Chapter 3

Pathology of Salivary Gland Disease

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Core Features

- Salivary gland lesions are rare and can be pathologically challenging due to their wide morphologic spectra.
- Non-neoplastic diseases
  - Acute and chronic non-autoimmune sialadenitis each have fairly characteristic pathologic features though they may have a variety of etiologic factors and pathogenetic mechanisms.
  - Autoimmune sialadenitis is largely comprised of the myoepithelial sialadenitis seen in Sjögren's syndrome, though several autoimmune diseases may manifest in the salivary gland. A complication may be B-cell lymphoproliferative disorders. A subset of chronic sclerosing sialadenitis belongs to this group of diseases.
  - Necrotizing sialometaplasia is a benign self-limited process that may histologically mimic squamous cell carcinoma or mucoepidermoid carcinoma. Subacute necrotizing sialadenitis is a relatively newly described related entity.
  - Sialadenosis is a manifestation of generalized metabolic disturbances while adenomatoid hyperplasia is often an incidental finding.
  - Salivary lymphoepithelial cysts of the salivary gland include salivary type, first branchial cleft cysts, and lymphoepithelial cystic disease of HIV. Dysgenetic polycystic disease is an extremely rare entity.
- Benign tumors
  - Pleomorphic adenomas are the most common benign tumors and have a broad histologic spectrum. These tumors can recur if incompletely excised and may rarely metastasize without having histologic features of malignancy.
  - Basal cell adenomas are benign tumors with specific histologic patterns. The membranous type is associated with cylindromatosis gene (CYLD1) mutations, cutaneous syndromes, and can be multifocal and is more likely to undergo malignant transformation. Canalicular adenomas are minor salivary tumors that are clinicopathologically distinct from basal cell adenomas.
  - Myoepitheliomas also have varied patterns and should show at most a few ducts.
  - Warthin's tumor is linked to smoking and older age and is thus demographically distinct from other cystadenomas. Morphologically it has a characteristic lymphoid stroma resembling a lymph node.
  - Oncocytoma and oncocytosis are benign tumors and tumor-like lesions comprised of solid nests of large polygonal cells with abundant granular eosinophilic cytoplasm that may occasionally mimic metastatic renal cell carcinoma.
  - Sclerosing polycystic adenosis is a rare clonal proliferation that resembles fibrocystic disease of the breast, and though benign, may show changes resembling salivary duct carcinoma.
- Malignant tumors
  - Adenoid cystic carcinoma is a slow growing but relentless malignancy for which stage, histologic grade based on solid component, and p53 expression are important prognosticators. These characteristically overexpress c-kit.
  - Mucoepidermoid carcinoma is the most common salivary malignancy with three cell types (mucous, intermediate, and epidermoid). Most grading systems are three tiered and generally correlate with prognosis; mucoepidermoid carcinomas of the submandibular gland appear more aggressive than those of the parotid gland.

Core Features

- Malignant mixed tumors can be subcategorized into carcinoma ex-pleomorphic adenoma, true malignant mixed tumor (carcinosarcoma), and metastasizing mixed tumor.
- Acinic cell carcinoma is a low-grade tumor that can rarely dedifferentiate into an aggressive high grade tumor.
- Epithelial-myoepithelial carcinoma is a rare biphasic low-grade neoplasm characterized by clear myoepithelial cells and small ducts and may mimic other clear cell lesions of the head and neck.
- Basal cell adenocarcinoma resembles its benign counterpart, basal cell adenoma, and is distinguished mainly by the presence of invasion, though ancillary studies such as immunoperoxidase stains for Ki 67, p53, bc1-2, and epidermal growth factor receptor may help in diagnosis.
- Myoepithelial carcinoma also resembles its benign counterpart and is separated mainly by the presence of invasion, mitoses, and necrosis. Nuclear pleomorphism may be a poor prognostic sign.
- Salivary duct carcinoma is a high grade carcinoma that expresses androgen receptor and her-2-neu. It can be confused with low-grade cribriform cystadenocarcinoma, a recently characterized entity that resembles a low-grade mammary type ductal carcinoma.
- Rare malignant tumors include cystadenocarcinomas, large cell carcinoma, small cell carcinoma, and primary squamous cell carcinomas; all but cystadenocarcinomas behave in an aggressive fashion.

Introduction

The major salivary glands are the paired parotid, submandibular, and sublingual glands. Several hundred smaller minor salivary glands are distributed throughout the mucosa of the oral cavity. Morphologically and functionally similar small aggregates of glands are also present throughout the nasopharynx, sinonasal tract, larynx, trachea, and bronchi. These have also been referred to as minor salivary glands, but are probably more correctly referred to as mucoserous glands. Embryologically they all arise from ingrowths of surface epithelium, are histologically similar, and are affected by the same diseases. The anlage of the parotid can be recognized by the fifth week of embryologic life, the submandibular by the sixth, and the sublingual by the seventh. The parotid is considered to be of ectodermal origin while the submandibular and sublingual glands take origin from endoderm. Origin from surface epithelium is the most likely explanation for the occasional finding of sebaceous glands in the major salivary glands. As the epithelial buds of the future salivary glands enlarge, elongate, and branch they develop lumens and their terminal portions expand into acini lined on the luminal side by a single layer of epithelial cells and on the abluminal side by a single layer of myoepithelial cells. The acini of the parotid gland are lined exclusively by serous cells which are packed with zymogen granules. The acini of the submandibular gland are also mainly serous, but also contain acini lined exclusively by mucous cells and others by serous and mucous cells. The mixed acini are lined by mucous cells with crescentic caps of serous cells known as demilunes of Gianucci. The sublingual gland while composed primarily of mucous acini also contains lesser numbers of serous and mixed acini. Minor salivary glands of the palate, retromolar trigone, and ventral tongue are predominately mucous while those of the lateral tongue, lips, and buccal mucosa are seromucous. Those associated with the circumvallate papillae are referred to as von Ebner's glands and are serous. The acini are drained by a series of ducts the smallest of which are the intralobular intercalated ducts. They are lined by a single layer of cuboidal epithelium and a layer of myoepithelial

cells. These in turn drain into the striated ducts so named because of longitudinal infolding of the cell membranes which appears as striations under light microscopy. The striated ducts are also intralobular, but lined by a single layer of epithelium with eosinophilic granular cytoplasm. The intense granular eosinophilia is due to numerous mitochondria. Striated ducts typically lack myoepithelial cells, and are present only in the major salivary glands. Striated ducts drain into the interlobular ducts which are lined by pseudostratified columnar epithelium devoid of a myoepithelial layer. In the major salivary glands these ducts drain into major excretory ducts (Stensen's duct in the parotid gland, Wharton's duct in the submandibular gland, and Bartholin's duct in the sublingual gland) and the epithelium of these ducts changes to squamous as they exit through the oral mucosa. In addition, the sublingual gland also contains several accessory ducts known as Rivinus' ducts. As a result of late encapsulation during embryologic development the parotid gland, unlike the submandibular and sublingual glands, contains intraparenchymal lymph nodes. Late encapsulation is also responsible for the presence of salivary gland structures, usually ducts and less frequency acini, in intra- and periparotid lymph nodes [177, 197, 288, 385, 391, 462].

Lesions of salivary glands are not common but can be pathologically challenging due to their wide range of histologic patterns. Inflammatory and non-neoplastic conditions of salivary glands far outnumber neoplasms which account for less than 3% of all tumors of the head and neck. Approximately one in six parotid tumors, one in three submandibular tumors, and one in two minor salivary gland tumors will be malignant. While tumors of the sublingual gland are extremely uncommon, approximately 80% are malignant [43, 57, 184, 198, 539].

Non-neoplastic Diseases

Acute Sialadenitis

Clinical Features

Acute sialadenitis may involve any salivary gland, though the major salivary glands, particularly the parotid, are most commonly affected [399, 462]. Causes may be bacterial or viral. This entity typically presents unilaterally with localized erythema, swelling, and tenderness in the affected region. Purulent exudate can often be expressed from the excretory duct orifices. Acute viral sialadenitis, in contrast, is preceded by prodromal symptoms including fever, myalgia, and headache and is typically bilateral [399, 462].

Pathology

Grossly, for both acute bacterial and viral sialadenitis, the lobular architecture of the salivary gland is maintained, though the lobules may be expanded and friable with the color ranging from red to yellow. Areas of liquefaction indicative of abscess formation may be present. Cytomegalovirus (CMV) sialadenitis may show no gross abnormalities.

Microscopically, acute bacterial sialadenitis is characterized by acinar destruction with interstitial infiltrates comprised mainly of neutrophils. Multiple small abscesses with necrosis are common. Occasionally, the bacteria can be seen with special stains such as gram stain and acid fast stain, particularly in cases where antibiotics have not yet been administered. Acute viral sialadenitis is rarely examined histopathologically, but consists of a lymphocytic and monocytic infiltrate in the interstitium with vacuolar change in the acini. CMV sialadenitis shows minimal inflammation, but instead may show viral inclusions in both the acini and ducts [195].

Pathogenesis

Bacterial sialadenitis typically occurs as the result of salivary stasis and subsequent retrograde contamination of the salivary ducto-acinar units by oral flora [399, 515]. The parotid is thought to be more prone to bacterial infection since its secretions are predominantly serous and thus lack the protective constituents (IgA, sialic acid, lysozomes) seen in mucinous secretions of the other salivary glands [555, 556]. Causes of salivary stasis include postsurgical setting, dehydration, medical illness, advanced age, radiation, medications, neonatal setting, sialectasia, and sialolithiasis [394, 399, 473]. Bacterial sialadenitis is often polymicrobial. The most common bacterial isolate in acute sialadenitis is *Staphylococcus aureus*. Streptococcal species, most notably the Viridans streptococcal organisms, are also common, and more recently, the contributing role of anaerobic bacteria such as Bacteriodes, peptostreptococcal, and fusobacterial species has been recognized. Rarely, mycobacterial infection may present as an acute sialadenitis rather than a chronic granulomatous sialadenitis (see below) [91, 399, 462, 473, 515].

Viral sialadenitis is typically systemic and can be most commonly attributed to the mumps paramyxovirus. Additional viral isolates include influenza, parainfluenza, Coxsackie A and B, Epstein-Barr, echovirus, and lymphocytic choriomeningitis virus [399, 462]. In the setting of human immunodeficiency virus (HIV), CMV and adenovirus have also rarely been implicated in acute viral parotitis [399].

Prognosis

The prognosis is largely dependent on the patient's underlying disease and its successful treatment. For instance, the reported high mortality (20–50%) reflects the generally poor health status in patients with acute bacterial sialadenitis. A small number will progress to a chronic sialadenitis after resolution of the acute sialadenitis [399].

Chronic Non-autoimmune Sialadenitis

Clinical Features

Chronic non-autoimmune sialadenitis is clinically characterized by a variety of symptoms ranging from a long-standing swelling or mass to xerostomia and superinfection. It may be a result of sialolithiasis which most commonly occurs in the submandibular gland [399, 462]. Chronic sialadenitis, often resulting in xerostomia, is a common and dreaded complication of radiotherapy for head and neck malignant neoplasms [266, 565].

Chronic non-autoimmune sialadenitis is often attributable to a specific etiologic factor such as recurrent obstruction (i.e., sialolithiasis), irradiation, or granulomatous disease [195, 462]. A subset of cases, referred to as chronic recurrent sialadenitis or parotitis, based on the most common site of occurrence, are marked by recurrent painful episodes of swelling and expression of a gray or whitish flocculent material from the duct. Chronic recurrent sialadenitis typically occurs in children or young adults, and may be unilateral or bilateral [60, 462, 503]. Other rare categories of chronic non-autoimmune sialadenitis include infectious granulomatous disease [91, 195].

Pathology

Chronic sialadenitis on gross examination ranges from unremarkable to a firm tan with expansion or atrophy of the lobular architecture depending on the degree of inflammation and chronicity. With sialolithiasis, stones may be grossly evident with associated obstructive changes of sialectasia and periductal fibrosis (Fig. 3.1a).

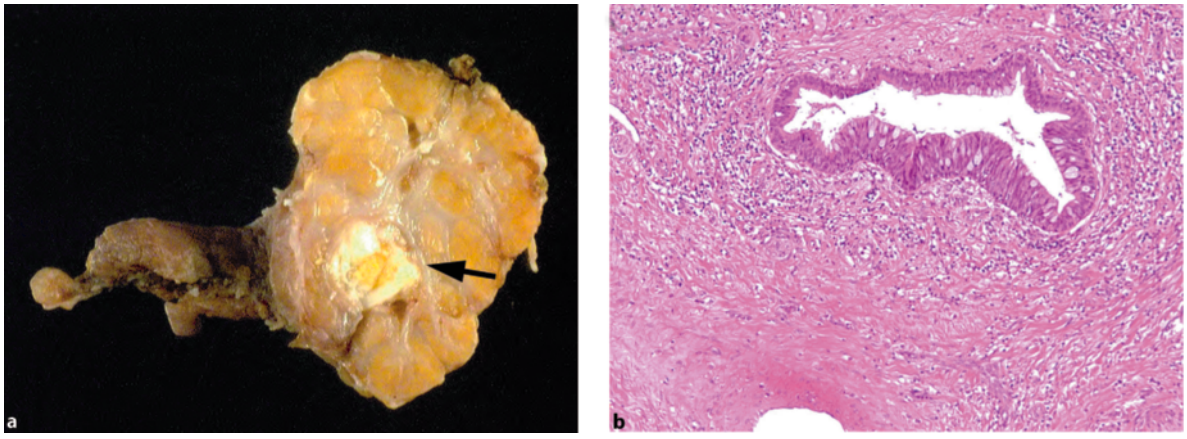

Fig. 3.1: Chronic sialadenitis from sialolithiasis. **a** Submandibular gland with a large sialolith (*arrow*), and mildly ectatic ducts with periductal fibrosis represented by the fibrous white lines radiating from the stone (gross image). **b** Chronic sialadenitis with periductal fibrosis and a mixed chronic inflammatory infiltrate around a large duct that shows mucinous metaplasia (H&E, 100×)

Mucus extravasation may be noted as well [195]. Radiation sialadenitis may show a fibrous white cut surface with involvement of adjacent soft tissue. When the residual lobules are noted, they may be attenuated with interstitial fibrosis.

Microscopically, the classic findings of chronic sialadenitis are a chronic inflammatory infiltrate composed of lymphocytes, plasma cells and macrophages, fibrosis, acinar atrophy, and mucous cell metaplasia of the ductal system (Fig. 3.1b) [462]. A common regenerative phenomenon is the presence of intercalated duct hyperplasia that may be diffuse or nodular. In sialolithiasis, dark calcific stone fragments are noted within the ducts which may have a concomitant squamous metaplasia. Infectious granulomatous sialadenitis ranges from the caseating granulomatosis seen in tuberculosis to foamy histiocytic aggregates seen in atypical mycobacterial infections. Intra- and periparotid lymph node involvement may be seen in the latter [319]. Acid fast stains will highlight the mycobacterial organisms.

Pathogenesis

The predilection of sialoliths to form in the submandibular gland is thought to be a result of the alkaline pH and high mucin content of its secretions. The nidus for stone formation has been postulated to arise as a result of bacteria or organic debris [399, 462]. However, recent scanning electron microscopy and X-ray crystallography studies refuted this as a major cause, finding only hydroxyapatite crystals rich in calcium phosphates [326].

The mechanisms for radiation sialadenitis are not entirely understood, but recent T-cell subset evaluations suggest a possible immune-mediated component of injury [266, 565]. Tuberculous sialadenitis is rare; only 49 cases of tuberculous parotitis have been reported since 1966 [352]. In a review by van der Walt and Leake, tuberculous sialadenitis comprised 8/57 cases of granulomatous sialadenitis [590].

Prognosis

The prognosis depends on the etiologic factor, if identified, and the severity of disease. While surgical treatment of chronic sialadenitis leads to resolution of symptoms of pain and prevention of superinfection with fistula or sinus tract formation [19], xerostomia, often seen in radiation sialadenitis, does not resolve [266, 565].

Autoimmune Sialadenitis

Clinical Features

The majority of autoimmune sialadenitides are in the histopathologic spectrum of myoepithelial sialadenitis (MESA), a term coined as early as 1972 by Donath and Seifert [158], also known as benign lymphoepithelial lesion. The clinical correlates are varied and include terms such as Mikulicz disease, sicca complex, Sjögren's syndrome, and chronic punctate sialadenitis [462].

Other systemic autoimmune diseases that can affect the salivary glands, usually the parotid include Wegener's granulomatosis, sarcoid, and Kimura's disease [383]. Recent evidence indicates that a subset of chronic sclerosing sialadenitides (Kuttner tumor) have an autoimmune etiology [332].

Myoepithelial sialadenitis may present as unilateral or bilateral enlargement of salivary glands, at any age with or without autoimmune disease, but most commonly manifests in females in their fifth to sixth decades as a reflection of the close association with Sjögren's syndrome. Sialograms show sialectasia which ranges from punctate to cavitary [462].

Sjögren's syndrome is an autoimmune exocrinopathy characterized by keratoconjunctivitis, xerostomia, and often other extrasalivary manifestations. It can exist as a primary disease or as a secondary disease associated with other systemic autoimmune diseases, typically rheumatoid arthritis and occasionally progressive systemic sclerosis [224].

Salivary gland involvement in Wegener's granulomatosis, characterized by upper and lower respiratory tract and renal disease, is rare with the parotid being most commonly affected [383]. Fauci et al. [206] report an incidence of less than 1% (n=158) in their experience. In contrast, salivary gland involvement in sarcoidosis is not infrequent ranging from 4% to 30%. A rare syndromic variant of sarcoidosis known as Heerfordt syndrome is characterized by uveitis, bilateral parotitis, and facial nerve palsy [383].

Kimura's disease occurs typically in young Asian males and is characterized clinically by painless lymphadenopathy of the head and neck region, including periparotid and intraparotid lymph nodes [383, 536]. Chronic sclerosing sialadenitis presents as a firm localized swelling of the salivary gland mimicking a neoplasm, most commonly involving the submandibular gland [462]. While originally categorized as a non-specific localized chronic sialadenitis, when excluding cases that are attributable to

sialolithiasis or other localized obstruction, at least a subset present with autoimmune extrasalivary disease such as primary sclerosing cholangitis, idiopathic retroperitoneal fibrosis, and lymphoplasmacytic sclerosing pancreatitis warranting placement in the autoimmune sialadenitis category [323, 332].

Pathology

The gross manifestations of myoepithelial sialadenitis are similar to chronic non-immune sialadenitis, ranging from a diffuse to a multinodular expansion. In some cases, the gross cut surface is a tan-pink reminiscent of a lymph node, however, the lobular architecture is maintained distinguishing this from lymphoma. Wegener's granulomatosis may show areas of liquefaction necrosis as a result of vasculitis. Sarcoidosis and Kimura's disease may show preferential enlargement of the intra/periparotid lymph nodes. Chronic sclerosing sialadenitis on gross examination resembles a salivary gland neoplasm and with a well-circumscribed tan-white appearance.

The histologic hallmark of MESA is the presence of epithelial-myoepithelial islands infiltrated by lymphocytes (Fig. 3.2). However, the process begins as a collection of lymphocytes centered on an intralobular duct. This lymphoid infiltrate, when a cluster of at least 50 lymphocytes per 4 mm^2 defines a lymphoid focus, is the basis for grading of labial minor salivary gland biopsies for the diagnosis of Sjögren's syndrome [139, 458]. As these lymphoid infiltrates progress, germinal centers may form, and acinar atrophy ensues. A proliferation of ductal epithelium-myoepithelium arises, obliterating duct lumina and eventually giving rise to classic epithelial-myoepithelial islands. A few studies suggest that these islands may not contain a myoepithelial component, but are composed of metaplastic intercalated ducts with an altered immunophenotype [309, 333].

