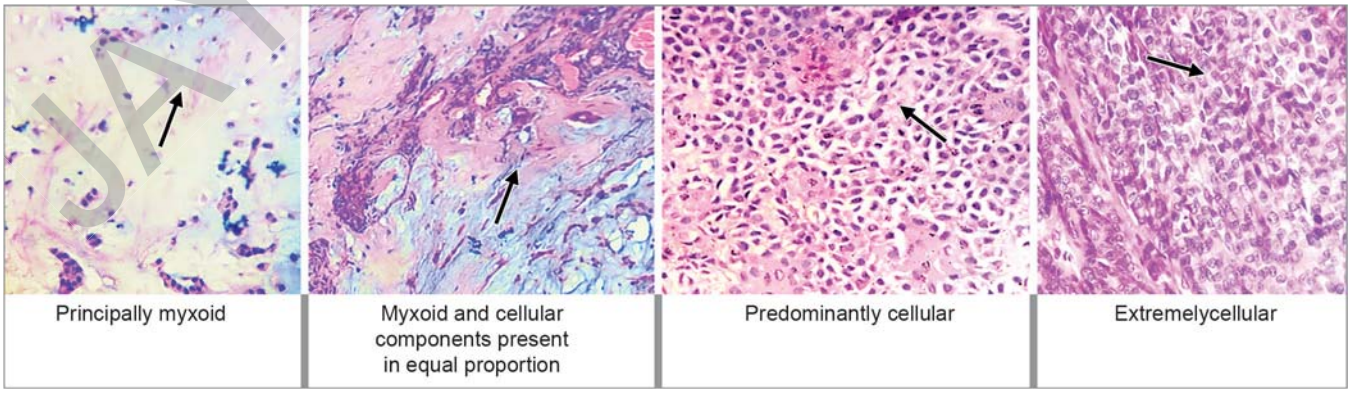


Fig. 4.18: Histological variants of pleomorphic adenoma [Foote and Frazell (1954)].

- It predominantly affects the parotid glands, however submandibular, sublingual and minor salivary glands are also frequently affected.
- Clinically, pleomorphic adenoma usually produces slow growing, painless, well-delineated, nodular exophytic growths.
- Lesions are mostly solitary and may be present in the mouth for years together without giving any symptoms.
- The surface of the lesion is generally nonulcerated, smooth and lobulated, moreover most of the lesions have a soft, rubbery consistency.
- The cut surface of the lesion exhibits a well-circumscribed, lobulated, globular mass, which has a variegated surface and is surrounded by a capsule.
- Microscopically the neoplasm exhibits proliferation of glandular, basophilic epithelial cells in the form of diffuse sheets or clusters.
- These neoplastic have a tendency to form duct-like structures, which are often filled with eosinophilic mucins.
- The connective tissue stroma of pleomorphic adenoma often characteristically exhibits metaplastic changes, which results in the formation of mucoid, myxoid, chondroid and osseous tissues within the tumor.
- Treatment is done by surgical excision, for parotid lesions care must be taken during surgery not to damage the facial nerve.

Differential Diagnosis of Pleomorphic Adenoma

- Polymorphous low-grade adenocarcinoma
- Adenoid cystic carcinoma
- Epithelial myoepithelial carcinoma
- Squamous cell carcinoma
- Mucoepidermoid carcinoma
- Warthin's tumor
- Oncocytoma
- Adenocarcinoma
- Fibroma, lipoma, chondroma or myxoma

(For more details, *See* Annexure-1)

Special Investigation

- Genetic abnormalities in different salivary gland neoplasms depicted in **Table 4.11**
- **FNAC:** Aspiration cytology can be helpful in making the diagnosis of pleomorphic adenomas.
- **MRI:** Magnetic resonance imaging is a reliable diagnostic method in determining the extent of the disease present in major glands.
- **Special stain:** Special stains may be used for the detection and differentiation of specific tissue components, e.g., myxoid, osseous or chondroid tissues of the neoplasm.

Immunohistochemistry: Immunohistologic analysis may provide important information regarding the biological and histological nature of tissues present in this neoplasm. The luminal cells of pleomorphic adenoma are positive for cytokeratin 3, 6, 10, 11, 13, and 16, whereas the neoplastic myoepithelial cells are irregularly positive for cytokeratin 13, 14, and 16 and pan-cytokeratin. The neoplastic myoepithelial cells are positive for vimentin, S-100 protein, glial acidic fibrillary protein, alpha-smooth muscle actin, HHF-35, calponin, and smooth muscle myosin, especially in the myxoid areas and/or in the solid areas.

