



MINI-SYMPOSIUM: HEAD AND NECK PATHOLOGY

Non-neoplastic lesions of the salivary glands: New entities and diagnostic problems

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KEYWORDS

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disease

Summary The histopathology of the salivary glands is a complex and difficult area of diagnostic pathology. In the latest WHO classification there are 40 named neoplasms many of which have variable histological features that can challenge even the most experienced specialist pathologist. In addition, the salivary glands can be affected by a range of non-neoplastic conditions, some of which have only recently been described. These often present clinically like tumours and may have pathological features similar to some of the neoplasms, making diagnosis difficult and errors serious. The purpose of this paper is briefly to review non-neoplastic lesions of the salivary glands and to aid the diagnostic pathologist by describing the key histopathological features of each. The entities covered include: sclerosing polycystic adenosis, cheilitis glandularis, salivary gland hyperplasias, necrotizing sialometaplasia, subacute necrotizing sialadenitis, non-neoplastic oncocytic lesions, salivary gland cysts, lymphoepithelial cysts, polycystic (dysgenetic) disease and HIV associated cystic disease.

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Introduction

The histopathology of the salivary glands is a complex and difficult area of diagnostic pathology. In the latest World Health Organization (WHO) classification¹ there are 40 named neoplasms, many of which have variable histological features that

can challenge even the most experienced specialist pathologist. In addition, the salivary glands can be affected by a range of non-neoplastic conditions, some of which have only recently been described. These often present clinically like tumours and may have pathological features similar to some of the neoplasms, making diagnosis difficult and errors serious. The purpose of this paper is briefly to review non-neoplastic lesions of the salivary glands and to aid the diagnostic pathologist by describing the key histopathological features of each.

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Sclerosing polycystic adenosis

This is a recently described, rare, reactive inflammatory lesion of salivary glands that can simulate neoplasia both clinically and histologically.² The pseudoneoplastic appearances resemble those of benign fibrocystic disease of the breast. Of the 32 reported cases, only two have involved minor glands, two the submandibular gland while the remainder affected the parotid glands.²⁻⁵ Most cases formed slow-growing, painless masses of less than 2 years' duration. Macroscopically most lesions were well circumscribed but unencapsulated, with a minority forming multifocal nodules. Microscopically the lesion is characterized by densely collagenized, sparsely cellular fibrous tissue surrounding ill-defined salivary gland ductal and acinar lobules and areas of cystically dilated ductal structures (Fig. 1). The latter are lined by epithelium which can be attenuated or hyperplastic and may show intraluminal papillary projections. In addition, the lining may contain mucocytes, vacuo-

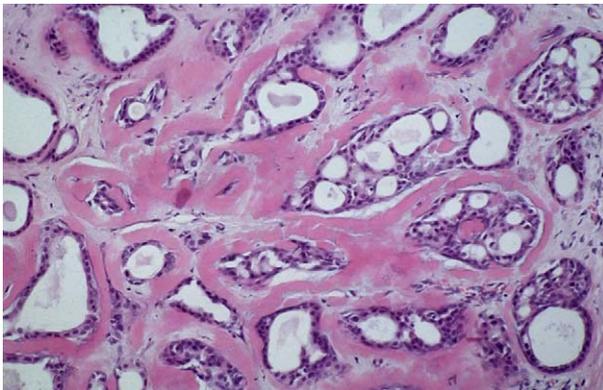


Figure 1 Sclerosing polycystic adenosis showing dilated cyst-like spaces and cells forming a cribriform pattern in a densely hyalinized stroma.

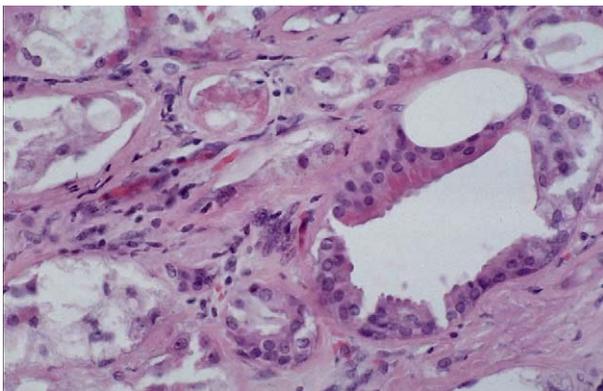


Figure 2 Sclerosing polycystic adenosis showing ducts lined by columnar, eosinophilic and vacuolated cells in a patchily inflamed fibrous stroma.