Salivary glands in the setting of secondary Sjögren's syndrome due to progressive systemic sclerosis may show periglandular fibrosis without inflammation in addition to MESA [458]. Wegener's granulomatosis manifests as a classic triad of vasculitis, necrosis, and granulomatous inflammation, however, only 16% of cases with parotid involvement have the complete triad [383]. Sarcoid is characterized by tight epithelioid granulomas and a lymphoid infiltrate. Biopsies of salivary glands in the lip for the diagnosis of sarcoid show granulomas in 53% of cases [442].

Chronic sclerosing sialadenitis bears a remarkable similarity to lymphoplasmacytic sclerosing pancreatitis [323]. It is characterized by periductal fibrosis with a dense lymphoplasmacytic infiltrate with lymphoid follicles. Eosinophils are variably present. Kitagawa et al. demonstrated the presence of obliterative phlebitis in all cases as demonstrated by elastic stain [332].

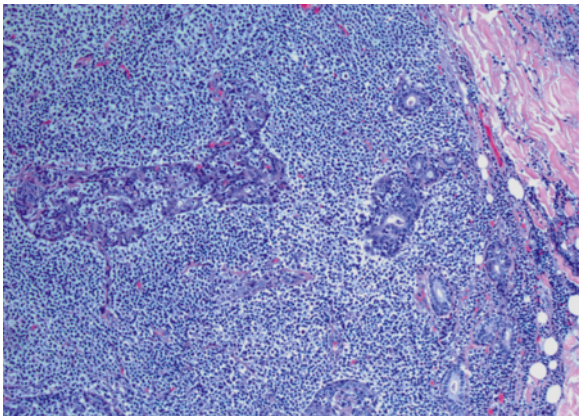

Fig. 3.2: Myoepithelial sialadenitis (MESA) with a florid lymphoid infiltrate and prominent epithelial myoepithelial islands permeated by lymphocytes (H&E, 100×)

Pathogenesis

While Sjögren's syndrome often has a characteristic serology, including anti SS-A, anti SS-B, and occasionally ANA and rheumatoid factor, the pathogenesis of the disease is not entirely clear and is multifactorial as with most autoimmune diseases [224]. In addition to HLA-DR associations, recent studies suggest that polymorphisms in genes, such as minor histocompatibility antigen HA-1, and TNF may play a role in the disease process. Humoral dysregulation and B-cell hyperactivity is thought to be another pathogenic mechanism for Sjögren's syndrome [224, 277].

Similarly, though the serologic manifestations are well known, the pathogenesis of Wegener's granulomatosis, sarcoidosis, Kimura's disease, and chronic sclerosing sialadenitis are not well understood. The classic serologic manifestation of Wegener's granulomatosis is a positive C-ANCA. Sarcoidosis often manifests with hypergammaglobulinemia as well as non-serologic laboratory abnormalities such as hypercalcemia, elevated alkaline phosphatase, and angiotensin-converting enzyme levels. Kimura's disease is characterized by elevated IgE levels

and eosinophilia, while the association of chronic sclerosing sialadenitis with elevated IgG4 levels has been noted recently [323, 332, 383].

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Prognosis

As with most sialadenitides, the prognosis is related to the severity and treatment of the underlying disorder [75]. Severe recurrent parotitis is amenable to surgical treatment [19]. Of note, patients with Sjögren's syndrome have a forty-fold increased risk for development of small B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type [224].

Special Considerations

Myoepithelial Sialadenitis and Mucosa-associated Lymphoid Tissue (MALT) Lymphomas

The majority of salivary gland lymphomas are of the MALT type and arise in the setting of MESA. This association was noted as early as 1971 by Azzopardi and Evans [31]. The transition from MESA to MALT lymphoma is postulated to occur as a result of antigenic stimulation, though unlike gastric MALT lymphoma, the etiologic agent (*H. pylori* in gastric MALT lymphoma) has not been identified [32].

Histologic distinction of MESA from early MALT lymphoma is obfuscated by the detection of clonal proliferations in otherwise typical appearing MESA [214, 337]. These MESA clones have a limited VH repertoire even among different patients, suggesting antigenic stimulation from a common epitope [32]. While these clones may eventually give rise to MALT lymphoma, clonality in the setting of typical or even atypical MESA without a significant mass lesion does not indicate lymphoma. The earliest histologic changes of MALT lymphoma are the presence of "halos" of monocytoid or centrocyte-like B cells that are slightly paler on low power magnification [301]. These coalesce into sheets and eventually form mass lesions. Involvement of intra- and periparotid lymph nodes is often seen.

Immunohistochemical and flow cytometric analysis show a population of B cells that are CD19 positive, CD20 positive, CD5 negative, CD10 negative, and CD23 negative. CD43, typically seen on T cells may be aberrantly expressed. MALT lymphomas will often but not always show light chain restriction [1].

Mucosa-associated lymphoid tissue lymphomas have several associated characteristic translocations and trisomies though the frequencies of these vary by site. In the salivary gland, the most common translocation is t(14;18)(q32;q21) which is the fusion of IGH/MALT1, while trisomy 3 was the most common alteration overall. The significance of these alterations is unclear at this point [552].

Myoepithelial Sialadenitis and Carcinoma

In rare instances, MESA can have malignant transformation of the epithelial component. Carcinomas arising in MESA are typically lymphoepithelial carcinomas resembling undifferentiated non-keratinizing nasopharyngeal carcinoma, though keratinizing squamous cell carcinomas have been described [44, 89, 428]. Lymphoepithelial carcinomas of the parotid, akin to their nasopharyngeal counterparts, are often associated with Epstein-Barr virus (EBV) infection. Wu et al. demonstrated the presence of EBV small RNA-1 (EBER-1) in MESA with carcinomatous transformation in both the benign and malignant areas, while typical MESA was negative for EBER [620].

Necrotizing Sialometaplasia

Clinical Features

Necrotizing sialometaplasia (NSM), originally described by Abrams et al. in 1973 [3] is a benign self-healing salivary gland lesion that can mimic malignancy. NSM typically occurs in the fourth decade (mean age 45.9 years) with a male predilection (male:female ratio 1.9:1) [85, 222, 311, 462]. Although the palate is the most frequently involved site, NSM has been described in mucoserous glands throughout the upper and lower respiratory tract [85, 380, 484, 630]. The usual presentation is that of a single unilateral ulcer at the junction of the hard and soft palate [85, 222, 462]. Roughly 10% are bilateral, and 15% are asymptomatic [85].

Pathology

Grossly, NSM is typically a well-demarcated, raised, erythematous ulcer. The underlying salivary tissue is a soft friable gray tan [195, 462]. In a review of 184 cases,

the mean size was 1.9 cm (range 0.7–5.0 cm) [85]. The defining microscopic features are: ulceration with pseudoepitheliomatous hyperplasia of the adjacent mucosa, infarction of the salivary lobule, with mucus extravasation, varying degrees of fibrosis, and squamous metaplasia of the ductoacinar units (Fig. 3.3a, b). The latter may be prominent and thus misread as mucoepidermoid carcinoma or squamous cell carcinoma. However, the key distinguishing feature of NSM from the malignant lesions that it may mimic is the maintenance of the lobular architecture despite the often extensive squamous metaplasia. On small biopsy specimens, this may be difficult to assess. Though a high index of suspicion of this lesion is the main requirement for its diagnosis in such a situation, a recent study suggests that NSM in contrast to squamous cell carcinoma does not show evidence of immunohistochemical staining for p53, Ki-67, and bcl-2 and thus may be a useful adjunct for distinguishing between these lesions [418]. It is very important to have an accurate diagnosis of NSM to avoid unnecessary surgery.

Pathogenesis

The classic NSM is thought to be the result of spontaneous infarction of mucoserous glands. However, a clinically and histologically identical picture is seen as a result of surgery, radiation, trauma, or vasculitis among other distortive injuries [26, 487]. The self-limiting nature and histologic features suggest vascular compromise with ischemic injury and subsequent regeneration as the main pathogenic mechanism [85, 462]. The occasional association with repeated emesis seen in bulimia and other disorders raises the possibility of chemical injury as a contributing factor [4, 496].

Prognosis

Prognosis is excellent. NSM is a self-limiting lesion lasting from a few days to a few months and does not recur [85].

Subacute Necrotizing Sialadenitis

Clinical Features

Subacute necrotizing sialadenitis (SANS) is a recently described idiopathic reactive process of minor salivary glands with only 26 cases reported in the literature [106, 222, 371, 588, 612]. SANS shares several clinical and pathologic features with NSM.

In contrast to NSM, SANS occurs typically in the second decade. However, similar to NSM, SANS typically occurs as a painful mass of the palate, though they are non-ulcerated in contrast to NSM. The male predominance is more pronounced (approximately 3:1) though

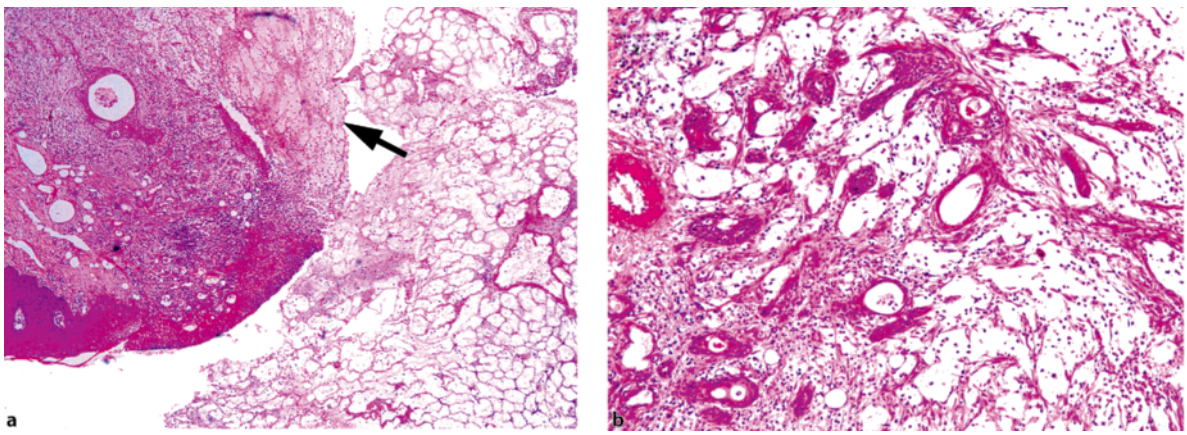

Fig. 3.3: Necrotizing sialometaplasia. **a** Palate with ulcerated squamous mucosa (*left*) and necrotic mucous acini (*right*) showing loss of cellular detail and focal extravasation of mucin (*arrow*) (H&E, 20×). **b** Squamous metaplasia or "sialometaplasia" is noted in the ducts (H&E, 100×)

this may reflect sampling bias, as many of these cases were obtained from a military population [222, 612].

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Pathology

Grossly, these are non-ulcerated submucosal masses ranging from 0.3 to 2.5 cm. The histologic criteria put forth by Werning et al. [612] are: acinar cell necrosis and loss, and a mixed inflammatory infiltrate comprised of neutrophils, eosinophils (occasionally prominent), and plasma cells. In contrast to NSM, SANS does not show squamous metaplasia or fibrosis. Ultrastructurally, dense particles have been identified in the acini that either represent viral particles or lysosomes [222, 612].

Pathogenesis

The etiology of SANS is unclear. Because of similar clinical and pathologic characteristics, SANS is viewed by some as a variant of NSM [371]. However, the association in a significant number of patients with upper respiratory tract infections, close living quarters, and a winter month predilection raises the possibility of a viral etiology. Further in support of this is the presence of dense viral-like particles ultrastructurally in the acini in several cases [222].

Prognosis

As in NSM, prognosis is excellent. SANS is also a self-limiting disease with an even more rapid course than NSM; all cases reported resolved within 4 weeks [222, 371, 588].

Sialadenosis

Clinical Features

Sialadenosis is a diffuse enlargement of salivary glands described in several conditions. Sialadenosis usually involves the parotid glands, and less commonly the submandibular glands [121, 157, 462]. Minor salivary gland involvement has also been reported [408]. It is frequently bilateral and has an equal sex distribution. It is typically painless and the enlargement may impart a striking facial appearance. Causes can be categorized as: nutritional (alcoholism, cirrhosis, eating disorders, kwashiorkor, and pellagra), endocrine (diabetes mellitus, thyroid disease, gonadal dysfunction), and neurochemical (vegetative state, lead, mercury, iodine, thiouracil, isoproterenol) [157, 462].

Pathology

Grossly, the salivary glands are unremarkable except for enlargement. Histologically, sialadenosis is a mixture of acinar hypertrophy and fatty infiltration. Morphometric studies have shown an increase in mean acinar cell diameter (approximately 75 microns) as compared to normal (approximately 50 microns) [267]. Additionally zymogen granules are increased in number and size by light and electron microscopy [160]. Most importantly, no inflammation or fibrosis is identified, distinguishing sialadenosis from the sialadenitides. While amyloidosis may present with diffuse enlargement of the salivary glands, histologically, there will be interstitial fibrosis with the characteristic pale amyloid deposition that can be demonstrated with a Congo red stain [195].

Pathogenesis

Despite the variety of predisposing conditions, sialadenosis is thought to be a neurosecretory disorder. Ultrastructural and animal experimental studies point to a disturbance in the autonomic innervation of the salivary glands as the initiating factor for sialadenosis [121, 123, 157, 160, 161].

Prognosis

The persistence of sialadenosis is dependent on the severity and duration of the underlying disease. However, there is usually little morbidity associated with the condition itself; most surgical treatment is performed for cosmetic purposes.

Adenomatoid Hyperplasia

Clinical Features

Adenomatoid hyperplasia is a proliferation of the mucous acini of minor salivary glands. The incidence of this le-

sion is likely higher than reported in the literature [16, 39, 86, 95, 462]. Adenomatoid hyperplasia typically presents as a painless mass located on the hard and soft palate in up to 95% of cases [39]. Rarely, adenomatoid hyperplasia is located on the retromolar trigone [86, 116]. While it can present at any age it is more common in the fourth decade with a slight male predominance. The typical clinical concern is that of a benign salivary gland tumor [462]. We have occasionally noted these lesions in uvulopalatopharyngoplasty specimens suggesting their role in some cases of obstructive sleep apnea.

Pathology

Grossly, these lesions range from 0.5 to 3 cm [462]. They are usually non-ulcerated well-circumscribed masses. Histologically, the lesion is comprised of expanded lobules of mucous acini. Occasionally, there is mucus extravasation, but without an inflammatory reaction. The overlying mucosa is unremarkable.

Pathogenesis

The pathogenesis is unclear. While Arafat et al. [16] raise the possibility of a hamartomatous origin to this lesion, Barrett and Speight [39] report 14 of 20 (70%) cases to be associated with dentures and/or tobacco suggesting a localized response to trauma. But this apparent association may be the result of sampling bias since the most common clinical setting for the detection of adenomatous hyperplasia is during dental examination [462].

Prognosis

Prognosis is excellent. Recurrences are not seen after excision.

Salivary Duct Cysts

Clinical Features

Salivary duct cysts are also known as sialocysts, simple cysts, and retention cysts. Unlike mucus extravasation phenomenon, salivary duct cysts are true cysts with an epithelial lining [56]. Salivary duct cysts are the most common salivary cysts, comprising about 1.5% of all salivary gland disease in one study [507].

Pathology

These cysts are unilocular and may grossly contain tan serous to gray mucoid material. Long-standing cysts can develop sialoliths. Histologically, these cysts are lined by a cuboidal, columnar, or squamous epithelium. Oncocytic metaplasia may be seen in older individuals. However, these cysts are not associated with lymphoid elements [462].

Pathogenesis

Sialocysts usually occur secondary to obstruction from various causes [56, 195, 462].

Prognosis

Prognosis is excellent. Rare complications include superimposed infections. Recurrences are rare and result from incomplete excision [462].

Lymphoepithelial Cysts

Clinical Features

Lymphoepithelial cysts refer to a group of lesions that include true first branchial cleft cysts, salivary-type lymphoepithelial cysts, and HIV-associated sialadenitis, which may also have overlap with MESA.

True branchial cleft cysts typically present shortly after birth or in childhood though they may not be symptomatic until adulthood. They usually present as a painless unilateral mass near or occasionally in the parotid gland, often with associated sinus tracts and fistulae. Superinfection may cause pain [454, 462, 575].

Salivary duct derived lymphoepithelial cysts rarely present at birth and are not associated with sinus tracts or fistulae. HIV-associated lymphoepithelial cysts have become increasingly common, comprising up to 60% of parotid lymphoepithelial cysts [564]. These tend to be bilateral and associated with lymphadenopathy. The incidence of parotid gland involvement in HIV is about

3–5% [307]. Occasionally these may be the presenting symptom of HIV infection [390]. While the parotid gland is the most frequent site for HIV-associated lymphoepithelial cysts, cysts in the submandibular glands have also been described [262].

Pathology

True first branchial cleft cysts of the parotid region can be divided into type I and type II. Type I anomalies are considered reduplication of the ectodermal component of the ear canal while type II anomalies also include mesodermal components as well [18, 212, 454]. The type II anomalies are more closely associated with the parotid parenchyma [454, 462]. Grossly, these cysts are adjacent to or in the parotid gland and contain cloudy to cheesy material representing keratinaceous debris. In type II anomalies, the cyst wall may grossly contain cartilage. Histologically, branchial cleft cysts will contain a combination of squamous and ciliated respiratory type epithelium. Type II lesions will also contain skin adnexal structures and cartilage. Both types may have lymphoid tissue with germinal centers in the periphery.

Lymphoepithelial cysts may have a nodular inner lining that grossly represents lymphoid tissue. Salivary type lymphoepithelial cysts are lined by a thin squamous or columnar epithelium, and are surrounded by a prominent lymphoid infiltrate with all the architectural features of a lymph node including sinusoidal spaces and primary and secondary germinal centers [56, 467]. Lymphoepithelial cysts in HIV often contain epithelial-myoepithelial islands seen in MESA, and an additional finding is that of multinucleated giant cells [169, 595]. Immunohistochemical detection has identified p24 antigen in the macrophages and giant cells seen in HIV-associated lymphoepithelial cysts [93, 347, 386, 583, 595]. The lymphoid infiltrate differs from that in non-HIV-associated lymphoepithelial cysts and MESA in that it is comprised largely of $CD8^+$ lymphocytes [118, 382].

Pathogenesis

True branchial cleft cysts in the parotid region are derived from the first branchial pouch and are duplication defects. While, initially, the term branchial cleft cyst was used interchangeably for all parotid lymphoepithelial cysts [551, 608], this term has now been reserved only for those cysts that have clinical or histologic features of first branchial pouch derivatives, e.g., early age of onset, presence of sinuses or fistulae, ciliated respiratory epithelium, and the presence of mesodermal elements in type II anomalies. The presence of salivary inclusions within the lymphoid stroma of some lymphoepithelial cysts, as well the documentation of a high amylase content in cyst fluid suggest that most lesions called lymphoepithelial cysts are of the salivary type [230, 467]. These cysts are thus thought to represent cystic dilation of salivary inclusions of the intra- and periparotid lymph nodes.

Human immunodeficiency virus-associated lymphoepithelial cysts are also thought to arise from cystification of salivary elements. However, the histologic spectrum along with three-dimensional reconstruction of 100 parotid lesions [308] suggest that these cysts are cystic dilation of the native ductal system of the salivary gland in the setting of MESA-type lesion akin to that seen in autoimmune disease rather than dilatation of salivary gland inclusions within a lymph node [307, 308].