TABLE 4.11: Genetic abnormalities in different salivary gland neoplasms.

Neoplasm	*Underlying genetic defect*
Pleomorphic adenoma	➢ PLAG-1 and HMGI-C genes ➢ **Chromosomes 3p21,** 8q12 and 12q13–15 rearrangements
Mucoepidermoid tumor and adenocarcinoma	Over-expression of HER-2 gene
Adenoid cystic carcinoma and carcinoma ex-pleomorphic adenoma	Molecular alterations in 12q, 6q and 8q
Warthin's tumor and mucoepidermoid tumor	Translocations of chromosomes 11q21 and 19p13

Treatment

Complete surgical removal of the small lesion is generally curative.

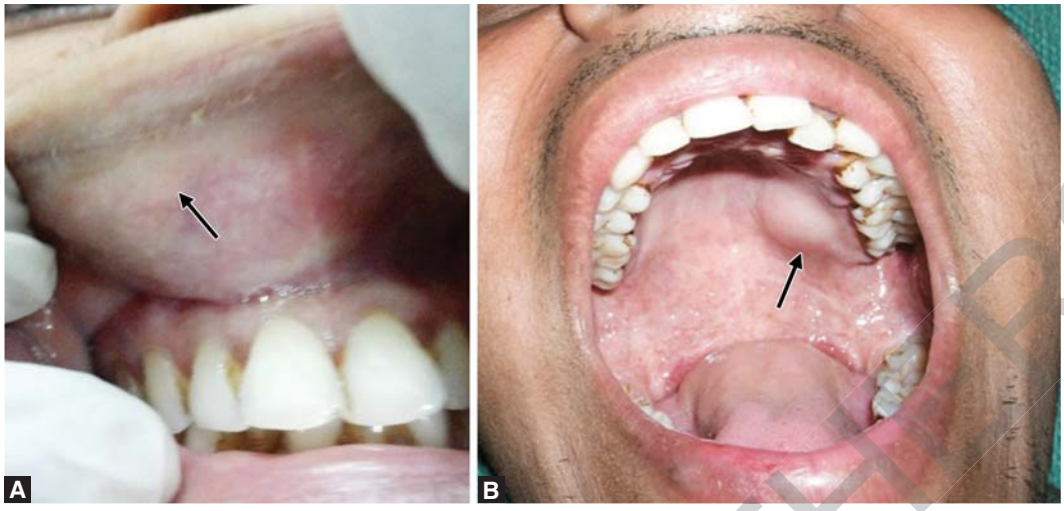
For parotid lesions, surgical excision (lobectomy or gland extirpation) is the frequent choice. Recurrence rate is less than 2%, facial nerve palsy and the auriculotemporal syndrome may be the common complications occurring following surgical intervention in the neoplasms of the parotid gland.

4.1 CASE-BASED QUESTIONS

A 39-year-old female presents with a **slow-growing, painless, firm, mobile swelling** (~3 × 2 cm) over the left parotid region for 1 year. Facial nerve intact. FNAC shows **mixed epithelial and myoepithelial cells in chondromyxoid stroma**.

Questions

1. **Write provisional diagnosis of this case?**
2. **Write differentiated diagnosis of this case?**
3. **What is the confirmatory test for this lesion?**



Figs. 4.19A and B: (A) Monomorphic adenomas of lip; (B) palate.

Monomorphic Adenoma

Definition

Monomorphic adenomas are a group of rare benign salivary neoplasms, characterized by proliferation of a single epithelial cell type that has a distinctive architectural pattern.

Monomorphic adenomas do not exhibit the wide cellular diversities, which are normally encountered in pleomorphic adenomas.

Types of Monomorphic Adenomas
- Basal cell adenoma
- Canalicular adenoma
- Sebaceous adenoma
- Glycogen rich adenoma
- Clear cell adenoma

Among the different types of monomorphic adenomas, basal cell adenoma is the most common type, moreover only the basal cell adenomas and the canalicular adenomas exhibit distinct clinicopathological characters.