lated cells, sebaceous cells, apocrine cells and foci of squamous metaplasia (Fig. 2). In some areas interconnecting cellular bridges form a cribriform pattern and this is occasionally associated with hyaline globules of basement membrane material forming collagenous spherules. Areas of atypical hyperplasia of densely granular, eosinophilic acinar cells can be readily mistaken for acinic cell carcinoma. In some cases, ducts show dysplastic changes resembling in situ carcinoma and focal islands of similar cells have also been described.³ However, the lobular architecture is preserved and a layer of myoepithelial cells has been described surrounding the ducts and lobules. There is a variable mixed chronic inflammatory infiltrate and, in some areas, xanthomatous macrophages are a conspicuous feature. One case with a significant lipomatous component has been reported and oncocytic change may be seen.⁵

The most important differential diagnoses are acinic cell carcinoma, adenocarcinoma (NOS) and cystadenocarcinoma. The lobular nature of polycystic sclerosing adenosis, together with the presence of a peripheral myoepithelial layer and the lack of evidence of infiltration should prevent confusion.

The treatment of choice appears to be a complete but conservative local excision. About a third of cases with adequate follow-up, however, have recurred with intervals ranging from ~5–22 years and, in a few cases, the recurrences were multiple. Although these recurrences are probably due to the presence of multifocal disease, the relatively high rate, together with the presence of dysplasia and/or carcinoma in situ means that the possible neoplastic potential of this process has yet to be fully characterized.⁴

Cheilitis glandularis

This is a rare disorder originally described in the minor labial salivary glands and characterized clinically by swelling and focal ulceration. Similar lesions have occasionally been described elsewhere in the oral cavity and the alternative name of *stomatitis glandularis* has been proposed.^{6,7} The large majority of cases affect the lower lip and there is a distinct preponderance in adult males. It has been classified into three types: simple, superficial suppurative and deep suppurative, which may represent part of a continuous spectrum.⁸

The initial lesion is typically an exfoliative cheilitis together with focal swellings of minor salivary glands with red or black puncta. These

often exude viscous, glary mucus, either spontaneously or with minimal pressure. This can progress to foci of frank suppuration with mucopurulent discharge and later scarring with deep fissures and abscess formation.

Microscopy shows variably dilated and tortuous minor salivary gland ducts, together with interstitial acute and chronic inflammation (Fig. 3). The ducts are frequently lined by oncocytic cells with foci of hyperplasia and there may be blunt intraluminal papillary projections. Mucous and squamous metaplasia may be present. The surrounding minor glands show acinar atrophy, interstitial fibrosis and inflammation. In addition, there may be interstitial mucous extravasation and occasionally epithelioid granuloma formation.

The differential diagnosis of cheilitis glandularis includes cystadenoma, cystadenocarcinoma and mucoepidermoid carcinoma. Cystadenomas are usually circumscribed and may be encapsulated. The majority are multilocular and there may be a papillary component. The cysts can be lined by a mixture of cells, including oncocytes, mucocytes, apocrine and sebaceous cells, together with foci of squamous metaplasia. However, the presence of surrounding and intermingled surviving salivary lobules and the obvious inflammatory component in cheilitis glandularis should prevent confusion with cystadenoma. Cystadenocarcinomas can be very well differentiated but the clinical history and the presence of an infiltrative component would aid diagnosis. Low-grade mucoepidermoid carcinomas are also frequently cystic, may be oncocytic and are often associated with a conspicuous inflammatory component due to mucous extravasation. The most useful distinguishing features in cheilitis glandularis showing mucous and squamous metaplasia is again the relationship of the dilated ducts with the surrounding minor salivary gland tissue,

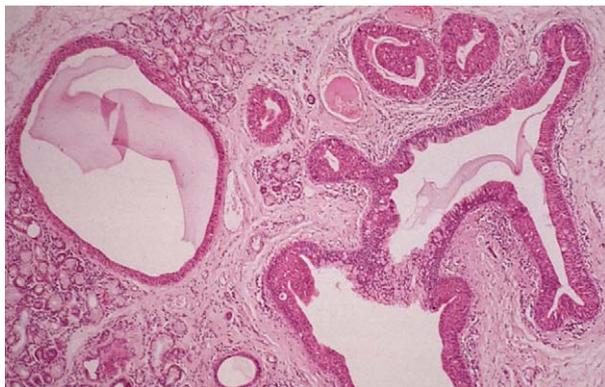


Figure. 3 Cheilitis glandularis: there are oncocytic dilated ducts with residual minor salivary gland tissue and heavily inflamed connective tissue.

the lack of any solid islands of tumour and the absence of infiltration.