Prognosis

The recurrence rate for all types of lymphoepithelial cysts is low to absent, however, branchial cleft cysts are more likely to recur than the others, and must be completely excised [18, 212].

Dysgenetic Polycystic Disease

Clinical Features

Dysgenetic polycystic disease is an extremely rare salivary gland disease with only 15 cases reported in the literature [45, 156, 211, 235, 396, 456, 511].

Dysgenetic polycystic disease occurs almost exclusively in the parotid glands of women with an age range of 6–65 years [235]. Only one case has been documented in the submandibular gland of a man [456, 511]. Usually this disease is bilateral, but unilateral disease has been documented [45, 156, 211, 235, 396, 456, 511]. The typical presentation is that of a non-tender mass [211, 511, 534].

Pathology

Grossly, these lesions present as spongy masses of the involved salivary gland. Histologically, there is variable replacement of the parenchyma by cysts of various size and shape. The epithelium is attenuated and cuboidal, and the cyst wall is delicate with minimal fibrosis or inflammation. Occasional invaginations and tufting of epithelium may be seen. The lumina may contain concentric eosinophilic secretions [534].

Pathogenesis

Dysgenetic polycystic disease is thought to be a result of some type of embryologic insult. Though it bears similarities to polycystic disease of other organ sites, such as kidney and liver, this entity has not been associated with extraparotid manifestations. At least three cases have a familial association, though the responsible genetic alteration has not yet been identified [198, 201, 492, 539].

Prognosis

This entity is sufficiently rare as to preclude definitive prediction of behavior. To date, recurrence has been described only occasionally [198, 539].

Benign Tumors

Pleomorphic Adenoma

Clinical Features

Pleomorphic adenoma, also known as benign mixed tumor, is the most common tumor of salivary gland origin, accounting for about 60% of all salivary tumors in large series [298]. Up to 80% occur in the parotid gland, 10% in the submandibular glands, and the rest in the minor salivary glands, throughout the upper and lower aerodigestive tract [449, 508, 624]. While most occur in the lower pole of the superficial lobe, the deep lobe can be involved. Extensions of deep lobe pleomorphic adenomas are the most common tumors of the parapharyngeal space constituting 40% of tumors in this region [198, 201]. Bilateral occurrences of pleomorphic adenoma are rare [201, 462]. Pleomorphic adenomas can occur in any decade, but the mean age is 46 years with a slight female predilection [96, 291, 329]. The typical presentation is that of a painless, slowly growing mass.

Pathology

Grossly, pleomorphic adenomas are typically well-circumscribed ovoid masses. They usually range from 2 to 5 cm in greatest dimension [559], though tumors as large as 50 cm in diameter, weighing over 6 kg have been reported [354, 509, 527]. Larger tumors often have a bosselated surface and may distend overlying skin and cause erosion of bone and remodeling deep to the tumor. In the major glands, they usually have a complete capsule, while in the minor glands they may not. Pleomorphic adenomas usually show a lobulated glistening gray tan cut surface representative of the chondromyxoid stroma characteristic of this tumor (Fig. 3.4a). Areas with less chondroid appear as a homogeneous white tan color. Larger tumors may have areas of calcification/ossification, hemorrhage, and necrosis. Such areas of heterogeneity should be sampled to exclude malignant degeneration. Satellite nodules in primary tumors are rare, but are typical of recurrent tumors.

Histologically, pleomorphic adenoma, as with many salivary tumors, is a biphasic tumor comprised of epithelial (ductal) and myoepithelial cells. It is named for its various histologic patterns or "pleomorphism," rather than actual cellular atypia. The myoepithelial component often predominates with spindled to ovoid cells with wispy pink cytoplasm embedded in a pale chondromyxoid blue gray stroma. These myoepithelial cells are often seen streaming off the ductal component blending into the stroma (Fig. 3.4b). A unique pattern within areas of myoepithelial predominance is a palisaded growth resembling that seen in schwannoma [111]. Cartilaginous differentiation is often seen. Occasionally, osseous metaplasia and even lipomatous metaplasia may be present [201]. Tyrosine-rich crystals are occasionally seen within the chondroid stroma [145, 201].

The tumors can show various epithelial differentiation such as oncocytic, squamous, mucinous, and sebaceous metaplasia, and can be mistaken for squamous cell carcinoma or mucoepidermoid carcinoma, if the overall architecture and configuration is not taken into consideration [445]. The proportions of epithelial and myoepithelial

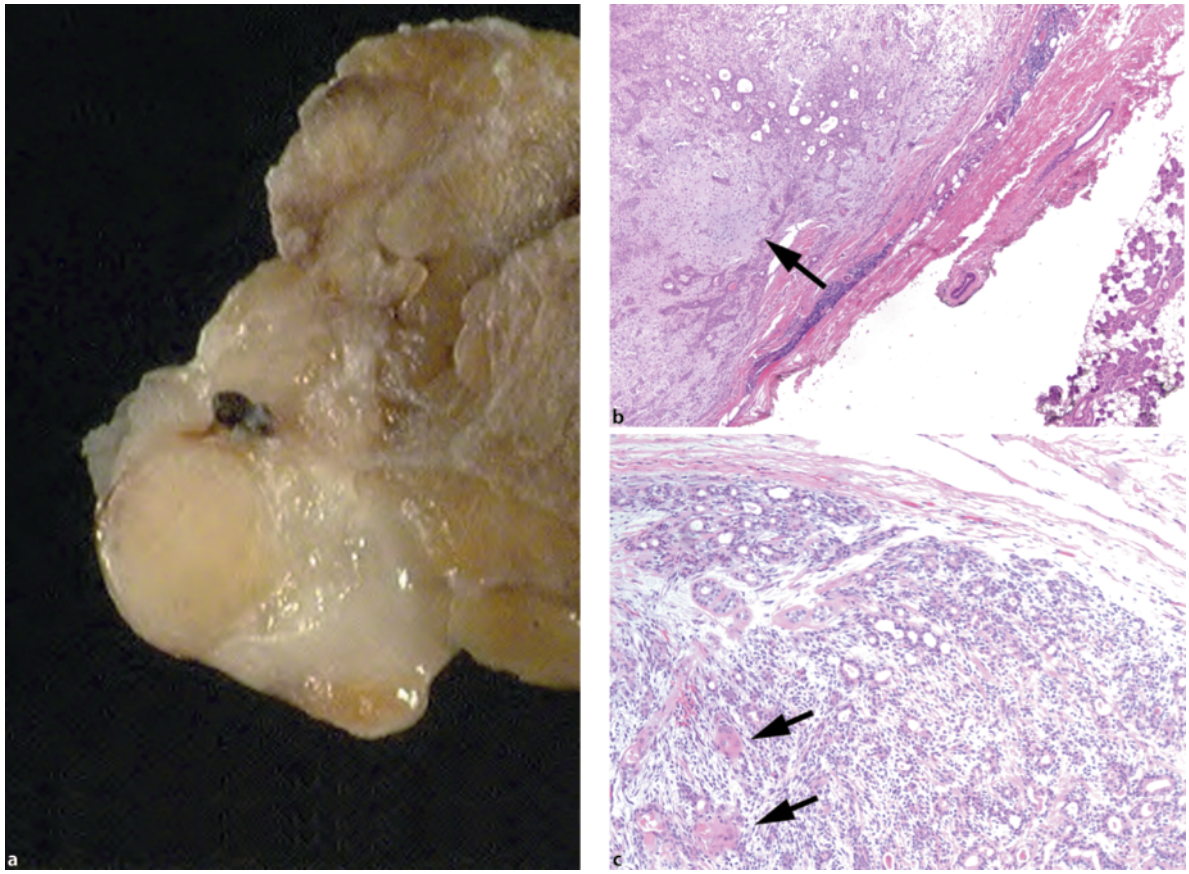

Fig. 3.4: Pleomorphic adenoma. **a** A small well-circumscribed tumor of the tail of the parotid showing a homogeneous glistening gray-tan cut surface (gross image). **b** An encapsulated pleomorphic adenoma with ducts (*top*) and nodular areas of chondroid differentiation (*arrow*) (H&E, 40×). **c** Cellular pleomorphic adenoma with back-to-back ducts lined by myoepithelial cells almost resembling epithelial-myoepithelial carcinoma. Focal squamous metaplasia is present (*small arrows*) (H&E, 100×)

cells vary greatly. Myoepithelial-rich pleomorphic adenomas may be indistinguishable from myoepithelioma if the ductal component is not found. At the other end of the spectrum, cellular pleomorphic adenomas, which contain tubulotrabecular proliferations of ducts and myoepithelial cells with minimal stroma can be mistaken for malignant tumors such as epithelial-myoepithelial carcinoma and adenoid cystic carcinoma if only limited biopsy material is available (Fig. 3.4c).

Immunohistochemically, the ductal components are positive for various cytokeratins: 7, 8, 14, and 19, typically of low molecular weight. The myoepithelial cells are positive for p63, smooth muscle actin, calponin, vimentin, muscle-specific actin, and variably for S-100 protein and glial fibrillary acidic protein (GFAP) [629]. GFAP, though not a sensitive myoepithelial marker, has the benefit of highlighting areas of chondroid stroma, which can distinguish pleomorphic adenoma from other similar histologic types [297]. Similarly, bone morphogenic proteins and type II collagen are expressed in these areas as well [97, 388]. While immunostaining for S-100 also highlights the stromal component, it may also stain some ductal areas [97].

Pathogenesis

Roughly 70% of pleomorphic adenomas have cytogenetic alterations that likely play a central role in tumorigenesis, and can be stratified into four groups: those with 8q12 rearrangements, those with 12q13-15 rearrangements, those with miscellaneous clonal changes, and those that are karyotypically normal [325, 598]. Bullerdiek et al. [597] note that the karyotypically normal individuals are usually a decade older than those with 8q12 rearrangements.

The 8q12 abnormalities are typically translocations involving the PLAG1 gene, juxtaposing this zinc finger gene with a ubiquitously expressed translocation partner gene. The two most common translocations, t(3;8) (p21;q12) and t(5;8) (p13;q12), result in CTTNB1-PLAG1 and LIFR1-PLAG1 fusions, respectively [240, 241]. PLAG1 alterations result in increased IgF2 expression, which is likely contributory to the development of pleomorphic adenoma [5]. The 12q13-15 abnormalities are also usually translocations, involving the HMGA2 (HMGIC) gene that encodes a transcription factor involved in the modulation of DNA structural conformation. The most common alterations are ins(9;12) and t(3;12), which result in HMGA2-NFIB and HMGA2-FHIT fusions, respectively [189].

Interestingly, a t(3;12) was reported in two cases (siblings) of familial pleomorphic adenomas [28, 242, 289, 356, 479]. The aforementioned translocations are also implicated in radiation-associated pleomorphic adenomas [242].

Prognosis

While pleomorphic adenoma is a benign tumor, it has the capacity to recur and to undergo malignant transformation. Recurrence rates range from 0.8% to 6.8% in large series with long-term follow-up [287]. While complete excision is required to ensure a favorable outcome, preservation of anatomic structures is also a major concern. Ghosh et al. [102, 477] argue that the recurrence rate is low (1.8%) even with tumor less than 1 mm from the margin. Capsular rupture and subsequent tumor spillage may play a role in the recurrence of pleomorphic adenoma, however, Henriksson et al. [78, 247, 610] report that the presence of pseudopodia or capsular infiltration was a more significant predictor of recurrence. Recurrent pleomorphic adenomas have a higher likelihood for second recurrence of about 6–15%. Uninodular recurrences have a better outcome than multinodular recurrences [78, 247, 610].

Rarely, a histologically benign pleomorphic adenoma can metastasize and behave like a low-grade malignancy, however, there are no features that can predict this rare occurrence. However, many of these tumors metastasized after at least one initial local recurrence, suggesting the possibility that altered anatomy secondary to surgery gave access to vascular and lymphatic channels [24]. As many as 40% of patients with metastasizing pleomorphic adenomas die with disease [133, 429, 626]. True malignant transformation is rare as well. Clinical features predictive of malignant transformation are age, tumor size, and a long history of a mass in the parotid gland and submandibular location. The presence of hyalinized stroma is the most predictive histologic parameter for malignant transformation [462, 626].

Basal Cell Adenoma

Clinical Features

Basal cell adenomas tend to occur over the age of 50 years with a slight female predilection of 2:1 [199]. They usually occur in the parotid (75%) or submandibular gland (approximately 5%) [626]. These lesions are quite rare in the minor salivary glands when excluding canalicular adenomas which were previously categorized with basal cell adenoma [623, 625]. They typically present as a slowly growing solitary painless mass [462]. A special variant of basal cell adenoma, the membranous type (dermal analog tumor) can be associated with multiple trichoepitheliomas and cylindromas (Brooke-Spiegler syndrome) [429].

Pathology

Grossly, these tumors are a well-circumscribed, solid homogeneous gray-white to tan-brown occasionally mimicking an enlarged lymph node. Rarely, cystic change may be seen grossly [625]. Most tumors are less than 2 cm in diameter [142]. Membranous type basal cell adenomas can be multifocal [429].

Despite the archaic term for these tumors, "monomorphic adenomas," basal cell adenomas can show a va-

riety of histologic patterns: tubular, trabecular, cribriform [141], solid, and membranous. Other than the membranous type, these morphologic patterns have no clinical significance. The common feature to all of these tumors is a "basaloid" morphology to the tumor, namely a proliferation of small dark cells that have a peripheral cuboidal to columnar layer with varying degrees of stratification and palisading. These tumors are reminiscent of cutaneous epidermal and adnexal tumors such as basal cell carcinoma, trichoepithelioma, and cylindroma. Microscopic cystic change is fairly common, present in as many as 65% of tumors, predominating in the tubular/trabecular patterns [622, 625]. Within the center of these tumors, various lines of differentiation can be seen ranging from squamous to sebaceous to mucinous. Basal cell adenomas may have a myxoid or hyaline stroma, and rarely a myoepithelial-rich cellular stroma [606]. However, in contrast to pleomorphic adenoma, the stroma, regardless of cellularity, is distinct from the basaloid proliferation, with no intermingling. Mitoses are rare to absent, as is necrosis, and there is no infiltration of surrounding tissue or perineural invasion, which distinguishes basal cell adenomas from their malignant counterparts, basal cell adenocarcinomas.

The tubular pattern is composed of ductal structures surrounded by a cuboidal to palisaded basal layer, while the trabecular pattern consists of ribbons or cords of cells traversing a myxoid or hyaline stroma resembling a canalicular adenoma in areas (Fig. 3.5a). The solid and cribriform variants consist of broader nests or islands of cells

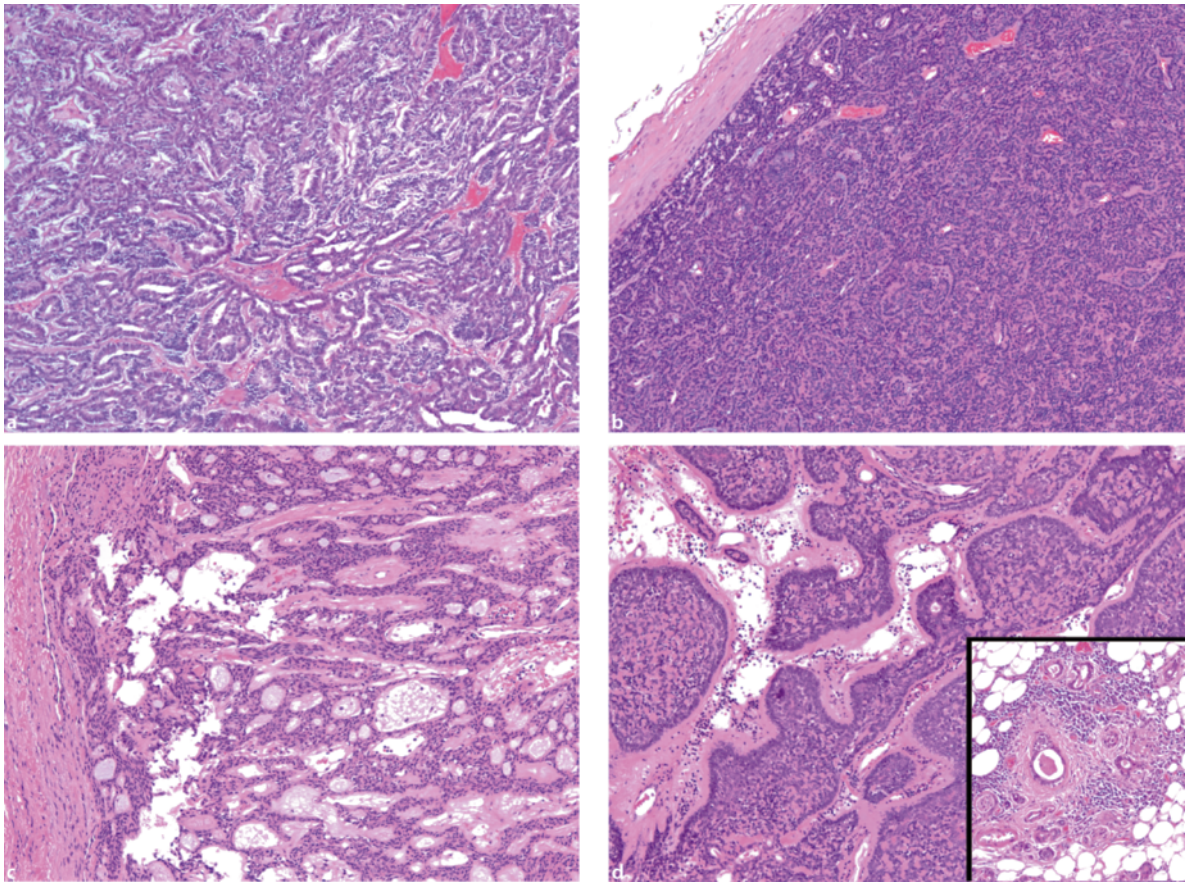

Fig. 3.5: Patterns of basal cell adenoma (all H&E, 100×): **a** tubulotrabecular, **b** solid, **c** cribriform, and **d** membranous or dermal analogue type. *Inset* for **d** a focus of striated duct hyperplasia adjacent to the main tumor

with peripheral palisading, and "cookie cutter" holes in the latter (Fig. 3.5b, c). This latter variant can be confused with adenoid cystic carcinoma. However, the cribriform basal cell adenoma does not infiltrate the surrounding tissue like adenoid cystic carcinoma. Additionally, though often small and dark, the nuclei in this subtype are more vesicular and less angulated than adenoid cystic carcinoma nuclei.

The membranous type of basal cell adenoma consists of nests of cells arranged in a "jigsaw" pattern identical to cutaneous cylindromas. Also similar to cylindroma, is the abundance of hyaline droplets within the nest, occasionally resembling adenoid cystic carcinoma, though the hyaline droplets of membranous basal cell adenomas are smaller, and the nests are more rounded. The surrounding salivary tissue of membranous basal cell adenomas seen in syndromic and multifocal lesions may show areas of striated duct hyperplasia (Fig. 3.5d *inset*) with a focally basaloid appearance representing precursor lesions and explaining the multifocality seen in some of these distinct subtypes of basal cell adenoma [627].