Clinical Features of Different Monomorphic Adenomas (Fig. 4.19)

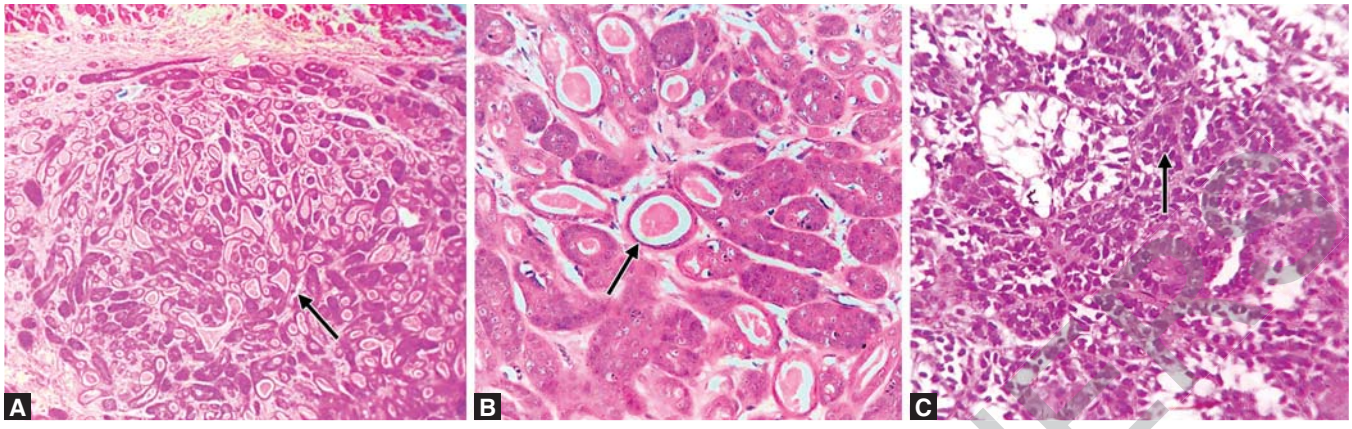
The monomorphic adenomas are generally slow growing, encapsulated lesions, similar to pleomorphic adenomas, however they have a much lower tendency for recurrence after treatment.

Basal cell adenoma

- This monomorphic adenoma commonly occurs almost exclusively in adults (mostly in the 6th decade of life) and more frequently seen among females.
- More than 80% lesions arise in the major salivary glands.
- The lesion involves parotid in about 75% cases, where it develops mostly from the superficial lobe.
- 20% of the lesions are seen in the oral cavity and intraoral lesions commonly arise from the upper lip and buccal mucosa.
- Clinically, basal cell adenomas present slow enlarging, firm, encapsulated, freely movable lesions and they usually measure less than 3 cm in maximum diameter.
- On palpation, these lesions are firmer than pleomorphic adenomas and have a smooth surface.
- One subtype, the membranous basal cell adenoma, deserves separate mention; this form of the tumor appears to be hereditary, often occurring in combination with skin appendage tumors, such as dermal cylindromas and trichoepitheliomas.
- Multiple bilateral tumors may develop within the parotids.

Canalicular adenoma

- Canalicular adenomas usually occur in the 7th decade of life and are rarely seen among children.
- Like other adenomas, these are also more prevalent among females.
- It occurs almost exclusively in the minor salivary glands.
- Minor salivary glands of the upper lip are the most frequent sites of development of this neoplasm (75% cases), followed by buccal mucosa (25% cases), however involvement of the major gland is rare.
- Canalicular adenomas clinically appear as small, painless, movable encapsulated lesions being covered by a smooth intact epithelium.
- The color of the overlying mucosa is generally normal, however in some cases the covering epithelium may have a slight bluish tinge and thus it can be mistaken for a mucocele; (although, mucoceles are rare in upper lip).
- Capsule may or may not be present and there can be multifocal growth on some occasions.



Figs. 4.20A to C: Photomicrograph of monomorphic adenoma: (A) Basal cell adenoma; (B) Tubular type (high-power); (C) Monomorphic adenoma (tubular type).