The aetiology of cheilitis glandularis is unknown but suggested causes or predisposing factors include genetic predilection, trauma, tobacco use, poor oral hygiene, actinic damage and immunodeficiency.⁹

Most cases respond either to a combination of intralesional or topical steroids and antibiotic treatment, or local surgical excision. However, cases of the deep suppurative type have been associated with the development of squamous cell carcinoma in 18–35% of cases, so closer follow up or more radical treatment may be needed in these patients.

Salivary gland hyperplasia

The terminal duct of salivary glands is a unit consisting of the secretory acinus, intercalated duct and associated myoepithelial cells. Hyperplasia of this complex has two distinct forms: acinar adenomatoid hyperplasia and ductal adenomatoid hyperplasia (DAH).^{10,11} *Acinar adenomatoid hyperplasia* is a rare, idiopathic condition typically affecting the intraoral minor salivary glands, especially those of the palate.¹² It usually presents as a painless, sessile swelling at the junction of the hard and soft palates that frequently mimics a salivary gland tumour clinically. There is an equal sex ratio and the majority of patients are middle-aged. Most cases have been reported in Caucasians and the condition appears to be very uncommon in Asians.¹³ No cases have been reported in association with sialosis (sialadenosis) of the major salivary glands.

Microscopy shows lobules of hyperplastic but otherwise unremarkable mucous acinar cells and essentially normal appearing ducts. In most cases the overlying palatal mucosa was normal but, in one instance, it showed a lichenoid reaction and in another case pseudoepitheliomatous hyperplasia was reported. Occasionally there are foci of interstitial mucous extravasation and an associated inflammatory reaction. The condition is entirely benign and excision is curative.

DAH is very rare and is usually seen as a fortuitous feature in surgical material from major salivary gland specimens, especially tumour resections. There is a 3:1 male predominance and the large majority of cases are seen in the sixth decade.

Microscopy shows one or several unencapsulated foci of proliferation of ducts with structural

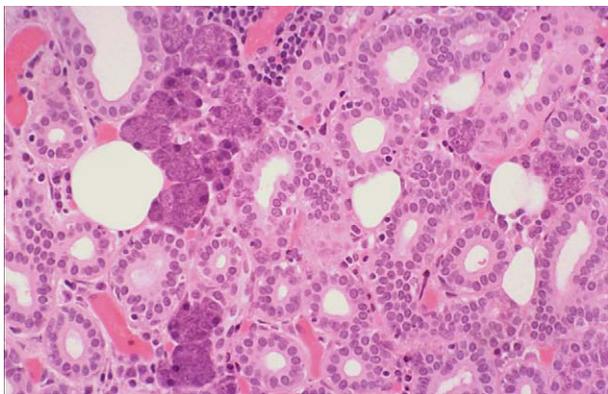


Figure 4 Ductal adenomatous hyperplasia showing a uniform proliferation of duct-like structures engulfing residual normal acini.

similarities to the normal intercalated ducts (Fig. 4). They are densely packed with little supporting stroma and consist of an inner layer of cuboidal cells and an outer layer of myoepithelial cells. There may be residual areas showing acinar differentiation with cells containing basophilic zymogen granules.