Immunohistochemically, these tumors are strongly and diffusely positive for p63 a progenitor cell marker that is expressed in basal and myoepithelial cells [436]. These tumors may also show varying degrees of true myoepithelial differentiation, staining positively for various smooth muscle markers [296, 519]. Nagao et al. were able to use a combination of a mitotic activity of less that 4 per 10 high power fields along with a low proliferation index by Ki-67 immunostaining, low apoptotic index by TUNEL labeling, and negativity for biomarkers p53, and EGFR to effectively separate basal cell adenomas from basal cell adenocarcinomas [125].

Pathogenesis

For most sporadic basal cell adenomas, the pathogenesis is unclear. Cytogenetic alterations have been only rarely characterized in non-membranous basal cell adenomas, with a trisomy 8 and chromosome 13 alterations being the major abnormalities described [576]. With regards to membranous basal cell adenomas, alterations at the CYLD1 gene locus at chromosome 16q12-13 are seen in both sporadic and familial/syndromic cases, suggesting that this alteration is vital to this subtype's pathogenesis [378]. CYLD1 is a deubiquitinating enzyme whose loss of activity correlates with activation of the NF-kB pathway, hinting at a mechanism of tumorigenesis [375].

Prognosis

Basal cell adenomas have a low rate of recurrence, except for the membranous subtype, which may recur in about 25% of cases. Because of the propensity for multifocality in membranous basal cell adenomas, some of these cases may represent separate tumors rather than true recurrences [179]. Malignant transformation is rare, again favoring the membranous type of basal cell adenoma [137, 179, 210].

Canalicular Adenoma

Clinical Features

Canalicular adenoma, previously categorized with basal cell adenoma, is a rare tumor comprising less than 1% of all salivary tumors [137, 179, 210]. The mean age is 65 years with a female predilection (ratio: 1.8:1) [179, 553]. The anatomic distribution of canalicular adenomas is distinctive, with a marked tendency to involve minor salivary glands of the upper lip in about 80% of cases. The second most common site is the buccal mucosa, where these tumors occur in almost 10% of cases [210]. The remainder of cases occur in the palate [486], and only rarely in the parotid gland [179]. They typically present as painless, slowly growing submucosal nodules. Rarely, multiple/multifocal canalicular adenomas can occur and present clinically with as many as 13 discrete masses, typically occurring in the upper lip and buccal mucosa [462].

Pathology

Grossly tumors are well circumscribed and range from 0.5 to 2.0 cm [209]. They are a homogeneous tan to yellow-tan. Cyst formation is common [627]. Histologically, at low power magnification, these tumors show a characteristic beaded appearance of thin anastomosing cords of cells embedded in a loose paucicellular myxoid stroma with prominent vascularity (Fig. 3.6). On higher magnification, the cords are comprised of two rows of bland monomorphic columnar cells with some stratification. The palisading columnar cells of canalicular adenomas resemble the basal layer of tubular/trabecular basal cell adenomas, however, there are no other cell morphologies as seen in the latter. Additionally the appearance of the tumor cords "floating" in a loose vascular stroma is characteristic and only focally, if ever, seen in basal cell adenoma.

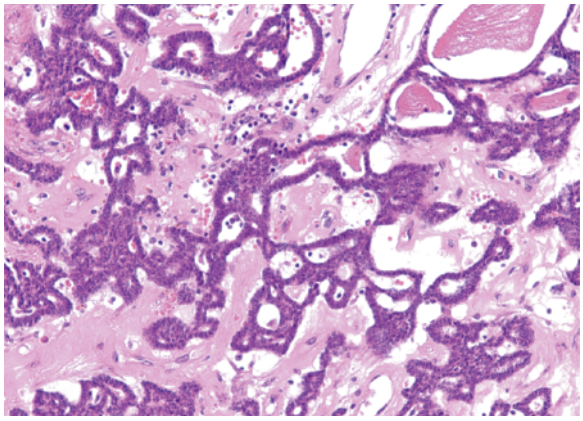

Fig. 3.6: Canalicular adenoma with thin cords of columnar epithelium streaming through a myxohyaline stroma (H&E, 100×)

Immunohistochemically, these tumors are uniformly positive for vimentin, S-100, and cytokeratins and only rarely for GFAP [164]. Muscle markers such as smooth muscle actin, calponin, and smooth muscle myosin heavy chain are uniformly negative suggesting a pure ductal epithelial differentiation [164]. Furthermore, canalicular adenomas are negative for p63, which is a key distinguishing factor immunophenotypically from the strongly p63-positive basal cell adenomas/carcinomas [328].

Polymorphous low-grade adenocarcinoma can be in the differential diagnosis of canalicular adenoma, but as its name suggests, polymorphous low-grade adenocarcinoma has a greater variation in growth pattern and cell type, and will show areas of infiltration and often perineural invasion, though distinction may still be admittedly difficult on small biopsy. Additionally, multifocality of canalicular adenomas may be mistakenly interpreted as infiltration. Both polymorphous low-grade adenocarcinoma and canalicular adenoma are immunophenotypically very similar, though p63 can often be positive in the former [210].

Pathogenesis

The pathogenesis is not well understood, though the presence of multifocality in some cases suggests a field effect [179, 367].

Prognosis

The prognosis is excellent and recurrences are extremely rare. Additionally, some of these recurrences may represent separate tumors [36, 179, 498].

Myoepithelioma

Clinical Features

Myoepitheliomas account for about 1.5% of all salivary tumors. This tumor is primarily one of adults with a peak incidence in the third to fourth decades (range 8–82 years) [62, 63]. The parotid gland is the most common site ranging from 40% to 50%, followed by the minor salivary glands in the palate [462]. Myoepitheliomas of the sinonasal mucoserous glands are rare [101, 143]. Myoepitheliomas usually present as slow-growing painless masses.

Pathology

Grossly, these tumors are a well-circumscribed uniform gray tan. In the parotid gland they usually have a thin fibrous capsule, but in the palate, they may not [143]. The majority measure less than 3 cm [143, 462]. Microscopically, myoepitheliomas have a varied morphology.

In a review of 40 cases, Dardick et al. [524] delineated different cell types: spindled (32.5%), epithelioid (45.0%), hyaline (7.5%), clear (2.5%), and mixed (12.5%). The spindle cell type consists of bland sheets of cells with ovoid nuclei and delicate amphophilic to eosinophilic cytoplasm arranged in interlacing fascicles (Fig. 3.7a). There may be loose myxoid change, occasionally imparting a reticulated or net-like arrangement, but there is never chondroid metaplasia as seen in pleomorphic adenomas [558]. The epithelioid cell type (Fig. 3.7b) consists of cords or solid sheets of polygonal round cells with amphophilic to eosinophilic cytoplasm occasionally arranged in pseudoglandular spaces. Occasionally the cytoplasm is granular and oncocytic with accumulation of mitochondria as seen in oncocytic epithelial lesions [50, 143]. The hyaline or plasmacytoid cell type (Fig. 3.7c) consists of sheets of cells with eccentrically located nuclei and a droplet of prominent dense hyaline eosinophilic cytoplasm. The ultrastructural correlate to these droplets are accumulations of intermediate filaments that in immunoelectron

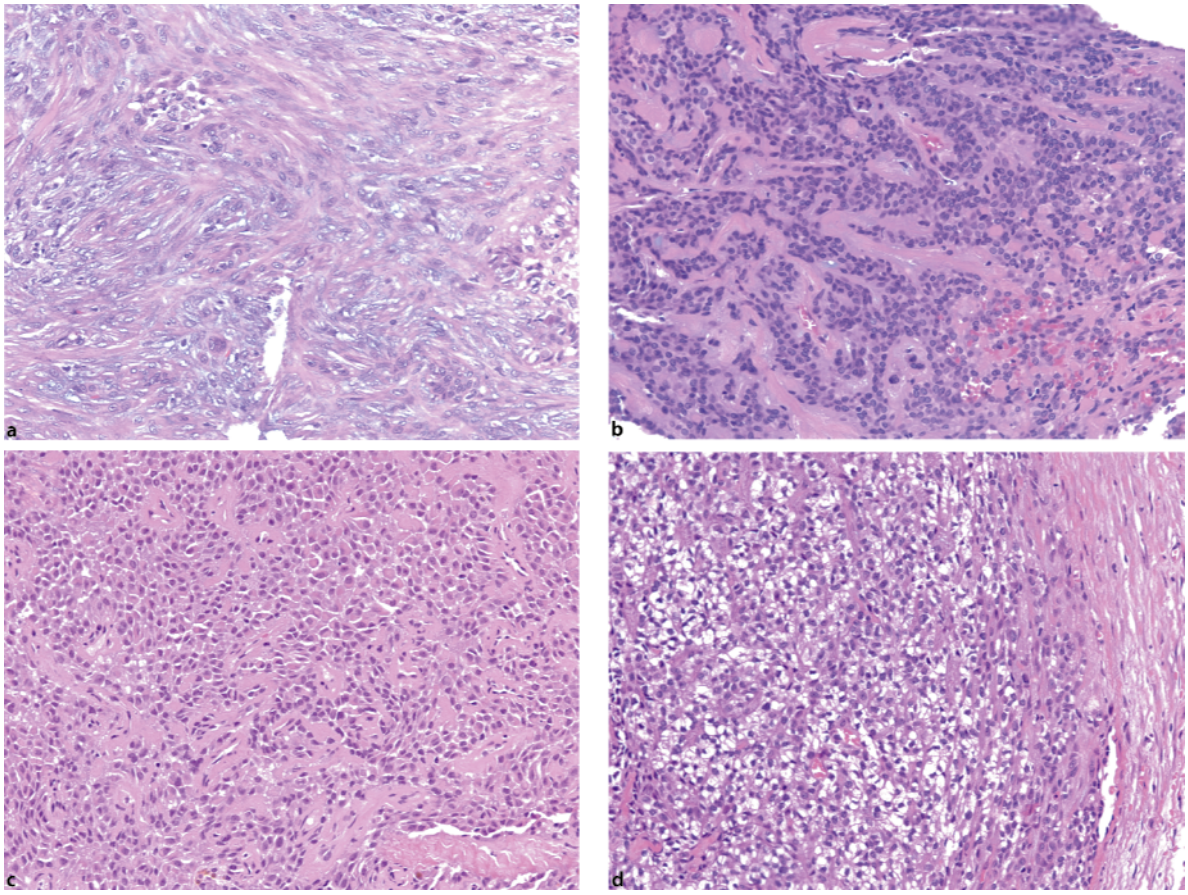

Fig. 3.7: Variants of myoepithelioma (all H&E, 200×): **a** spindled, **b** epithelioid, **c** plasmacytoid, and **d** clear cell type

microscopy show staining for muscle-specific actin [101, 364]. The clear cell type (Fig. 3.7d) most closely resembles the epithelioid cell type but instead shows clear cytoplasm indicative of glycogen accumulation [524]. Additionally, squamous metaplasia can be seen in all subtypes of myoepithelioma, particularly after fine-needle aspiration [101]. Within the oncocytic myoepitheliomas, sebaceous differentiation has rarely been described [495].

The number of true ducts that are allowed in myoepithelioma is debatable and arbitrary, but if there are more than scattered ducts present within a myoepithelial tumor, perhaps a better designation would be a myoepithelial-rich pleomorphic adenoma, or possibly even an epithelial-myoepithelial carcinoma, particularly when the myoepithelial component is of the clear cell subtype [495]. Myoepitheliomas are distinguished from their malignant counterparts by the absence of infiltration [10, 557]. Other useful morphologic features include a low mitotic count, absence of necrosis, and perineural and angiolymphatic invasion [10, 557].

Immunohistochemically, myoepitheliomas will stain with both actins and cytokeratins as well as GFAP and S-100 to varying degrees [231]. These markers are less likely to be expressed in the plasmacytoid and clear cell types, though vimentin, which is rarely expressed in non-neoplastic myoepithelial cells, is strongly and uniformly positive in all cell types in myoepithelioma [476, 500, 606]. The second generation muscle marker calponin shows promising results, staining myoepithelial cells more consistently than smooth muscle actin [167]. Additionally,

p63, a basaloid/myoepithelial stem cell marker is also strongly and consistently expressed in myoepithelioma [300] serving as a useful adjunct using the traditional myoepithelial markers.

Pathogenesis

As with many rare salivary gland tumors, the pathogenesis of myoepithelioma is poorly understood. In one myoepithelioma, a t(1:12)(q25;q12) along with deletions of parts of chromosomes 3 and 9 has been described [606]. By comparative genomic hybridization, gross cytogenetic alterations were only present in 25% (3/12) of cases [220, 606]. In 3/12 myoepitheliomas, p53 mutations have been identified [498]. Additionally, p53 homologues p63 and p73 have a unique isoform expression profile in myoepitheliomas as compared to normal salivary tissue, namely the truncated transcriptionally inactive forms (ΔN isoforms) increased in myoepitheliomas [10, 73].

Prognosis

Prognosis is generally favorable; recurrences are relatively rare and are usually related to incomplete excision [495]. Malignant transformation is uncommon [485]. In one series, myoepithelial carcinomas had an antecedent myoepithelioma in only 8% (2/25) of cases [179, 217]. Some authors regard all clear cell myoepitheliomas as tumors of uncertain malignant potential even if they are histologically benign [604]. However, this may stem from the past usage of the term clear cell myoepithelioma interchangeably with epithelial-myoepithelial carcinoma [517].

Warthin's Tumor

Clinical Features

Warthin's tumor, which Warthin himself [420] called *papillary cystadenoma lymphomatosum*, is morphologically similar to other cystadenomas, but the demographic, pathologic, and morphologic features of this lesion are sufficiently distinct to separate it from these other cystadenomas. Warthin's tumor is the second most common salivary tumor overall, comprising 3% of all salivary tumors in the United States [179], though the incidence may be as high as 30% in smaller regions such as central Pennsylvania [517]. The mean age at diagnosis is 62 years, rarely occurring before the age of 40 years [341, 468]. This tumor more commonly occurs in males, though the male to female ratio has decreased dramatically within the past 50 years to about 2:1 [179, 517]. These trends in sex incidence as well as the aforementioned regional variation are likely attributable to the strong link between Warthin's tumor and smoking. Warthin's tumor has an eight times higher incidence in smokers than in non-smokers [535].

Warthin's tumor is essentially restricted to the parotid gland and its lymph nodes, with the tail of the parotid being the most common site of involvement. It is also the salivary gland tumor which occurs most commonly bilateral/multifocal (up to 20%) [587]. Rarely extraparotid Warthin's tumors have been described, comprising as high as 8% of all Warthin's tumors, essentially all occurring in the cervical lymph nodes [517]. Rare examples have been described in the other glands [462], but on close scrutiny these are either from the anterior tail of the parotid or adjacent lymph nodes. Most patients present with a painless mass that may fluctuate in size in as many as 40% of patients. Rarely, infarcted Warthin's tumors (see below) may cause pain [517].

Pathology

Grossly these tumors range from 1 to 10 cm (mean 3.5 cm) [504]. They are typically well circumscribed and often cystic to varying degrees. The cyst lining is often a nodular tan-white with papillary excresence s and the fluid contents are characteristically a granular brown reminiscent of "motor oil." The actual parenchyma is a nodular tan to dark brown (Fig. 3.8a). Microscopically, Warthin's tumor is comprised of a papillary proliferation lined by a double layer composed of surface columnar oncocytic epithelium (Fig. 3.8b) and a smaller basal layer of small cuboidal cells with myoepithelial characteristics. Mucinous, sebaceous, and squamous metaplasia have been seen in Warthin's tumor [200]. The surrounding stroma contains a highly ordered lymphoid architecture similar to an actual lymph node, with germinal centers often found in cores of the epithelial papillae. When Warthin's tumor arises in a lymph node, it may be mistaken for metastatic carcinoma, particularly papillary thyroid carcinoma. However, papillary thyroid carcinoma does not form a two cell layer proliferation, and will have characteristic nuclear features (clearing, overlap, grooves, elongation, and pseudoinclusions) which are absent in Warthin's tumor.

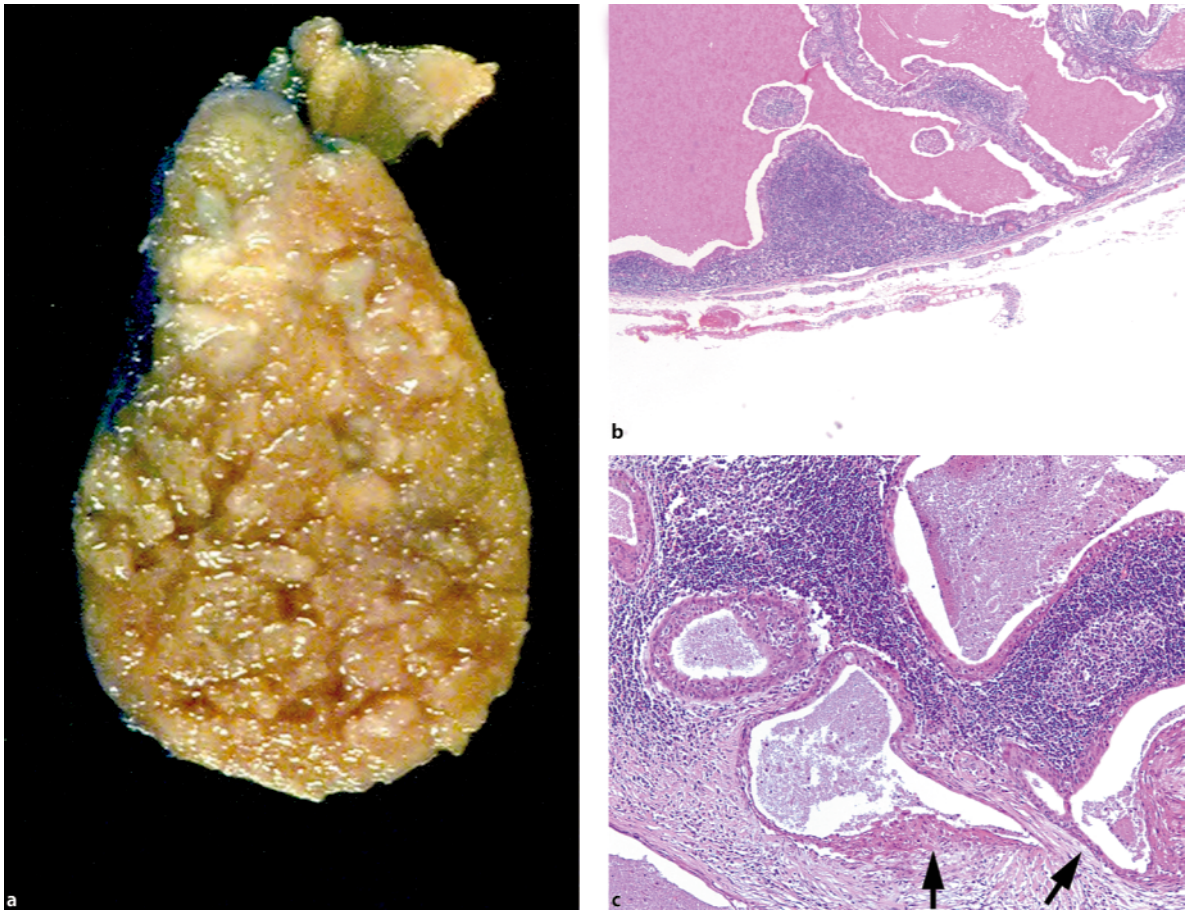

Fig. 3.8: Warthin's tumor. **a** A solid tan-brown tumor of the parotid with central papillary architecture (gross image). **b** A papillary cystic tumor lined by columnar oncocytic cells with a prominent lymphoid stroma including a capsule resembling that of a lymph node (H&E, 20×). **c** "Infarcted" Warthin's tumor with a transition to squamous metaplasia with surrounding fibrosis (*arrows*) (H&E, 100×)

The degree of epithelial proliferation varies greatly, and Seifert et al. classified Warthin's tumor into four histologic subtypes based largely on this epithelial to stromal ratio [153]. Their "type 4" Warthin tumor is of diagnostic interest as this represents Warthin's tumor with extensive squamous metaplasia. This so-called metaplastic or infarcted Warthin's tumor often shows extensive squamous metaplasia (Fig. 3.8c), necrosis, fibrosis, and histiocytic infiltrates, thought to be a result of mechanical or vascular induced changes [462]. In at least some cases, this is secondary to fine-needle aspiration [517]. This variant can be mistaken for a mucoepidermoid carcinoma or a metastatic squamous cell carcinoma. However, infarcted Warthin's tumor will still have a papillary configuration similar to typical Warthin's tumor. Additionally many infarcted Warthin's tumors will on careful examination still show areas of oncocytic columnar epithelium.