Histopathology (Fig. 4.20)

Basal cell adenoma

- Basal cell adenomas histologically present clusters of proliferating neoplastic glandular epithelial cells in the form of oval shaped nests.
- The outermost layer of cells, which surround each cell nest are cuboidal type, while the inner core of cells are uniform in size and resemble basal cells of the stratified squamous epithelium.
- The lesion is usually surrounded by a well-defined fibrous capsule.
- The individual, small, well-defined cell nests often resemble basal cell carcinoma of skin.
- In some lesions, there may be proliferation of basaloid cells in diffuse sheets within which keratin pearl formation may be seen.

On the basis of their microscopic appearance basal cell adenomas are divided into four subtypes—solid type, trabecular type, tubular type and membranous type.

1. **Solid type:** In solid type of basal cell adenoma, the neoplastic cells proliferate in solid sheets.
2. **Trabecular type:** This pattern of basal cell adenoma exhibits elongated, anastomosing cords of basal cells, which are surrounded by mature connective tissue stroma.
3. **Tubular type (Fig. 4.20B):**
   - In this pattern, nests of basal cells often surround a duct-like structure.
   - The ducts are filled with homogeneous eosinophilic material and are lined by cuboidal epithelial cells.
4. **Membranous type: This type of basal cell adenomas exhibit islands of n**eoplastic basaloid cells surrounded by a hyalinized basal lamina.

Canalicular Adenoma (Fig. 4.21)

Canalicular adenomas are histologically shows proliferation of neoplastic cells that produce numerous, elongated anatomizing networks of cuboidal and columnar cells, which give the impression of multiple, interconnecting channels or canals and hence the term canalicular has been given. The channels are lined by epithelium and separated by a loose connective tissue stroma with prominent vascularity.

- The nuclei of the cuboidal or columnar cells are elongated or oval and are monomorphic.
- The ductal luminas are often prominent with nuclei polarized towards the basement membrane.
- The connective tissue stroma is myxomatous and is composed of an eosinophilic, hypocellular mucoid matrix.
- The proliferating neoplastic cells are surrounded by a well-delineated capsule.

Canalicular histologic pattern can be seen in both canalicular adenoma and the canalicular carcinoma, an uncommon malignant salivary gland neoplasm.

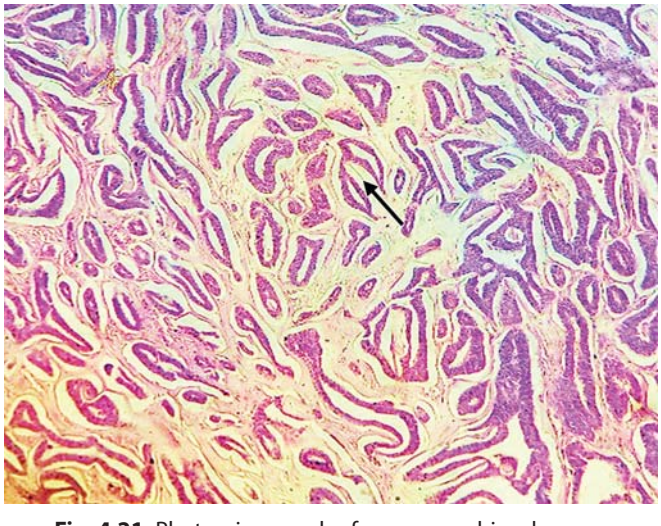


Fig. 4.21: Photomicrograph of monomorphic adenoma (canalicular type).

Clinical Features

- **Sex:** Female predilection
- **Site:** Intraoral salivary gland especially upper lip
- **Age:** 3rd to 6th decade of life.

Treatment

Monomorphic adenomas are mostly nonaggressive lesions and are treated by surgical excision along with little bit of surrounding normal tissue. Recurrence is extremely uncommon.

Myoepithelioma

These are rare salivary gland neoplasms and they account for only 1.5% of all salivary gland tumors. Myoepithelioma is also considered a type of basal cell adenoma without ductal component.

Clinical Features

- **Age:** Mostly occurs in the 5th and 6th decade of life.
- **Sex:** More common in females.
- **Site:** Mostly occurs in relation to parotids (40%) followed by palatal minor glands (21%).

Clinical Presentation

Slow growing, painless mass, the parotid lesions never cause facial nerve palsies and the palatal lesions never ulcerate.