Since epithelial–myoepithelial carcinoma is the salivary gland tumour most frequently associated with DAH, it has been speculated that DAH may be a precursor of this tumour and this may also explain the frequent presence of an element of epithelial–myoepithelial carcinomas in hybrid salivary tumours.^{11,14}

Necrotizing sialometaplasia

Necrotizing sialometaplasia is a benign, self-limiting condition that can simulate malignancy, both clinically and microscopically. It was first described by Abrams et al in 1973¹⁵ and many hundreds of cases have subsequently been reported.¹⁶ The most common sites are the minor salivary glands of the oral cavity and oropharynx and especially the palate. Cases have been recorded in the larynx, sinonasal tract and elsewhere in the upper aerodigestive tract. The mean age at presentation is 46 years and there is a 2:1 male predominance. The lesion usually presents as a firm, erythematous nodule that may be several centimetres in size and frequently ulcerates. Bilateral lesions are present in as many as 20% of cases. The lesions may be painful or painless and can also be associated with paraesthesia or anaesthesia.¹⁷

Microscopically there is coagulative necrosis of minor salivary gland tissue with the ghost outlines

of the acinar cells retaining a lobular distribution (Fig. 5). There is frequently mucous extravasation and a mixed acute and chronic inflammatory infiltration. There is usually regenerative hyperplasia of the adjacent salivary ducts with squamous metaplasia. This forms rounded islands and cords of squamous epithelium which show no significant dysplasia (Fig. 5(A)), but occasionally morphologically normal mitotic figures can be seen. Mucous metaplasia may also be present. When the lesion has ulcerated there may be irregular hyperplasia of the overlying or adjacent epithelium which may extend into the underlying tissue as pseudoepitheliomatous, flame-like downgrowths. The lesions heal spontaneously in one to several months, depending on size.

The aetiology of necrotizing sialometaplasia is unknown but salivary gland infarction is probably a unifying feature. Predisposing factors include tobacco usage, vascular diseases such as thromboangiitis obliterans, Raynaud disease, sickle cell disease and trauma. Cases have been described in forced vomiting in bulimia, following local anaesthesia and in excision specimens following previous biopsies.¹⁸

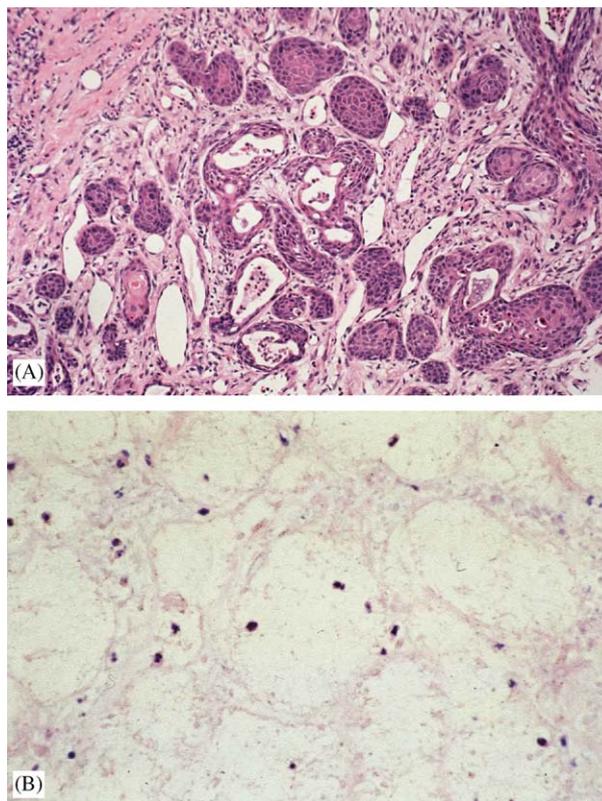


Figure 5 Necrotizing sialometaplasia showing (A) islands of squamous metaplasia with areas of transition from normal ducts and a vascular, heavily inflamed fibrous stroma and (B) ghost outlines of necrotic acini.

The main differential diagnoses of necrotizing sialometaplasia are squamous cell carcinoma and mucoepidermoid carcinoma. The lobular distribution, lack of cytological atypia and transition from more normal ducts should aid differentiation. In addition, low-grade mucoepidermoid carcinomas usually have some cystic elements partially lined by mucocytes rather than incorporated into the squamous islands as in necrotizing sialometaplasia. Finally the ghost-like necrosis and the intensity and acute or chronic nature of the inflammatory infiltrate seen in necrotizing sialometaplasia would be unusual in an epithelial malignancy.