Immunohistochemical stains are not usually used for diagnostic purposes, but as with most oncocytic lesions, the epithelial cells of Warthin's tumor are ultrastructurally composed of mitochondria, which can also be stained by for phosphotungstic acid–hematoxylin (PTAH) or immunohistochemically with antibodies to mitochondrial components such as cytochrome c [566, 568]. The im-

munohistochemical profile of the lymphoid component is that of a reactive lymph node [22].

3

Pathogenesis

Despite being a fairly common and well-described identity, the pathogenesis of Warthin's tumor is not well understood and is still debated. The prevailing theory for its initial development is that Warthin's tumor is a proliferation of the intercalated and striated ducts of heterotopic salivary inclusions in intra- and periparotid lymph nodes rather than a tumor with a prominent lymphoid response. Since the parotid does not have a complete capsule, the lymph nodes and parotid parenchyma have the ability to intermingle embryologically [506]. While many other salivary gland neoplasms may have a prominent lymphoid stroma [392, 447], the fact that Warthin's tumor almost exclusively occurs in the parotid gland and its associated lymph nodes, and the presence of lymph node architectural elements, occasionally including capsular sinuses, give credence to this hypothesis. Also the involvement of the lymphoid component by metastatic carcinoma, granulomatous disease, and lymphomas in a distribution similar to that in lymph nodes further supports this belief [17, 290]; this is not simply a papillary oncocytic proliferation with a tumor-associated lymphoid response.

Another point of contention is whether this represents a true neoplasm or a reactive proliferation. Initial studies demonstrated cytogenetic alterations in some Warthin's tumors such as loss of the Y chromosome, 6p abnormalities, and t(11;19) which is interestingly also seen in mucoepidermoid carcinomas. However, loss of the Y chromosome is a senescent change that can be seen normal tissues, and many of the cytogenetic alterations seen in these series are usually only minority cell components in an otherwise normal stemline [362, 363]. More recently, Warthin's tumor has not been shown to have monoclonality, either by X chromosome-linked human androgen receptor analysis or by loss of heterozygosity profiling [233, 493, 628].

Regardless of origin and clonality, smoking likely contributes significantly to the pathogenesis of the tumor. One mechanism includes mitochondrial DNA damage resulting in mutations [517]. Possible contributing mechanisms other than smoking include autoimmunity and EBV infection [504, 617].

Prognosis

Prognosis with surgical excision alone is excellent with a recurrence rate of 2–5% [617]. Even these may represent separate tumors, since Warthin's tumor is often multifocal. Malignant transformation is extremely rare with an estimated occurrence of 0.1–2% [523]. Interestingly mucoepidermoid carcinoma is the most common histology, though squamous cell carcinoma and oncocytic carcinomas have been described [179].

Cystadenomas

Clinical Features

Cystadenomas are rare benign cystic salivary tumors that resembles Warthin's tumor, though the clinicopathologic features of this tumor are different. In contrast to Warthin's tumor, there is actually a slight female predilection, and there is no association with smoking [179, 600]. The mean age at presentation is 57 years [80]. The major site of involvement is the parotid gland (45%), though unlike Warthin's tumor, other cystadenomas can be in sites such as the lip and buccal mucosa [523]. Rarely these tumors have been described in the supraglottic larynx as well [243, 522].

Pathology

Cystadenomas range from unicystic (approximately 20%) to multicystic. The multicystic lesions may often have a larger central cyst. These cysts may be filled with a serous or mucinous fluid, and papillary excrescences may be evident within the cysts though these are far less prominent than in cystadenocarcinomas. The histology recapitulates the gross appearance, and the cysts are lined by one to two cell layers comprised of a mixture of oncocytic, mucinous, and focally sebaceous, or squamous epithelium. Papillary oncocytic cystadenomas and mucinous cystadenomas are the most common subtypes. The papillae of the former have a simple architecture with no ramification and minimal multilayering of cells [397]. Luminal tyrosine crystals are occasionally seen [248].

Lymphoid stroma is sparse to absent in contrast to Warthin's tumor. Cystadenocarcinomas and cystic salivary duct carcinomas tend to have more architectural

complexity with solid areas and angulated cystic spaces rather than the round contours seen in cystadenomas. Additionally, they will have more cytologic atypia and mitotic activity than cystadenomas. Cystadenomas may resemble low-grade mucoepidermoid carcinomas, but the former, even when they are mucinous, will be lined mostly by columnar epithelium and will not have the three cell populations seen in mucoepidermoid carcinoma. Acinic cell carcinomas may mimic cystadenomas, however, the acinar cell lining in the cysts can be highlighted by a periodic acid-Schiff (PAS) reaction after diastase stain.

Pathogenesis

The pathogenesis is not well understood. While these tumors bear a superficial resemblance to Warthin's tumor, demographics, the lack of a defined risk factor, and the site distribution suggest that these arise through distinct mechanisms.

Prognosis

The prognosis for this benign tumor is excellent; complete excision should be curative. One case of a carcinoma arising in a cystadenoma has been described.

Lymphadenomas

Clinical Features

Lymphadenomas consist of both sebaceous and non-sebaceous tumors. They are rare tumors that also bear resemblance to Warthin's tumor because of their prominent lymphoid stroma, though their epithelial constituents are different.

Sebaceous lymphadenomas, described as early as 1960 [20, 34, 146, 151, 213, 215, 344, 397, 594, 605, 621] are far more common than non-sebaceous lymphadenomas [74, 110, 345, 379]. They tend to occur in the elderly, beyond the sixth decade, and are almost always seen in the parotid gland [403, 461]. All reported non-sebaceous lymphadenomas to date have been described in males (age 13–79 years), exclusively in the parotid gland [379].

The typical presentation is that of a painless mass, mimicking a pleomorphic adenoma. Sebaceous lymphadenomas may occasionally be cystic, clinically resembling Warthin's tumor [379].

Pathology

Sebaceous and non-sebaceous lymphadenomas are grossly solid or cystic well-circumscribed tan masses. Histologically, sebaceous lymphadenomas will have solid to cystic nests of sebaceous cells, foamy polygonal epithelial cells with a slight basaloid appearance on the periphery of the nests embedded within a lymphoid stroma reminiscent of a lymph node (Fig. 3.9a, b). While some reports of non-sebaceous lymphadenomas show a cystic, albeit non-papillary, bilayered oncocytic proliferation within a lymphoid stroma, such tumors may be better classified as variants of Warthin's tumor [248]. The term non-sebaceous lymphadenoma should be reserved for solid basaloid or tubular benign neoplasms with a prominent lymphoid stroma.

These lymphadenomas may mimic MESA, lymphoma, or lymphoepithelial carcinoma. However, the circumscription, lobular nested appearance, and bland cytology of lymphadenomas separate it from lymphoepithelial carcinoma. Unlike MESA, lymphadenomas should only have a localized lymphoid stromal component without significant sialadenitis outside the lesion. Lymphomas should have effacement of lymphoid architecture characterized by abnormal non-polarized follicles or an absence altogether [162]. Sebaceous lymphadenocarcinoma is among the rarest of salivary tumors and can be separated from lymphadenomas by its infiltrative pattern and other features of malignancy such as perineural and angiolymphatic invasion.

Pathogenesis

Lymphadenomas are thought to have an origin from epithelial rests within lymph nodes, similar to Warthin's tumor [385]. In support of this theory is the occasional coexistence of mixed sebaceous lymphadenoma-Warthin's tumors [578]. Sebaceous components are thought to be ectodermally derived and formed embryologically along lines of closure [29, 109]. Ultrastructurally and chemically, the constituents of sebaceous glands in the parotid gland and sebaceous glands of the skin are identical [82].

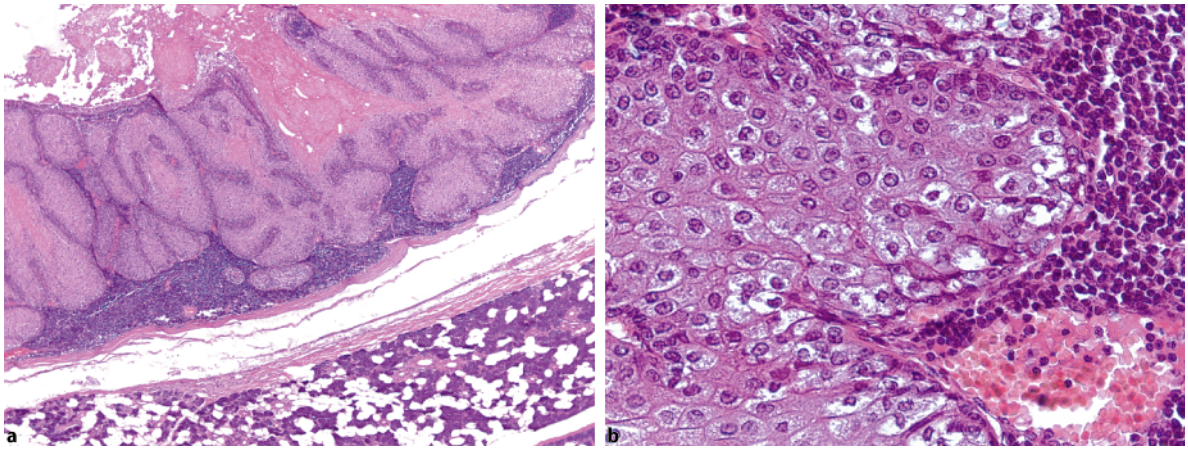

Fig. 3.9: Sebaceous lymphadenoma. **a** A solid and cystic proliferation with a lymphoid stroma reminiscent of a lymph node (H&E, 40×). **b** The proliferation is comprised of foamy polygonal cells defining the sebaceous cell type (H&E, 400×)

Prognosis

Prognosis is excellent; resection is curative.

Oncocytoma and Oncocytosis

Clinical Features

The distinction between oncocytoma and oncocytosis is often arbitrary. Oncocytoma is a rare monomorphic salivary tumor that resembles oncocytosis, which is a diffuse or multifocal proliferation of oncocytes. Oncocytoma is the preferred terminology if an oncocytic lesion is solitary or dominant and/or encapsulated. Hence, by this definition an oncocytoma can arise in the setting of oncocytosis.

It accounts for 1% of salivary tumors. Both oncocytoma and oncocytosis occur usually in the sixth decade, mirroring the increase in the number of oncocytes in salivary glands that is seen with increasing age [324]. About 20% of patients with oncocytoma have an antecedent history of radiation exposure [82]. They may be solitary, bilateral (7%), or arise in the setting of multinodular oncocytic hyperplasia. The parotid gland is the most common (84%) site while the remainder arise almost exclusively in the submandibular gland [381]. Rarely oncocytomas of the minor salivary glands have been described [82].

Clinically oncocytosis presents as unilateral or bilateral salivary gland enlargement, typically of the parotid gland [82, 459]. Multifocal nodular oncocytic hyperplasia is far more common than diffuse oncocytosis.

Pathology

Grossly, oncocytoma is a solid well-circumscribed mass measuring 3–4 cm. Diffuse oncocytosis presents as a diffuse enlargement while multifocal nodular oncocytic hyperplasia has at least two nodules within the salivary parenchyma. As with oncocytic lesions at other sites, oncocytosis and oncocytoma are a tan brown to dark mahogany brown. Oncocytosis can be divided into two main pathologic categories of conditions that clinically and histologically mimic neoplasia: multifocal nodular oncocytic hyperplasia and diffuse oncocytosis.

Microscopically, diffuse oncocytosis involves the entire gland with minimal if any residual normal salivary tissue. In contrast, oncocytoma and multifocal nodular oncocytic hyperplasia consist of solid/trabecular, well-demarcated proliferations of oncocytes, cells with abundant granular pink cytoplasm and round nuclei, embedded in otherwise normal-appearing salivary tissue. Oncocytomas may have capsules, particularly in the parotid gland (Fig. 3.10a). The ultrastructural correlate of the granular cytoplasm of oncocytes is the abundance of mitochondria. Clear cell change can be seen in these lesions and reflects the accumulation of glycogen (Fig. 3.10b) [462, 524].

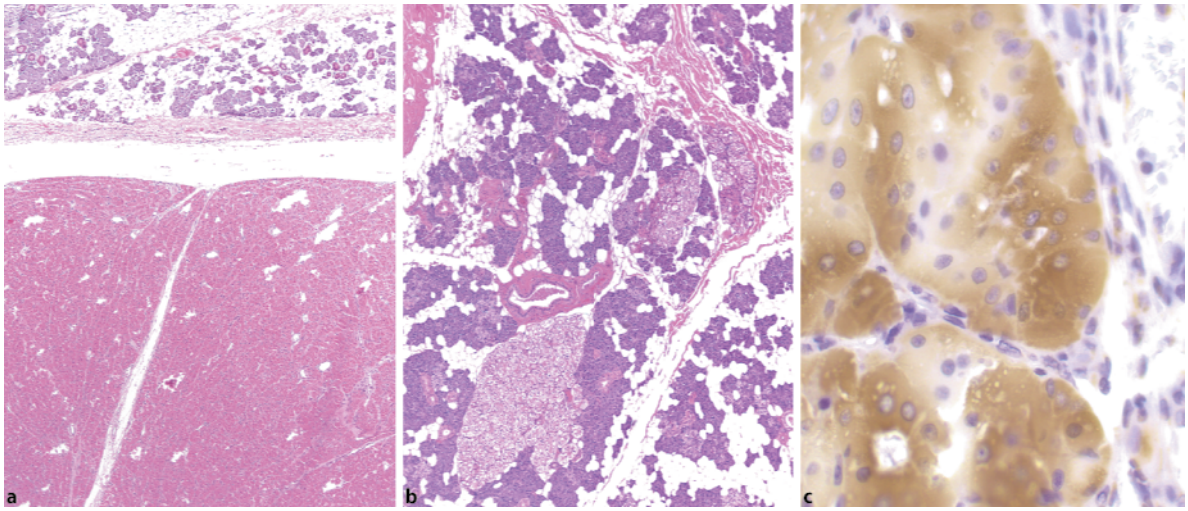

Fig. 3.10: Oncocytoma and oncocytosis. **a** An encapsulated parotid tumor comprised of solid "pink" or oncocytic cells (H&E, 40×). **b** Clear cell oncocytosis of the parotid (H&E, 100×). **c** Immunohistochemical stain for cytochrome c showing positivity in an oncocytoma (DAB chromogen, 400×)

In contrast, oncocytic carcinomas are characterized by necrosis and perineural and vascular invasion. Metastatic carcinomas, particularly renal cell carcinoma and Hürthle cell thyroid carcinoma can mimic oncocytosis or oncocytoma, however, immunohistochemical stains are helpful in ruling out these metastatic tumors [29, 109]. Other considerations include acinic cell carcinoma, oncocytic mucoepidermoid carcinoma, and oncocytic myoepitheliomas. A battery of histochemical stains, PAS with diastase treatment for acinic cell carcinoma, mucicarmine for mucoepidermoid carcinoma, and myoepithelial markers such as smooth muscle actin and vimentin for myoepithelioma, can help to exclude these entities. Additionally oncocytomas, because of their mitochondria, will be positive by phosphotungstic acid–hematoxylin stain or by immunohistochemistry toward mitochondrial cytochromes (Fig. 3.10c) [100].

Pathogenesis

The pathogenesis of oncocytosis and oncocytoma is unclear, but is likely a progression from the age-related precursor of oncocytic metaplasia [381]. While mitochondrial abnormalities are a plausible pathogenic mechanism, mitochondrial DNA C-tract mutations are noted to be rare in these lesions [82].

Prognosis

The prognosis is excellent for lesions classified both as oncocytoma and oncocytosis [87, 178]. Recurrence rates for oncocytomas are roughly 10% in oncocytoma, and may be a result of multifocality rather than incomplete excision. Recurrent cases also tend to have marked clear cell change [8, 90, 279, 537].

Miscellaneous Rare Benign Tumors and Tumor-like Lesions

Ductal Papillomas

Clinical Features

Ductal papillomas are a rare group of benign papillary neoplasms of the large excretory duct. There are three major subtypes of ductal papillomas of salivary gland origin that are about equally rare: intraductal papilloma, inverted ductal papilloma, and sialadenoma papilliferum.

Intraductal papillomas are rare with only 40 cases reported using strict criteria [87]. They are typically a tumor of minor salivary duct origin, though tumors in the parotid, submandibular, and sublingual glands have been described [87, 99, 127, 148, 236, 271, 283, 321, 342, 614,

618]. They typically occur in the fifth or sixth decade as a painless submucosal mass (range 29–77 years) without a gender predilection [236].

Inverted ductal papillomas are also rare with only 35 cases reported [401]. Inverted ductal papilloma is a tumor of minor salivary origin (lip and buccal mucosa) with the only tumor reported in the major salivary gland being debatable [87, 178, 257, 582]. There is no sex predilection and the mean age of occurrence is 53 years. These tumors typically present as a painless submucosal mass with a central dilated pore reflecting their localization to the salivary excretory duct orifice.

Sialadenoma papilliferum resembles its skin adnexal counterparts syringocystadenoma papilliferum and hidradenoma papillferum [87] and is rare with under 50 cases reported, and estimated incidence of approximately 0.2% [87]. These tumors also typically occur in the fifth to sixth decade and they are most frequent on the palate, but unlike other ductal papillomas, they present as granular papillary masses reflecting their often extensive surface component.

Pathology

Grossly, inverted ductal and intraductal papillomas are well-circumscribed masses, the latter more cystic, that are typically less than 3.0 cm. Sialadenoma papilliferum is a granular tan mass that involves the surface mucosa [489]. Microscopically, inverted ductal papilloma has an endophytic growth of transitional/basaloid cells with microcysts reminiscent of its Schneiderian counterpart inverted papilloma. The nests of basaloid cells have central cleft-like spaces that are lined by columnar excretory duct-type mucinous cells. Intraductal papilloma is histologically composed of a cystic dilation of the excretory duct with a papillary arborizing proliferation of a mixture of oncocytic or mucinous cells. Histologically sialadenoma papilliferum shows surface papillary projections of oncocytic columnar cells intermingling with the surface squamous epithelium with a well-demarcated submucosal component that is comprised of large-caliber ducts with uniform "saw tooth" like papillary luminal invaginations.

All ductal papillomas may be mistaken for other papillary salivary gland tumors, particularly cystadenomas and cystadenocarcinomas. Cystadenomas and cystadenocarcinomas are deeper within the salivary gland parenchyma and can be multicystic unlike ductal papillomas [342]. Nonetheless, this distinction in some cases is not well defined. In the pancreas, intraductal papillary mucinous neoplasms and mucinous cystic neoplasms are separated by the fact that the former maintains its connection to the ductal system [401]. In contrast, the understanding of cystadenomas and cystadenocarcinomas of the salivary gland from this standpoint is rudimentary if at all existent; and the possibility that many of these cystadenomas may actually be intraductal papillomas or "papillomatosis" has not been examined in the literature.