Macroscopic Findings

Myoepitheliomas macroscopically appear as well-circumscribed, frequently encapsulated growths, with features similar to pleomorphic adenomas except the absence of grossly myxoid or chondroid areas. The lesions have solid, tan-yellow, glistening surface, the palatal lesions may not always have capsules but the parotid lesions are almost always encapsulated.

Histopathology (Fig. 4.22)

Microscopically, myoepitheliomas exhibit three distinct patterns:

a. **Spindle cell pattern:** It is the most common histologic type and consists of proliferating spindle shaped neoplastic cells having eosinophilic cytoplasm. The neoplastic cells are often arranged in diffuse sheets or in interlacing fascicles. Myoepitheliomas are hypercellular lesions although there is limited mucoid or myxoid stroma present in them. Due to the presence of spindle shaped myoepithelial cells, it is always difficult to distinguish myoepithelioma from lesions like fibrous histiocytoma, neurilemmoma or leiomyoma, etc. (**Fig. 4.23**).

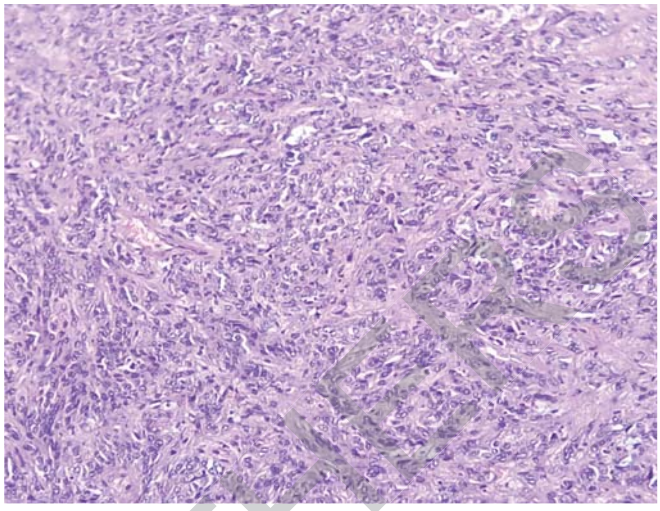


Fig. 4.22: Photomicrograph of myoepithelioma.

b. **Plasmacytoid pattern:** Microscopically this pattern reveals group of round cells with eccentric nuclei and eosinophilic cytoplasm. The neoplastic cells proliferate either as closely packed sheets of round cells or in group of cells separated by a loose myxoid stroma.

c. **Combination pattern:** This type exhibits the combined features of both plasmacytoid and solid patterns.

Malignant counterpart of this tumor is known as myoepithelial carcinoma or malignant myoepithelioma, it is a high-grade malignancy and often occurs in the preexisting pleomorphic adenomas.

Treatment and Prognosis

The tumor is treated by surgical excision. Recurrence is rare.

Oncocytoma (Other name: Oxyphilic Adenoma, Oncocytic Adenoma, Acidophilic Adenoma)

Definition

Oncocytomas are rare benign salivary gland neoplasms occurring primarily in the parotid and are composed of clusters of large eosinophilic granular cells (oncocytes).

Oncocyte is an epithelial cell characterized by an excessive number of mitochondria resulting in an abundant acidophilic granular cytoplasm. It can be benign or can undergo malignancy.

It was first reported by Duplay in 1875 and according to the multicellular theory of salivary gland neoplasms, oncocytomas originate from the striated duct cells.

Clinical Features

- Oncocytoma accounts for about 1% of all the salivary gland neoplasms; usually occur among older individuals, in their 8th decade of life.

Essentials of ORAL PATHOLOGY

A Comprehensive Textbook for Students

Salient Features

- This book maintains its hallmark simple, easy, and lucid language.
- Incorporates WHO 2022 updates on tumors, cysts, and salivary gland neoplasms, along with revised nomenclature.
- Includes additional flowcharts, tables, and summarizing boxes for enhanced readability and efficient revision. Frequently asked comparisons between similar-appearing pathologies have been incorporated.
- Features rare and valuable photomicrographs, significantly boosting the pictorial value of the content.
- Annexures on differential diagnosis of common odontogenic lesions and normal laboratory values added, for better understanding of concept.
- Infographics depicting normal oral histology and histologic lesions have been included.
- Emphasis on etiopathogenesis, with associated syndromes and related pathologies covered in this edition.

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