Subacute necrotizing sialadenitis

Subacute necrotizing sialadenitis is a rare, self-limiting and non-specific inflammatory lesion of minor intraoral salivary glands.¹⁹ It shows several features in common with necrotizing sialometaplasia and some believe that both lesions are part of a spectrum of inflammatory damage.²⁰ Most cases of subacute necrotizing sialadenitis present as painful, non-ulcerated and erythematous swellings of the palate and particularly the hard palate. They are usually unilateral and there appears to be a male predominance (male:female = 3.4:1), although this may represent case selection bias in reported cases.²¹ The majority of patients are in the second and third decades of life (mean age = 21.9 years) and the duration of symptoms is usually only several days and rarely exceeds a month.

Microscopy shows diffuse mixed inflammatory infiltration of the minor salivary glands with neutrophils, lymphocytes, histiocytes and frequently eosinophils. There is acinar loss and evidence of focal acinar necrosis. There is ductal atrophy and dilatation and areas of mucous extravasation are common. The lobular necrosis typical of necrotizing sialometaplasia is not seen and squamous metaplasia is not a feature. The lesions usually heal within 2–3 weeks and scarring is usually minimal. The microscopical features, age distribution, site predilection and typical lack of ulceration are thought to differ significantly enough from necrotizing sialometaplasia to make subacute necrotizing sialadenitis an independent entity.

The aetiology is unknown, but possible causes consistent with the clinical and microscopical features include infection and an allergic response. Some studies have shown electron dense bodies suggestive of viral particles.

Oncocytic lesions

A number of lesions containing oncocytes may affect the salivary glands. Most commonly these are defined neoplasms showing various degrees of oncocytic metaplasia. In these cases the diagnosis is made on the basis of the underlying tumour. As noted elsewhere, salivary cysts and cheilitis glandularis may also show areas of oncocytic metaplasia and small areas of ductal oncocytic change are often seen in glands from elderly patients. Lesions composed entirely of oncocytes fall into three categories—*oncocytoma*, *diffuse oncocytosis* and *multifocal nodular oncocytic hyperplasia*.^{22–24} The first two are relatively straightforward to diagnose. Oncocytomas are benign encapsulated tumours composed entirely of oncocytes that are arranged in a solid organoid or acinar pattern with no ducts. They characteristically contain light and dark cells and are solitary lesions.

Diffuse oncocytosis is also a solitary lesion and is usually found in elderly persons, associated with age changes such as acinar atrophy or fatty change. There is diffuse oncocytic change within salivary lobules, but the normal lobular architecture is preserved and normal ducts may be seen. Unlike oncocytomas, the lesions are poorly demarcated but they may contain dark and light cells. Often, only single lobules of the gland are involved but occasionally the whole parotid gland may show diffuse oncocytic change.

Multifocal nodular oncocytic hyperplasia is also thought to be a reactive lesion, but the diffuse multifocal nature of the lesion and common clear cell change may be confused with infiltrative growth and misdiagnosed as a neoplasm. This lesion may also be termed *focal adenomatous oncocytic hyperplasia* since it is characterized by focal accumulations of oncocytes within the acinar component of salivary lobules. Each nodule is diffuse, unencapsulated and with an irregular outline (Fig. 6). Occasionally a whole salivary lobule may be involved, resulting in a well-demarcated accumulation, but normal acini may be preserved at the margin of the nodules and small focal accumulations are seen elsewhere within the gland. The cells appear to be derived from acini, since ductal oncocytic change is not prominent. Light and dark cells, characteristic of oncocytoma, are not seen. The parotid is usually affected and between five and ten nodules are usually seen. If these features are adhered to, diagnosis is usually quite straightforward. The cells are pale eosinophilic, granular and PTAH stain is positive, which may also help in diagnosis. However, misdiagnoses may arise if the multinodular and unencapsulated