Pathogenesis

Other than the presumed excretory ductal origin, not much is know about the pathogenesis of ductal papillomas. Of note, inverted ductal papillomas, unlike Schneiderian papillomas, have no known human papilloma virus association [87]. Also, unlike its cutaneous counterpart syringocystadenoma papilliferum, sialadenoma papilliferum is not a part of the nevus sebaceous complex [439, 514].

Prognosis

Prognosis is generally thought to be excellent, though most series have little or no follow-up [6, 138, 190, 208, 248, 306, 313, 322, 368, 455]. Rare cases of malignant intraductal papillomas and transformation of sialadenoma papilliferum are described [313], but as a rule, excision is thought to be curative.

Sebaceous Adenoma

Clinical Features

While sebaceous differentiation can be seen in a variety of salivary tumors, purely sebaceous adenoma without a lymphoid component is extremely rare with less than 25 cases reported [173]. The mean age is roughly 62 years with a slight male predominance. Sites that are usually involved are the parotid gland and the oral cavity closely mirroring the distribution of Fordyce granules and ectopic sebaceous rests [208].

Pathology

These tumors are well circumscribed and composed of sheets or lobules of sebaceous cells. These must be distinguished from other clear cell neoplasms such as mucoepidermoid carcinoma, acinic cell carcinoma, and clear cell oncocytoma among others [613]. The oil red O stain on frozen sections and electron microscopy remain the two main supportive studies to prove sebaceous differentiation: the presence of intracellular lipids within the foamy cells.

Pathogenesis

Unlike cutaneous sebaceous adenomas there is no described association with Muir-Torre syndrome, a hereditary non-polyposis colorectal carcinoma syndromic variant, suggesting a different pathogenesis [248, 313]. While non-neoplastic ectopic sebaceous rests express androgen receptor just as in their cutaneous counterparts [67, 246, 254, 310, 525, 532], it is not clear whether sebaceous adenomas express this marker.

Prognosis

The prognosis is excellent; none of the cases reported have recurred after excision [254].

Sclerosing Polycystic Adenosis

Clinical Features

Sclerosing polycystic adenosis is an extremely rare cystic lesion resembling fibrocystic disease of the breast with only 37 cases described in the literature [254]. The mean age of occurrence is 44.5 years with no sex predilection [246, 525]. The typical presentation is that of a slow-growing usually painless mass, usually in the parotid.

Pathology

These tumors range from 0.3 to 6.0 cm and are grossly comprised of homogeneous tan masses with a microcystic cut surface. Microscopically, they are well circumscribed with cystic spaces lined by varying proportions of ductal and acinar cells. A spectrum of changes that can be seen in fibrocystic disease of the breast can also be seen in sclerosing polycystic adenosis including sclerosing adenosis, apocrine metaplasia, and atypical ductal hyperplasia [520]. Changes of salivary ductal carcinoma in situ have rarely been identified [77, 538, 546]. There is an outer myoepithelial layer to the ducts and tubules seen in sclerosing polycystic adenosis, distinguishing these lesions from an invasive salivary duct carcinoma.

Pathogenesis

While traditionally considered a non-neoplastic lesion, recent studies of X chromosome-linked human androgen receptor suggest a clonal and thus neoplastic origin to this lesion [77, 295, 481].

Prognosis

The prognosis is fairly good, even in cases with changes of salivary duct carcinoma in situ, with a local recurrence rate of 19%. No metastases or mortality have been reported with this disease.

Malignant Tumors

Adenoid Cystic Carcinoma

Clinical Features

The term adenoid cystic carcinoma was coined by Spies in 1930 [68, 349, 560]. Robin, Lorain and Laboulbene are credited with the first microscopic description which appeared in a paper they published in 1853 [77, 168, 226, 268, 599]. In 1859 Billroth suggested the term cylindroma and over the years numerous other terms have been proposed for this tumor including tubular carcinoma, tubular sarcoma, endothelioma hyalinum, adenocystic basaloid carcinoma, adenocystic carcinoma, adenoepithelioma, basaloma, and basal cell tumor to name just a few [168, 226, 599]. The preferred term is adenoid cystic carcinoma. It has the advantage of identifying the lesion as a carcinoma while avoiding confusion with the benign cutaneous appendage tumor known as cylindroma. The

term adenoid cystic carcinoma is still somewhat misleading however since the tumor is not cystic!

Although the majority arise from the major and minor salivary glands, identical tumors can arise from seromucous glands throughout the upper and lower respiratory tract and from the esophagus, lacrimal glands, ceruminous glands, Bartholin's glands, Cowper's glands, breast, uterine cervix, vulva, and rarely the ovary. Adenoid cystic carcinoma accounts for 10% of all salivary gland neoplasms and 30% of all minor salivary gland tumors [351]. It also accounts for 20% of all malignant salivary gland tumors making it the second most common salivary gland malignancy. It is the most common carcinoma of minor salivary glands where the most frequent location is the palate [114]. Adenoid cystic carcinoma makes up 12–15% of parotid gland carcinomas, 30–60% of submandibular gland carcinomas, and 35–55% of minor salivary gland carcinomas [168, 338, 474, 546]. Approximately 25% arise in the major salivary glands and 75% in the minor salivary glands [30, 114, 117].

Adenoid cystic carcinoma is most frequently encountered in individuals between 40 and 60 years of age. It rarely afflicts those younger than 20 years of age. Although some series have a slight female predominance others show either no sex predilection or a male predominance [30]. The most common symptom is a slow-growing frequently painless mass, a feature which may lull both patient and physician into a false sense of security. More ominous signs and symptoms include fixation to adjacent tissues and paraesthesia or paralysis due to the affinity of this tumor for perineural invasion. Ulceration may occur with intraoral tumors and obstruction and epistaxis with those arising from seromucous glands in the sinonasal tract.

Pathologic Features

Adenoid cystic carcinoma, despite its name, is grossly solid rather than cystic and firm. The tumor may be well or poorly circumscribed. The cut surface is pink tan and non-hemorrhagic. Close inspection of those that appear well circumscribed usually reveals areas of infiltration.

Microscopically the tumor is composed of ductal and myoepithelial cells. The predominant cell type consists of cells with dense angular nuclei and scant frequently clear cytoplasm. The cells are considered to be of myoepithelial origin. A second and much less frequent cell type has a nucleus with a more open chromatin pattern and contains more abundant pink cytoplasm. This second cell type is considered to be of ductal origin [30, 103, 114, 164, 182].

Three characteristic growth patterns have been described, namely tubular or trabecular, cribriform, and solid. While all three histologic patterns are often encountered in a single tumor, frequently one pattern predominates. The cribriform pattern is the most common and also most easily recognizable. Proliferation of myoepithelial-type tumor cells form nests in which the cells surround spaces or pseudolumens producing a classic sieve or Swiss cheese pattern (Fig. 3.11a, b). The pseudolumens are filled with dense eosinophilic basement membrane material produced by the myoepithelial cells or basophilic mucinous material [353]. This basement membrane material also surrounds nests of tumor cells. When this material is extensive it can result in disruption of the cribriform pattern in which case thin strands of tumor cells stream through this material. True lumens lined by ductal-type epithelium are rare and smaller than the pseudolumens. They may contain mucicarmine and PAS-positive diastase-resistant mucin. The stroma is commonly dense and hyalinized but may also be myxoid. There is a very strong predilection for perineural invasion.

The tubular growth pattern features ducts and tubules lined by an inner layer of epithelial cells and an outer type of myoepithelial cells. Tubular structures containing eosinophilic hyalinized or basophilic material are also present.

In the solid pattern of adenoid cystic carcinoma, rounded and lobulated solid nests and islands of tumor cells predominate containing few if any pseudolumens or true lumens. While cells similar to those seen in the tubular and cribriform growth patterns may be present, over all the cells in the solid pattern tend to be larger and the nuclei larger and less angular. Cellular pleomorphism and comedonecrosis can also be seen, features not typical of the tubular and cribriform growth patterns. Mitoses are often present and may reach counts as high as 5 or more per 10 high power fields. This is in contrast to the tubular and cribriform growth patterns where mitotic figures are infrequently encountered.

Immunohistochemical stains confirm the presence of both myoepithelial and epithelial cells in adenoid cystic carcinoma. The myoepithelial cells are positive for muscle-specific actin and usually stain for S-100 protein as well as vimentin, p63, and cytokeratin. The epithelial cells stain for cytokeratin, carcinoembryonic antigen, and

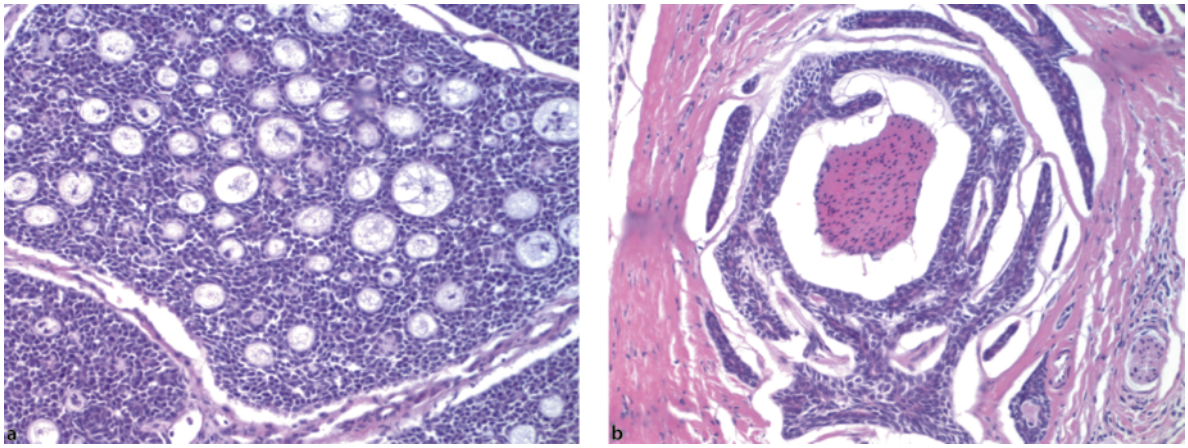

Fig. 3.11: Adenoid cystic carcinoma. **a** Cribriform growth pattern. Cells with dense angular nuclei and scant clear cytoplasm surround spaces producing a classic Swiss cheese pattern (H&E, 200×). **b** Perineural invasion (H&E, 200×)

epithelial membrane antigen and are negative for muscle-specific actin and vimentin. They may or may not express S-100 protein [469]. Recently adenoid cystic carcinomas have been shown to be positive for MUC3 [14, 204, 229, 406]. They may also be estrogen and progesterone receptor positive although not in all cases [182]. Approximately 90% are c-kit (CD117) positive [142].

Differential Diagnosis

Included in the differential diagnosis of adenoid cystic carcinoma are basaloid squamous cell carcinoma, basal cell adenocarcinoma, basal cell adenoma, cellular pleomorphic adenoma, polymorphous low-grade adenocarcinoma, and the basal cell and plexiform subtypes of ameloblastoma. The staining pattern with p63 is useful in distinguishing basaloid squamous cell carcinoma from adenoid cystic carcinoma. Basaloid squamous cell carcinomas consistently display diffuse staining of nearly 100% of the tumor cells with p63. Adenoid cystic carcinomas, on the other hand, show staining of a single peripheral layer of cells or compartmentalized staining with surrounding or interspersed p63 negative cells [463].

Basal cell adenomas, unlike adenoid cystic carcinomas, are characterized by peripheral palisading, a delicate fibrovascular stroma, a circumscribed rather than infiltrating growth pattern and lack of perineural invasion. Rarely, however, they may show trabecular and solid cribriform growth patterns reminiscent of adenoid cystic carcinoma [250]. Basal cell adenocarcinomas show areas of invasive growth and perineural invasion, features in common with adenoid cystic carcinoma, but otherwise resemble basal cell adenomas.

Cellular pleomorphic adenomas can resemble adenoid cystic carcinomas, however, careful examination of the junction of the cellular elements with the stroma aids in the distinction. In pleomorphic adenomas the myoepithelial cells spin off the epithelial elements and blend into the stroma. By contrast, there is a sharp demarcation between the cellular components of adenoid cystic carcinomas and the surrounding, often hyalinized, stroma. In addition, perineural invasion is not present in pleomorphic adenomas. Pleomorphic adenomas are also GFAP positive and adenoid cystic carcinomas are GFAP negative.

Perineural invasion occurs as often in polymorphous low-grade adenocarcinoma (PLGA) as in adenoid cystic carcinoma. However, the cells in PLGA are cuboidal to columnar with eosinophilic or clear cytoplasm and vesicular nuclei. The classic hyperchromatic angulated nucleus of adenoid cystic carcinoma is not present. Expression of c-kit may also be helpful as it is positive in virtually 100% of adenoid cystic carcinomas and in only approximately 50–60% of PLGA [268, 474, 546]. In addition, it has also been reported that where as 90% of tumor cells in PLGA are positive for epithelial membrane antigen, only the epithelial cells lining true lumens stain in adenoid cystic carcinoma [474].

Peripheral palisading is inconspicuous in the basal cell subtype of ameloblastoma and stellate reticulum is absent. The tumor is composed of islands and anastomosing cords of small basaloid cells. These features may lead to confusion in separating this tumor from adenoid cystic carcinoma. The plexiform subtype also lacks peripheral palisading and has a scant stellate reticulum. It consists of anastomosing cords of low columnar to cuboidal tumor cells. Lack of myoepithelial cells and absence of perineural invasion are useful features in separating these subtypes of ameloblastoma from adenoid cystic carcinoma.

Treatment and Prognosis

Surgical resection is the primary treatment for adenoid cystic carcinoma. Lymph node metastases are uncommon and, although controversial, neck dissection may be reserved for patients with clinically positive lymph nodes [94, 104, 268, 338, 351, 407, 474]. Distant metastases, on the other hand, develop in 20–60% of cases and most commonly involve the lung, liver, bone, and brain [77]. Radiation as the sole treatment has proven ineffective since the tumor is radiosensitive but not radiocurable. Postoperative radiotherapy, however, has proven effective in improving local control of the tumor [7, 204, 294, 450]. The best results appear to be obtained by using a combination of radical surgery and postoperative radiation therapy [122, 128, 338, 349, 393, 407, 499, 542, 586]. The usefulness of chemotherapy remains to be proven. Since adenoid cystic carcinomas are usually c-kit positive, clinical trials have been undertaken using Imatinib. These have yielded conflicting results [135].

Data from a combined series of over 800 cases of adenoid cystic carcinoma from all sites shows the following survival rates: 75% at 5 years, 40% at 10 years, 25% at 15 years, and 20% at 20 years [54, 264, 554]. In a series of 129 cases, univariate analysis showed that age over 45 years, paresthesia, advanced clinical stage, solid histological growth pattern, and increased expression of p53 correlated with a poor prognosis. Advanced clinical stage, solid histological growth pattern, and increased expression of p53 were found to be independent significant prognostic factors of a poor prognosis in multivariate analysis of this series [165, 183, 225, 226, 275, 376, 581, 586, 589, 599]. Studies looking only at the histologic growth pattern have shown that grade I tumors (predominately tubular with no solid component), grade II tumors (predominately cribriform with no more than 30% solid component), and grade III tumors (solid component greater than 30%) have cumulative 15-year survival rates of 39%, 26%, and 5%, respectively [71, 259, 339]. The prognostic significance of perineural invasion and DNA ploidy remain controversial [550].

Mucoepidermoid Carcinoma

Clinical Features

Mucoepidermoid carcinoma is the most common cancer of the salivary glands. Although it accounts for 30% of all cancer of the salivary glands, it forms only 10% of all salivary gland tumors and less than 5% of head and neck cancers [219]. Stewart et al. first reported this tumor in the United States in 1945 [83]. They coined the term mucoepidermoid tumor and suggested that it occurred in both a benign and malignant form. Foote and Frazell were the first to point out that all mucoepidermoid tumors are carcinomas albeit those which histologically appear low grade very rarely metastasize [71, 270, 343, 373].

Slightly more than 50–60% arise in the major salivary glands and of these, greater than 80% occur in the parotid, 8–13% in the submandibular gland, and 2–4% in the sublingual gland. Most of the remainder arise from minor salivary glands, usually in the palate. Seromucous glands at other sites such as the sinonasal tract, larynx, and trachea may also be the site of mucoepidermoid carcinomas on rare occasions [83, 258, 259].

Mucoepidermoid carcinoma most commonly occurs in adults (mean age 49 years), although no age group is excluded and indeed it is the most common salivary gland cancer in the pediatric age group [92, 601]. In some series it is more common in women by a ratio of 3:2 while in others there is no sex predominance [71]. The rare intraosseous (central) mucoepidermoid carcinomas, however, have an established female predominance [51, 71, 187].

The most common presenting symptom is a slowly enlarging painless mass of several years duration clinically mimicking a pleomorphic adenoma or other benign neoplasm. Pain and tenderness along with rapid enlargement may be seen with high-grade lesions [452, 563].

Pathologic Features

The gross appearance varies with the grade of the tumor. Low-grade mucoepidermoid tumors produce well-circumscribed though unencapsulated ovoid masses usually

2–4 cm in diameter. Solid gray-white or gray-pink areas are mixed with mucus-filled macrocysts while intermediate grade neoplasms are grossly similar but lack macrocysts. High-grade tumors may be similar in size but grossly are not well circumscribed and gross infiltration is often evident. They do not contain macrocysts although hemorrhage and necrosis, which are not infrequent, may lead to areas of cystic degeneration.

By definition, mucoepidermoid carcinomas are composed of three types of cells, namely mucous cells, epidermoid cells, and intermediate cells. Mucous cells are filled with mucin (mucicarmine and PAS-diastase positive) which compresses the small dark nucleus peripherally. Epidermoid (squamous) cells are polygonal with vesicular nuclei and abundant eosinophilic cytoplasm. Keratinization is rare and never extensive. Intercellular bridges are also not frequently encountered. The third type of cell is the intermediate cell, thought by some to be able to differentiate into mucous and epidermoid cells [88, 273, 315]. Intermediate cells are smaller than either mucous or epidermoid cells and do not stain with either PAS or mucicarmine stains. Intermediate cells range from small basaloid cells to cells just smaller than epidermoid cells and when numerous grow in syncytia. They are also negative with PAS and mucicarmine stains. Less frequently clear cells, oncocytes, spindle cells, and sebaceous cells may predominate. The clear cell variant of mucoepidermoid carcinoma is composed primarily of clear cells with well-defined cell borders and clear cytoplasm due to the presence of glycogen [107, 203, 282, 305, 372, 424, 584]. Oncocytic mucoepidermoid carcinomas show extensive oncocytic change [431]. Other variants include the spindle cell, sebaceous cell, and sclerosing variants [259]. The sclerosing type is characterized by dense central sclerosis with a prominent peripheral inflammatory response composed of lymphocytes, plasma cells, and frequently eosinophils. Possible etiologies of the sclerosis include a reaction to extravasated mucin and/or infarction. In addition there is at least one report of dedifferentiation in a low-grade mucoepidermoid carcinoma [83].