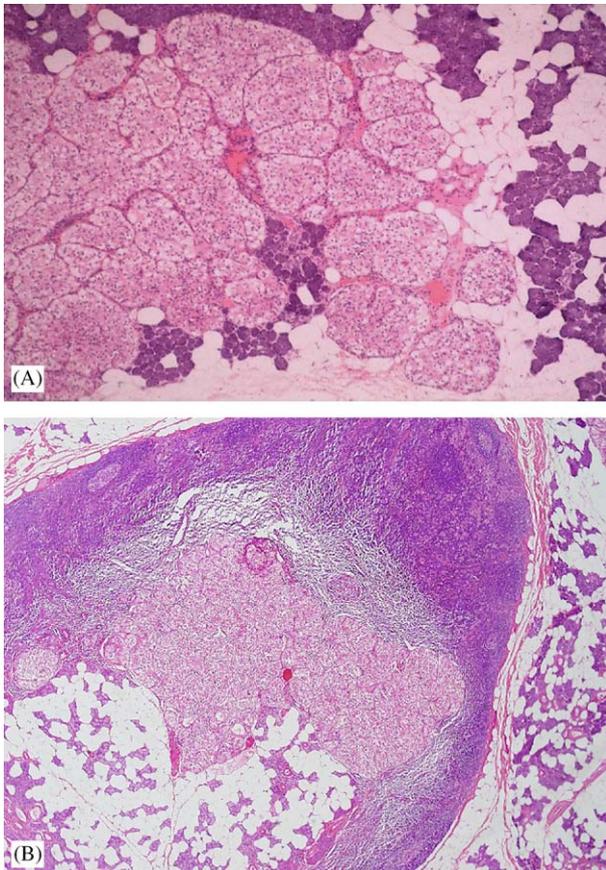


Figure 6 Multifocal nodular oncocytic hyperplasia showing (A) multiple nodules of predominantly clear cells showing pseudo-invasion of adjacent salivary acini and (B) oncocytic nodules occupying the hilum of an intraparotid lymph node simulating metastasis.

nature of the lesions is misinterpreted as infiltrative growth. Rarely, nodules may be found within intraparotid lymph nodes (Fig. 6B) and this must not be misinterpreted as metastasis. The main differential diagnosis is from acinic cell carcinoma, a distinction that may be made more difficult because both lesions may be characterized by clear cell change. Acinic cell carcinomas, however, although infiltrative, rarely have widely separated nodules and usually show more typical acinic areas with more basophilic cytoplasm with prominent periodic acid Schiff (PAS) positive secretory granules. Other features of acinic cell carcinoma may also be found, including microcystic or follicular change. Acinic cell carcinomas are negative for phosphotungstic acid haematoxylin, but may stain positively for amylase. In both lesions, the clear cells appear empty and usually do not contain mucus, but are PAS positive for glycogen. With a PAS/diastase stain, occasional secretory granules may be seen in the apical region of oncocytes in oncocytic hyperplasia, but the clear cells of acinic

cell carcinoma may be negative—a further cause of possible confusion.

Salivary gland cysts

Mucocele

Mucocele are the most common cystic lesions of salivary glands and the large majority form in the minor glands. The main types are extravasation, retention and superficial.

Extravasation mucoceles form about 90% of mucoceles. They are due to trauma to the excretory duct and escape of mucus into the surrounding tissues. However, only a minority of patients can recall a traumatic episode. The most common site, by far, is the lower lip (~50%) but other common sites include the buccal mucosa, floor of the mouth and ventrum of the tongue, palate and buccal mucosa. They typically form bluish, domed swellings that rarely exceed 1 cm in diameter except in the floor of the mouth. Here they are termed ranulae and can be several centimetres in diameter. The peak incidence is in the second and third decades and occasional cases are multiple.²⁵ In the early stages of development, microscopy shows ill-defined pools of mucus and acute inflammation. A central cavity becomes more defined and the cyst becomes lined, firstly, by granulation tissue that undergoes progressive fibrosis. The cyst becomes lined by compressed macrophages, many containing mucus (muciphages), and similar cells are seen floating freely in the cyst cavity. In developing mucoceles the true character of the process may not be immediately apparent unless muciphages are identified, either as foamy macrophages in haematoxylin & eosin (H&E) sections or by histochemical stains. Treatment is by excision of the cyst and related salivary gland or by cryosurgery. Cysts in the tongue, especially, have a tendency to recur, probably because the associated minor glands are mainly located deep within the lingual musculature. It should be noted that mucoceles in the upper lip are uncommon (~5%) and the possibility of a cystic salivary gland neoplasm should always be considered when examining cystic lesions from this site.

Mucous retention cysts are relatively uncommon and are usually seen in older individuals.²⁶ They are thought to be caused by intermittent duct obstruction and form unicystic cavities.²⁷ They are lined by modified duct epithelium that may be cuboidal or columnar and occasionally shows squamous or

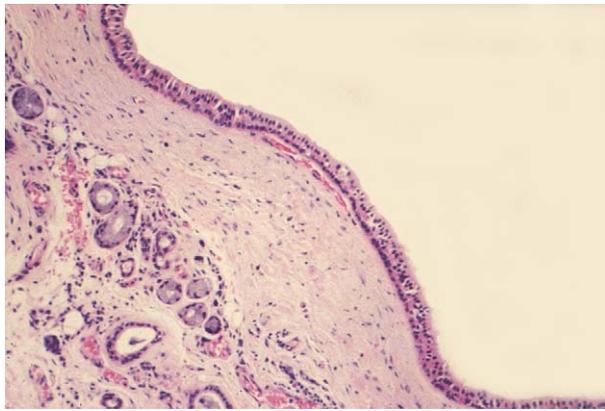


Figure 7 Mucous retention cyst lined by bi-layered ductal epithelium.

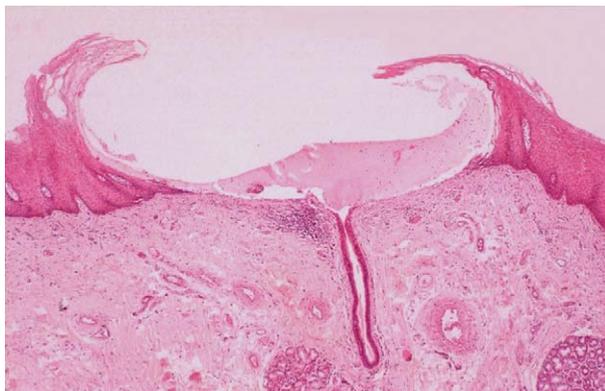


Figure 8 Superficial mucocele: there is a superficial blister-like lesion. The underlying salivary duct opens into the lesion.

mucous metaplasia (Fig. 7). Rarely there is oncocyctic metaplasia.²⁷

Some mucoceles are located immediately below the epithelium and raise a small blister that may rupture (Fig. 8).²⁸ They are seen most frequently in the region of the palatoglossal fold but they can be found elsewhere in the mouth, including the gingiva. They are often multiple and appear to be much more common in women than men. In clinical practice these lesions are not uncommon. Because they form subepithelial vesicles these lesions are sometimes confused with mucocutaneous vesiculating disorders, particularly mucous membrane pemphigoid, both clinically and microscopically.

Salivary duct cyst

Salivary duct cysts (sialocysts) are a form of retention cyst seen in the major salivary glands, particularly the parotid.²⁹ Some cases are associated with evident duct obstruction and occasion-

ally the cyst itself leads to obstructive symptoms. There is no sex predilection and most patients are in their fourth decade or older. They usually form unilocular, painless swellings that rarely exceed 3 cm in diameter. Microscopically they usually have a patchily inflamed, thick, fibrous wall lined by stratified squamous, columnar or cuboidal epithelium. There can be focal mucous or oncocyctic metaplasia and multiple blocks may need to be examined to exclude the possibility of a predominantly cystic low-grade mucoepidermoid carcinoma. Occasionally there is partial calcification of the cyst contents and granulomatous inflammation may be present in the cyst wall and adjacent gland.

Complete surgical excision is curative.

Lymphoepithelial cyst

Lymphoepithelial cysts are uncommon and are seen mainly in the parotid gland, although microscopically similar lesions have been described in the anterior floor of the mouth.^{30,31}

Their putative origin from the branchial arch system³² has been disputed and an origin from Neisse Nicholson rests appears to be more plausible.^{33,34} They resemble salivary duct cysts in clinical presentation and the average age of patients is 45 years. Microscopy shows an epithelial lined cyst with dense lymphoid aggregates containing prominent germinal centres in the cyst wall. The epithelial lining is usually stratified squamous but there may be focal areas of cuboidal or respiratory type epithelium and both mucous and sebaceous metaplasia have been reported.^{35,36}

Polycystic (dysgenetic) disease

This condition is very rare and appears to be developmental in origin.³⁷⁻⁴⁰ One case was familial.⁴⁰ It causes unilateral or bilateral polycystic swellings of the parotid gland and 90% of the reported cases have been in females. Most developed symptoms in childhood, particularly recurrent parotid swellings at mealtimes. Sialography shows punctate sialectasis.