Three histologic grades of mucoepidermoid carcinoma have been described. Low-grade tumors contain numerous cysts of varying size including macrocysts. These cysts are lined predominately by well differentiated mucin containing goblet cells. The cysts are filled with mucus which may extravasate producing an extensive inflammatory reaction in the surrounding stroma. Solid nests of intermediate and epidermoid cells are infrequent and there is essentially no cellular pleomorphism. Mitoses are very infrequent and there is no perineural invasion. Low-grade tumors are well circumscribed both grossly and microscopically (Fig. 3.12a, b). Intermediate-grade tumors have fewer and smaller cysts and fewer cysts lined exclusively by goblet cells. Intermediate cells tend to predominate and they, along with epidermoid cells, produce large cellular sheets. Pleomorphism is absent or minimal, mitoses are infrequent, and perineural invasion is very uncommon. Grossly intermediate-grade tumors are usually circumscribed but microscopically infiltration of the adjacent salivary gland tissue is present. High-grade

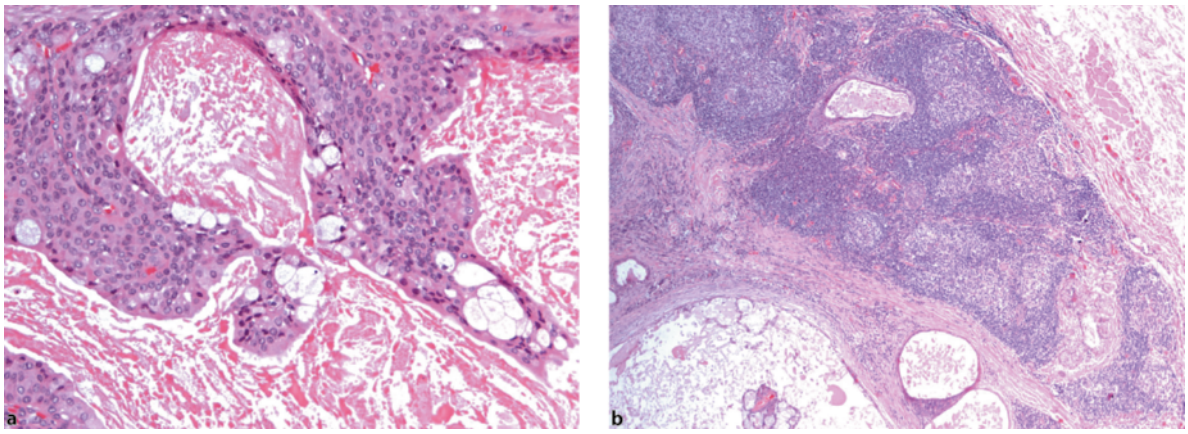

Fig. 3.12: Mucoepidermoid carcinoma. **a** Low-grade mucoepidermoid carcinoma. Tumor is cystic and contains cytologically bland mucous, epidermoid, and intermediate cells (H&E, 200×). **b** Low-grade mucoepidermoid carcinoma with prominent peripheral lymphoid inflammatory response (H&E, 200×)

tumors are characterized by a solid growth pattern composed of various mixtures of intermediate, epidermoid, and squamous cells. Cystic structures are infrequent and small. Mucous cells form less than 10% of the cellular component and indeed may be difficult to recognize unless the tissue is stained with mucicarmine or PAS-diastase. Cytologic and nuclear pleomorphism are present and mitoses are easily found. Perineural invasion may also be present. Grossly the high-grade tumors are not well circumscribed and microscopically tissue infiltration is seen. In an attempt to make grading more objective two numerical scoring systems have been proposed, one by Goode et al. [591] and the other by Brandwein et al. [276, 353, 607]. In one study 89% of high-grade mucoepidermoid carcinomas were aneuploid while 88% of low and intermediate tumors were diploid [11, 276, 607].

Mucoepidermoid carcinomas stain for cytokeratins and may focally stain for vimentin. Negative staining for GFAP and usually for muscle-specific actin and S-100 protein are consistent with an epithelial origin with no significant myoepithelial component. Mucoepidermoid carcinomas also express MUC1, MUC4, and MUC5AC [276]. MUC1 expression increases with tumor grade while staining for MUC4 decreases with grade [444, 591]. Positive staining for MUC5AC may be helpful in separating high-grade mucoepidermoid carcinoma from squamous cell carcinoma [469]. High-grade tumors are typically positive for HER2/neu and typically show greater than 20% nuclear staining for Ki-67, while low-grade tumors are negative for HER2/neu and show less than 20% nuclear staining for Ki-67 [601]. Mucoepidermoid carcinomas do not stain for estrogen receptor [574, 601].

Differential Diagnosis

High-grade mucoepidermoid carcinomas contain few mucin cells and frequently extensive areas of squamous differentiation making distinction from a squamous cell carcinoma difficult. In these cases use of mucin stains to identify the rare mucin-containing cells, positive staining for MUC5AC, and lack of extensive keratinization are useful in recognizing the tumor as a mucoepidermoid carcinoma.

Adenosquamous carcinoma of salivary glands is rare and usually arises in minor rather than major salivary glands. By definition it contains separate distinct foci of adenocarcinoma and squamous cell carcinoma unlike mucoepidermoid carcinoma where both cell types are intimately admixed.

The clear cell variant of mucoepidermoid carcinoma may mimic other primary and non-primary clear cell carcinomas. Proper classification usually comes down to identifying at least some areas containing mucous cells and intermediate and or epidermoid cells.

Cystadenomas and cystadenoma carcinomas tend to have less stroma than mucoepidermoid carcinomas. They also lack the solid proliferations of intermediate and epidermoid cells and typically show a papillary component.

Central mucoepidermoid carcinoma is usually low grade and must be distinguished from glandular odontogenic cysts. According to Waldron and Koh, some areas of glandular odontogenic cysts can be histologically identical to low-grade central mucoepidermoid carcinomas [339, 470]. The epithelial lining of glandular odontogenic cysts, however, is uniformly thin and lacks the more solid areas of epithelial proliferation seen in mucoepidermoid carcinomas [470].

Treatment and Prognosis

The treatment of mucoepidermoid carcinomas is surgical resection. Low-grade tumors are usually treated with wide local excision without neck dissection. Neck dissection in intermediate-grade tumors is probably only indicated if lymph nodes are clinically suspicious. High-grade cancer is treated with neck dissection. Prognosis is influenced by the grade and stage of the tumor, and patient age and sex [470]. Histologic grade is considered one of the most important factors in prognosis. Overall 5-year survival rates range from 92% to 100% for low-grade tumors, 62% to 92% for intermediate-grade tumors, and 0% to 43% for high-grade tumors [531]. Age over 40 years is also associated with a poor prognosis but it should be noted that most cancers in the first and second decades of life are histologically low-grade tumors [470]. Tumors of the submandibular gland have a worse prognosis than tumors of the parotid gland [202, 255, 350, 440, 475, 601, 619]. While all mucoepidermoid carcinomas are capable of metastasizing, metastases most often occur in high-grade lesions. In addition to lymph nodes, the usual sites of metastases are the lungs and bone [601].

Central (Intraosseous) Mucoepidermoid Carcinoma

Central mucoepidermoid carcinomas are rare with less than 100 cases having been reported [202, 440, 601]. They

are, however, the most common intraosseous salivary gland tumor [601]. They occur three times more often in the mandible (usually in the region of the third molar) than the maxilla and are twice as common in women. Although they have been reported in both the young and the very old, the mean age at diagnosis is 51 years [40, 72, 186, 194, 245, 360, 370, 415, 453, 567]. Usually low grade, they are thought to arise from the lining of odontogenic cysts or from entrapped salivary gland tissue [567].

Malignant Mixed Tumors

The term malignant mixed tumor is an all inclusive term encompassing three clinically and histologically distinct tumors. They are: (1) carcinoma ex-pleomorphic adenoma, (2) malignant mixed tumor (carcinosarcoma), and (3) metastasizing mixed tumor.

Carcinoma Ex-pleomorphic Adenoma

Clinical Features

Carcinoma ex-pleomorphic adenoma (CEPA) is by definition a carcinoma arising in a pleomorphic adenoma. While it makes up only 5–15% of all salivary gland carcinomas, it accounts for 99% of all malignant mixed tumors [245]. Thackray and Lucas have estimated that left unresected, approximately 25% of pleomorphic adenomas would eventually undergo carcinomatous change [239, 370, 410]. Approximately 80% arise in the major salivary glands and 20% in the minor salivary glands. Among the major salivary glands the parotid gland is the primary site in 81.7% of cases, the submandibular gland in 18%, and the sublingual gland is 0.3% [94, 219, 370, 540]. Origin in minor salivary glands occurs in approximately 20% of cases with the palate being the most frequent intraoral site [61, 186, 453].

Most series show a female to male ratio of 1.2 to 3:1 [61, 186, 194, 239, 245, 370, 540, 567]. In at least three series, however, men outnumbered women by a ratio of 2:1 [21, 41, 61, 130, 194, 245, 370, 540, 567]. The average age at diagnosis is 50–60 years which is approximately 10 years older than most individuals with pleomorphic adenoma. While cases have been reported in patients from the first to the ninth decade, CEPA is extremely uncommon in individuals below the age of 20 years [41, 239, 245, 490].

Reflecting its origin in a pleomorphic adenoma, the most common clinical presentation is sudden rapid enlargement of a long-standing (average 20 years) previously non or slowly enlarging painless mass. In 12–55% of cases this rapid enlargement will be painful and often associated with facial nerve palsy and fixation to the surrounding soft tissues [188]. A minority of patients present with a rapidly enlarging mass and no prior symptoms [41].

Scientific support for the origin of CEPA from pleomorphic adenomas was provided by Eneroth and Zetterberg. They undertook a microspectrophotometric DNA analysis of pleomorphic adenomas and demonstrated a difference in the DNA content between morphologically benign pleomorphic adenomas of short duration and those of long duration [21, 41, 61, 245, 369, 415, 453, 567, 569]. This finding supports the hypothesis that the risk of carcinomatous transformation in a pleomorphic adenoma increases with the age of the tumor. Origin in a small previously undetected pleomorphic adenoma could explain those cases of CEPA presenting without a history of a previous long-standing slowly enlarging mass.

Pathologic Features

Gross features suggestive of CEPA include foci of capsular invasion, hemorrhage, and necrosis in a tumor which in other areas shows classic features of a pleomorphic adenoma. In one series of 47 cases these tumors averaged 4.4 cm in greatest diameter in the parotid gland, 5.0 cm in the submandibular gland, and 2.2 cm in the minor salivary glands [61, 130, 219, 453, 490].

The carcinoma is usually a high-grade adenocarcinoma or an undifferentiated carcinoma although numerous other types including squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, myoepithelial carcinoma, clear cell carcinoma, papillary carcinoma, and terminal duct carcinoma have been reported (Fig. 3.13a, b) [453]. Thus when making the diagnosis of CEPA it is important to state the histologic subtype and degree of differentiation of the carcinomatous component. The ratio of pleomorphic adenoma to carcinoma in CEPA is highly variable. Hyalinization is frequently seen in the benign component of the tumor and indeed the presence of hyalinization in an otherwise classic pleomorphic adenoma is reason for additional sampling to avoid missing a small focus of CEPA [370, 453, 540]. On the other hand, residual pleomorphic adenoma may be reduced to a few microscopic foci. In one series residual foci of pleomorphic adenoma were 5 mm in 9% of cases [569].

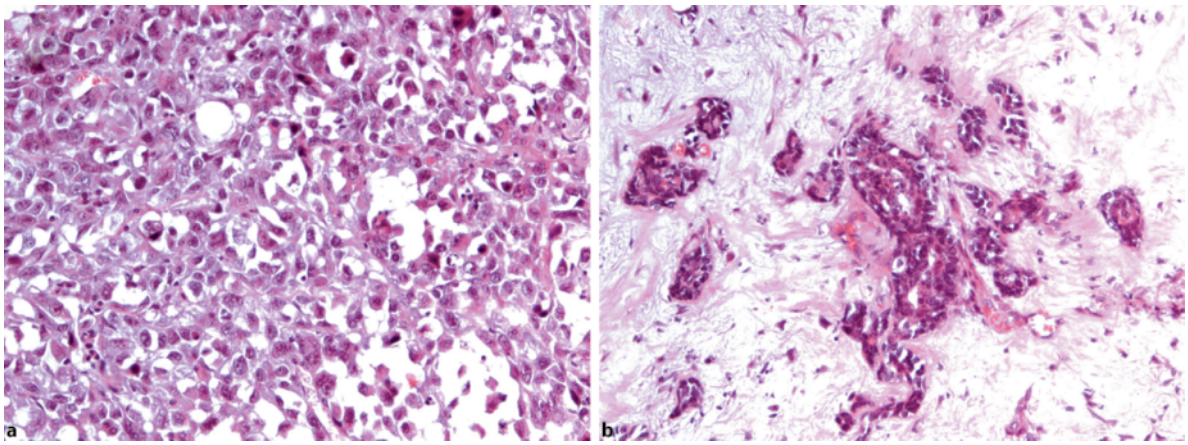

Fig. 3.13: Carcinoma ex-pleomorphic adenoma. **a** Area showing undifferentiated carcinoma (H&E, 200×). **b** Adjacent area of same specimen showing residual pleomorphic adenoma (H&E, 200×)

Treatment and Prognosis

The treatment of CEPA is wide surgical resection usually with a neck dissection. Features associated with an unfavorable prognosis include high tumor grade, large size, soft tissue invasion, perineural invasion, and lymph node metastases [81, 453]. Tortoledo correlated survival with the histologic subtype of the carcinoma and reported 5-year survival rates of 96% for terminal duct carcinoma, 62% for ductal carcinoma, 50% for myoepithelial carcinoma, and 30% for undifferentiated carcinoma [41, 130, 245, 370, 567]. He also found no deaths when the tumor invaded less than 6 mm. Brandwein reported no recurrences in patients with less than 1.5 mm of invasion and Olsen found that patients with less than 5 mm of invasion did not suffer recurrence [81, 154, 207].

Carcinoma ex-pleomorphic adenoma metastasizes exclusively as a carcinoma. Metastases develop in 30–70% of cases and distant metastases occur more frequently than regional metastases. These metastases seem to show a particular affinity for lungs and bone especially the vertebral column [81, 154, 370, 415].

In recent years much has been written about non-invasive (in situ or intracapsular) CEPA [207]. These are carcinomas which arise within a pleomorphic adenoma but have not penetrated the capsule of the pleomorphic adenoma. It has been stated that this finding has no adverse effect and the standard resection for a pleomorphic adenoma is curative [330, 331]. There is, however, at least one well-documented report in which a non-invasive CEPA metastasized to a lymph node [245, 261].

True Malignant Mixed Tumor

Clinical Features

True malignant mixed tumors (TMMT) may be regarded as carcinosarcomas since both the epithelial and stromal components are histologically malignant. Kirklin is credited with the first description of these tumors in 1951 and King was the first to refer to them as carcinosarcomas in 1967 [12, 234, 570].

As of 2000, 60 cases have been reported in the literature, the largest series having been reported by Gnepp in 1998 [66, 346]. TMMT comprise only 0.16–1.0% of all malignant tumors of salivary glands [245, 346]. Although most appear to arise de novo, approximately 33% of patients have either a clinical history or histologic confirmation of a coexisting pleomorphic adenoma [12, 223, 346]. The most common location is the parotid gland. Patients have ranged in age from 14 to 87 years and there is no sex predilection [12, 70, 223, 245, 261, 346, 547, 548, 570]. Signs and symptoms are similar to those of CEPA. Both carcinoma and sarcoma are seen in the metastases of TMMT.

Pathologic Features

The carcinomatous component is most often an adenocarcinoma, a squamous cell carcinoma, or an undifferentiated carcinoma [223]. The sarcomatous element is usually a chondrosarcoma, however, other types of sarcoma have also been reported including spindle cell sarcoma not otherwise specified, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, and rarely liposarcoma and rhabdomyosarcoma [66].

Fowler et al. studied the loss of heterozygosity in tumor suppressor genes in TMMTs and CEPAs. They found that the carcinomatous and sarcomatous components of TMMTs are closely related. These findings also suggested a common clonal origin for the benign and carcinomatous components of CEPA [219].

Treatment and Prognosis

The treatment is radical surgical resection which should be combined with radiation and chemotherapy. Even with such radical treatment most patients die within 5 years [245]. TMMTs metastasize more commonly via a hematogenous rather than lymphatic route with lung and bone being the most frequent sites of metastases.

Metastasizing Mixed Tumor

Clinical Features

Metastasizing mixed tumor is a pleomorphic adenoma, which despite its benign histology, metastasizes. Histologically it is identical to a pleomorphic adenoma and can only be recognized as malignant once it has metastasized. Lung and bone are the most frequent sites of metastatic disease.

Foot and Frazell are credited with the first report of this tumor in 1953 [292]. Gnepp was able to find only 32 reported cases in his 1993 literature search [228, 245, 611]. By 1997 the number had increased to 40 [76, 113, 260, 387]. Approximately 65% occur in the parotid gland and the mean age at presentation is 32 years [245, 610]. Initial signs and symptoms are consistent with those of a pleomorphic adenoma. In almost all cases metastases have been preceded by at least one and frequently numerous local recurrences of a pleomorphic adenoma [610]. The time from initial resection of the pleomorphic adenoma to the appearance of metastatic disease can be as short as 1 year or as long as 20 years.

Pathologic Features

Histologically metastasizing mixed tumors are essentially identical to pleomorphic adenomas and lack any characteristics of malignancy [387]. Flow cytometry has not been helpful in identifying these tumors [387]. A recent analysis of p53, bcl-2, M1B1, CD105, p27, and p21 expression also proved unrewarding in identifying differences between metastasizing and non-metastasizing pleomorphic adenomas [387, 419].

Treatment and Prognosis

Surgical excision is also the treatment of choice for the primary tumor, recurrences, and metastases [610].

Metastases may be related to implantation of tumor cells into blood vessels and lymphatics at the time of surgery [245]. In Wenig's review of 32 patients, 25 (78%) were alive with or without tumor or died of unrelated causes [441]. Gnepp reported follow-up on 20 patients, seven of whom (37%) had died of their disease [98].

Acinic Cell Carcinoma

Clinical Features

The first description of acinic cell carcinoma was published by Nasse in 1892 [361, 539]. Acinic cell tumor, the old name for this neoplasm, reflects the fact that its malignant behavior was not recognized until Buxton's publication in 1953 [539].

Acinic cell carcinoma is a rare low-grade carcinoma accounting for only 2–4% of salivary gland neoplasms [47, 98, 126, 361, 400, 465]. The parotid gland is the most common site (80%) followed by the minor salivary glands (16%) and the submandibular gland (4%). While 80% occur in the parotid gland, acinic cell carcinoma accounts for only 4% of all parotid tumors [47, 269, 357, 400]. Although some series have shown a male predominance and at least one no sexual preference, most report a female to male ratio of approximately 2:1 [47, 172, 400, 457,

494, 579]. The rate of bilateral involvement of the parotid gland is 3%. While this is low, the incidence of bilateral involvement by acinic cell carcinoma is second only to Warthin's tumor which has a 5–10% incidence of bilaterality [166, 409].

The tumor is most frequent in individuals between 40 and 50 years of age but may occur at any age. Although less than 4% of patients are younger than 20 years, it is second only to mucoepidermoid carcinoma among salivary gland carcinomas occurring in the pediatric population [172, 361].

Patients typically present with a history of a slowly enlarging painless mass that is not fixed to the surrounding soft tissue or skin. Pain is a symptom in approximately 22% of patients and facial nerve paresis or paralysis is encountered in approximately 3–8% [278, 361]. The median duration of symptoms prior to treatment is 2 years but may be as long as several decades [191].