The microscopical features are striking. The lobular structure is preserved but much of the parenchyma is replaced by a honeycomb of cysts of varying sizes (Fig. 9). Residual parenchyma, interlobular septa and excretory ducts lie between the cysts. The cysts are lined by a single layer of flattened or cuboidal cells. Some cells may be oncocyctic or show cytoplasmic vacuolation and many show luminal apocrine blebbing. There can be foci of mural thickening giving a pseudo-papillary

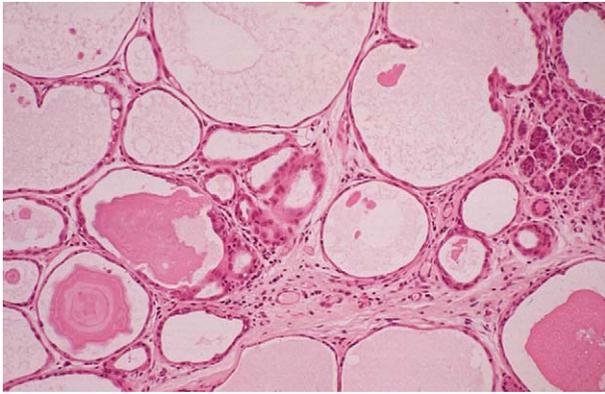


Figure 9 Polycystic (dysgenetic) disease: The parotid gland tissue is almost completely replaced by multiple cysts lined by attenuated ductal epithelium with some lumina containing concentrically laminated concretions.

appearance. Some cysts show constrictions giving an hourglass shape and the presence of incomplete septa extending into the cysts is characteristic. The cysts may fuse with striated ducts or distended acini. Many cysts contain amorphous eosinophilic material and some contain concentrically laminated concretions.

The microscopical differential diagnosis theoretically includes sclerosing polycystic sialadenitis, cystadenoma and cystadenocarcinoma. However, the generalized nature of polycystic (dysgenetic) disease within one or several glands, together with the clinical history, means that confusion is unlikely.

The condition is entirely benign but surgery may be undertaken for cosmetic reasons.

HIV-associated cystic disease

Approximately 5–10% of patients with HIV-1 infection develop parotid enlargement due to lymphoid hyperplasia.^{41,42} In some cases there is also the development of multiple lymphoepithelial cysts.⁴³ These lesions have also been termed AIDS-related parotid cysts (ARPC).⁴⁴ The condition appears to develop early in the disease and precedes the development of AIDS. Patients typically present with unilateral or bilateral painless swellings of the parotid gland and CT scans show multiple cysts in the affected glands. The microscopical features resemble those seen in lymph nodes in persistent generalized lymphadenopathy (Fig. 10). The early lymphocytic infiltrate has a focal periductal distribution that resembles the response seen in Sjögren's syndrome but with a reversed T4/T8 ratio.⁴¹ There is progressive and florid follicular hyperplasia with loss of the mantle zone lympho-

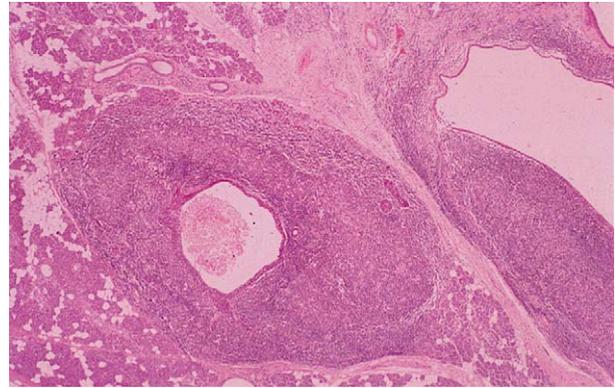


Figure 10 HIV-related salivary gland disease showing focal cystic lymphoepithelial lesions.

cytes and extension into the parotid parenchyma.⁴⁵ In some cases the mantle zone lymphocytes penetrate into the centre of the follicle in a process that has been called 'follicle lysis'.⁴⁶ Warthin–Finkeldy-type giant cells may be present in the lymphoid tissue.⁴⁷ The striated ducts show basal cell hyperplasia and form solid cords that resemble the 'epimyoeptithelial' islands of other lymphoepithelial lesions. Central breakdown of the islands leads to the formation of fully developed ductal cysts. Apparent regression of these lesions following antiviral treatment has been reported.⁴⁸

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