Pathologic Features

Grossly the tumors are solitary, firm or rubbery, and well circumscribed ranging in size from 0.5 to 13 cm (median 2.5 cm). Recurrent tumors are frequently multiple and may be poorly demarcated. The cut surface varies from tan to gray and is occasionally cystic [22, 404]. Microscopically multiple growth patterns occur, often within the same tumor. These have been categorized as solid, microcystic, papillary-cystic, and follicular with the solid and microcystic patterns being the most common (Fig. 3.14a–c). In the solid growth pattern the tumor cells grow in large sheets. The microcystic pattern is characterized by interspersed spaces of varying sizes. The microcyst formation may result from accumulation of secretions due to a lack of ducts or may possibly be an artifact of fixation [263, 465]. The papillary-cystic pattern has large cystic spaces containing branching projections of epithelium. In the follicular pattern cystic spaces are distended with a homogeneous proteinaceous material resulting in a pattern mimicking thyroid follicles.

The prototypical cell type is round to polyhedral with a uniform round eccentric nucleus and basophilic granular cytoplasm. These cells very closely resemble normal serous acinar cells and indeed the diagnosis of acinic cell carcinoma is predicated on identifying this cell type. Other cell types include those resembling intercalated duct epithelial cells, vacuolated cells, clear cells, and nonspecific glandular cells. Intercalated duct type cells are cuboidal with eosinophilic cytoplasm and centrally placed hyperchromatic nuclei. Vacuolated cells are similar in size to acinar type cells but have vacuolated acidophilic cyto-

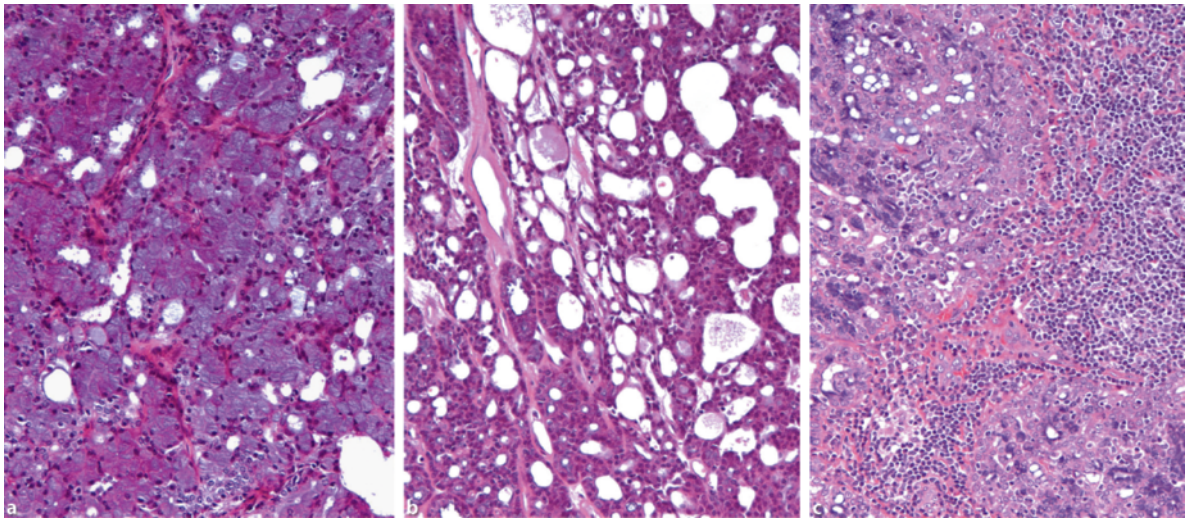

Fig. 3.14: Acinic cell carcinoma. **a** Neoplastic acinic cells with basophilic granular cytoplasm and growing in a predominately solid pattern (H&E, 200×). **b** Microcystic growth pattern (H&E, 200×). **c** Acinic cell carcinoma composed of granular acinic cells (dark granular cells) and non-specific glandular cells. Note presence of abundant lymphoid tissue (H&E, 200×)

plasm and a more open chromatin pattern. Their nuclei may exhibit slight pleomorphism. Although vacuolated, the cells do not contain lipid, glycogen, or epithelial mucin. Clear cells have pale or non-staining cytoplasm but otherwise resemble acinar or non-specific glandular cells. Non-specific glandular cells have eosinophilic cytoplasm, indistinct cell borders, and nuclei which are larger, more vesicular and more pleomorphic than those of the other cell types. Any one tumor may be composed primarily or exclusively of diagnostic acinar type cells or may contain a mixture of cell types. Mitotic figures are rare. Tumors composed primarily of acinar-type cells closely resemble normal serous salivary glands except for the lack of striated ducts. The stroma is typically scant and composed of thin delicate strands of fibrovascular tissue although some tumors may have a dense hyalinized stroma. A relatively frequent finding in the stroma is the presence of abundant lymphoid tissue complete with germinal center formation. This occurs in upward of 30% of acinic cell carcinomas [172, 175, 176].

Like normal acinar cells, the acinar cells of acinic cell carcinoma contain PAS-positive diastase-resistant zymogen granules. The cytoplasm does not stain with mucicarmine or alcian blue stains although, in some cases, intercellular cystic areas may contain material that is weakly mucicarminophilic [145, 172, 176]. Well-differentiated acinar cells are also positive for lactoferrin, amylase, alpha-1-antitrypsin, alpha-1-antichymotrypsin, carcinoembryonic antigen, Leu M-1, and vasoactive intestinal polypeptide [318, 448]. Acinic cell carcinomas are also immunoreactive for cytokeratin and approximately 10% are S-100 positive [353]. They are negative for c-kit and p53 overexpression is low [46, 47, 58, 180, 404, 443]. Acinic cell carcinomas have also been found to be MUC3 positive, MUC5AC negative, and MUC6 negative [361, 443].

Differential Diagnosis

The lack of both ducts and a normal lobular architecture aid in distinguishing acinic cell carcinoma from normal salivary gland parenchyma. Absence of mucous and epidermoid cells permits distinction of the microcystic form of acinic cell carcinoma from mucoepidermoid carcinoma. Identification of zymogen-containing acinar cells separates the papillary-cystic form of acinic cell carcinoma from cystadenocarcinoma. Lack of staining for thyroglobulin and thyroid transcription factor distinguishes the follicular variant of acinic cell carcinoma from metastatic thyroid carcinoma.

Pathogenesis

The name acinic cell carcinoma and the presence of acinar-type cells in the tumor would suggest origin from acinar cells. Most investigators, however, indicate an origin from the stem or reserve cells of the intercalated ducts [443].

Treatment and Prognosis

The treatment of acinic cell carcinoma is complete surgical resection. Neck dissection is usually not recommended because of a relatively low incidence of metastases to regional lymph nodes [361]. There have been only a few reported instances of a favorable response to radiation treatment, most tumors having been radio resistant. Radiation is usually reserved for tumors which cannot be completely resected or for those uncommon cases which have extensive perineural or lymphatic invasion [126, 361, 443].

Acinic cell carcinoma is a low-grade malignancy and there is no correlation between cell type or growth pattern and prognosis [180, 361, 443, 465, 541]. The recurrence rate averages 10–35% and the distant metastatic rate 13–16% [361, 409]. The lungs and bone are the most common sites of distant metastases. Survival rates range from 78 to 90%, 63 to 83%, and 44 to 67% at 5, 10, and 20 years, respectively [166, 521]. The clinical course may be protracted and cases of recurrence have been reported after a disease-free interval of 30 years [284, 521].

Most tumors are diploid and as a result DNA studies are usually not helpful in predicting outcome. El-Nagger, however, reported that in a study of 15 patients, none with diploid tumors developed metastases or died of disease while five of eight with aneuploid tumors developed metastases and four succumbed to their disease [521].

MIB-1 appears to be an independent prognostic factor. Patients with MIB-1-negative tumors have been shown to have significantly better survival than those with MIB-1-positive tumors [545]. In a study by Skalova, five of seven patients with MIB-1 values higher than 10% had unfavorable outcomes while none of the 17 patients with values lower than 5% suffered recurrences during follow-up periods as long as 30 years [286, 545].

Dedifferentiated Acinic Cell Carcinoma

A highly aggressive form of acinic cell carcinoma was reported by Stanley in 1988 [152, 166, 497]. He called these tumors dedifferentiated acinic cell carcinomas. In addition to well-differentiated classic acinic cell carcinoma each contained discrete areas of poorly differentiated adenocarcinoma or undifferentiated carcinoma. Transitional areas between the classic acinic cell carcinoma and the high-grade component are not seen.

Unlike classic acinic cell carcinomas, these tumors are highly malignant and metastasize early. It is therefore recommended that these cancers be treated by radical resection and neck dissection [286]. The dedifferentiated component is usually aneuploid [55, 105, 192, 227]. Henley reported a case in which p53 was negative immunohistochemically in both the low- and high-grade components. In addition, polymerase chain reaction and non-isotopic single-stranded conformational polymorphism analysis showed a germ line configuration of the p53 gene, exons five through eight, in both low- and high-grade components of the tumor [249, 562].

Polymorphous Low-grade Adenocarcinoma

Clinical Features

Polymorphous low-grade adenocarcinoma of salivary gland origin (PLGA) was previously known as terminal duct carcinoma and lobular carcinoma because of its histologic resemblance to these forms of breast carcinoma [2, 9, 48, 193, 327, 374, 596]. It is a rare neoplasm with distinctive clinical and morphologic features.

Most of these cancers arise from intraoral minor salivary glands where it accounts for approximately 10% of all intraoral minor salivary gland tumors and 25% of the malignant ones [512, 609]. Sixty to seventy percent involve the palate [238, 327, 402, 411, 471, 480]. Origin from minor salivary glands in the nose and nasopharynx and from the lacrimal glands has also been reported [105]. Origin in major salivary glands is very uncommon and, when it does occur, usually involves the parotid gland [577].

The tumors grow slowly producing a non-ulcerated painless mass ranging in size from 0.4 to 6 cm [105, 193]. Most patients are between 40 and 60 years of age although some patients have been in their early twenties and at least one was diagnosed in a 12-year-old child [105, 134, 252, 464, 571, 609]. PLGA is more common in women than men by a ratio of 2:1 [64, 163, 413, 463].

Pathologic Features

The name PLGA is appropriate because it reflects the main features of this neoplasm. The tumor is polymorphous in its histologic growth patterns but cytologically bland. It is its infiltrating growth pattern, tendency for recurrence, perineural invasion, and ability to metastasize that attest to its malignancy.

Grossly PLGAs are solid and well circumscribed but not encapsulated. The cut surface is homogeneous and tan to tan-yellow. Histologically any combination of six growth patterns, namely solid, tubular, fascicular, cribriform, linear single cell, and papillary/papillary cystic may be observed. Concentric growth around blood vessels and nerves is also characteristic. The tumor cells are cytologically bland and vary from cuboidal to columnar with eosinophilic or clear cytoplasm. Nuclei are round to oval with vesicular chromatin and small nucleoli. Mitotic activity and necrosis are usually not present. The tumor is supported by a stroma which may be scant or abundant and can vary from mucinous to hyalinized. Invasion of soft tissue may be local and easily overlooked. Perineural invasion is typical of PLGA and is seen as often or more often than in adenoid cystic carcinoma (Fig. 3.15a–c).

Polymorphous low-grade adenocarcinomas are positive for cytokeratin and vimentin. They are also strongly positive for S-100. Approximately 10–50% have been reported to be positive for GFAP, muscle-specific actin, and epithelial membrane antigen [105, 526]. Reported results of c-kit expression have been inconsistent [134, 252]. Proliferative activity as measured by Ki-67 is low ranging from 0.2 to 6.4 with a mean of 2.4% [64, 144, 232, 526].

Differential Diagnosis

Included in the differential diagnosis are pleomorphic adenoma, adenoid cystic carcinoma, and acinic cell carcinoma. Pleomorphic and monomorphic adenomas of minor salivary glands do not have a capsule, however, they have a pushing rather than infiltrating destructive margin and lack neurotropism. Adenoid cystic carcinomas infiltrate and have a marked predilection for perineural invasion, however, the prototypical cell of these tumors has an

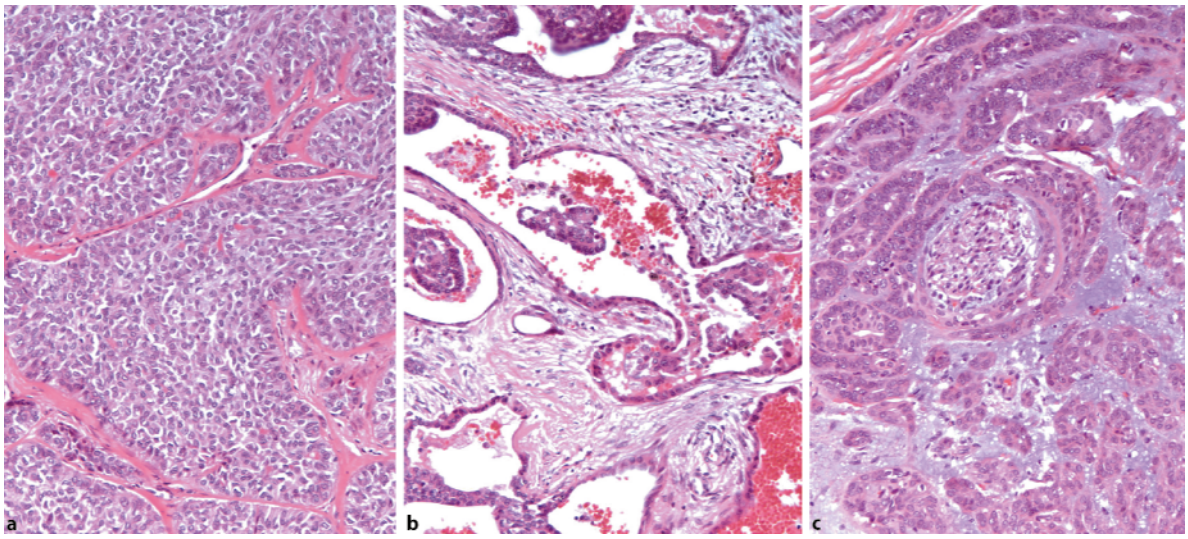

Fig. 3.15: Polymorphous low-grade adenocarcinoma. **a** Cytologically bland tumor cells with eosinophilic to clear cytoplasm. The tumor cells are growing in a solid pattern (H&E, 200×). **b** Papillary cystic growth pattern (H&E, 200×). **c** Tubular growth pattern with perineural invasion (H&E, 200×)

angulated hyperchromatic nucleus and scant cytoplasm. This is in contrast to the typical cell of PLGA which has a vesicular nucleus and more cytoplasm. Acinic cell carcinomas are rare in minor salivary glands and infrequently show perineural invasion. Although there is overlap in the immunohistochemical staining, PLGAs are less frequently and less diffusely positive for GFAP than pleomorphic adenomas. In addition it is the epithelial component that stains in PLGA in contrast to pleomorphic adenomas where the staining is in the stromal component [64, 163, 413, 463]. Positivity for vimentin and a much lower proliferative activity measured by Ki-67 can be helpful in separating PLGA from adenoid cystic carcinoma which shows just the opposite staining results [48, 105, 327, 414]. Some have found c-kit expression helpful in distinguishing between PLGA and adenoid cystic carcinoma while other have not [105].

Treatment and Prognosis

Treatment is complete surgical resection. PLGA is a low-grade indolent tumor with a tendency for local recurrence. In the past it has been associated with a recurrence rate of 20% although a more recent study by Castle et al. reports a recurrence rate of 9.1% [48, 327, 414]. The average time from initial surgery to recurrence is 7 years [193]. In 6–7% of cases there is metastasis to regional lymph nodes [48, 193, 530]. Tumors with a predominately papillary growth pattern have been associated with a higher incidence of cervical lymph node metastases [105, 193]. Postoperative radiation therapy is considered unnecessary due to the low-grade nature of this tumor. Distant metastases have occurred but are very uncommon [159]. Deaths due to tumor are infrequent and usually occur after a prolonged course [25, 217, 312, 572, 573].

Epithelial-myoepithelial Carcinoma

Clinical Features

Epithelial-myoepithelial carcinoma of salivary glands (EMC) is a rare but histologically distinctive low-grade carcinoma. The name was proposed in 1972 by Donath et al. who were the first to appreciate that the tumor is a carcinoma [416, 417, 544]. Prior names applied to this neoplasm include adenomyoepithelioma, clear cell adenoma, and glycogen-rich adenoma and reflect the misconception that it is a benign tumor.

Epithelial-myoepithelial carcinoma accounts for approximately 0.5–1% of all salivary gland neoplasms and favors women by a ratio of 2:1 [446, 466]. The vast majority arise in the major as opposed to the minor salivary glands. The parotid gland is the site of approximately 75% with an additional 10–12% arising in the submandibular gland. Origin from minor salivary glands primarily occurs in the palate [505, 561]. EMC has also arisen in extraoral mucoserous glands in the nasopharynx, larynx, and bronchi [572]. Interestingly a histologically identical tumor occurs in the breast where it is still known as an adenomyoepithelioma [129, 132, 256, 417, 491].

Epithelial-myoepithelial carcinoma is essentially a tumor of older adults (mean age 60 years) although rare cases have been reported in the pediatric age group and we have seen one unreported case in a 6½-year-old child [124, 159]. Patients usually present with an asymptomatic mass. Much less frequently signs and symptoms of a malignant neoplasm, such as facial paralysis and pain, are present. In some instances a mass has been present for several years prior to the patient seeking medical treatment [218].

Pathologic Features

Grossly these tumors are firm, solid, and frequently lobulated. The margins may be sharply circumscribed or infiltrative. The cut surface ranges from yellow to gray-white and cystic spaces are sometimes present. Those involving the palate frequently ulcerate. EMC have ranged in size from 1 to 8 cm.

Histologically four growth patterns have been described namely tubular, cribriform, solid, and papillary [573]. The tubular is the prototypical and most common growth pattern. The tubules are composed of duct-like structures having an inner (luminal) single cell layer of cytologically bland cuboidal epithelial cells with dense granular eosinophilic cytoplasm and an outer (abluminal) single or multiple cell layer of ovoid to polygonal myoepithelial cells with clear cytoplasm and eccentric vesicular nuclei. The epithelial cells are strongly positive with cytokeratin stains and negative for myoepithelial markers. The myoepithelial cells are usually only weakly positive for cytokeratin but stain strongly with myoepithelial markers (S-100, smooth muscle actin, p63, HHF35, and calponin). Their clear cytoplasm is due to the presence of glycogen. Pleomorphism and mitotic activity are absent or minimal although rarely tumors may show pleomorphism and increased mitotic activity. Histologic evidence of malignancy is reflected in areas showing an infiltrative growth pattern and perineural invasion. Prominent collars of PAS-positive diastase-resistant basement membrane material surrounds the duct-like structures which in turn form nests of tumor separated by fibrous bands of connective tissue. This results in a multilobulated appearance (Fig. 3.16). In the cribriform growth pattern two cell populations are still discernable and, while the cribriform pattern can mimic an adenoid cystic carcinoma, no hyaline material is present in the round spaces. The solid growth pattern consists of sheets of myoepithelial cells which, in some areas, may have a spindled shape. Ductal structures are scarce and may be difficult to find. The papillary growth pattern is encountered in cystic areas. The epithelium lining the cystic spaces and papillary structures maintains a biphasic pattern with luminal ductal epithelial cells and abluminal clear myoepithelial cells. In all growth patterns the myoepithelial cells predominate, however, occasionally areas may be present in which apparent atrophy of the clear cells has produced "naked ducts" lined only by a single layer of epithelial cells.

Differential Diagnosis

The differential diagnosis of EMC includes other salivary gland tumors containing clear cells, such as clear cell myoepithelioma, acinic cell carcinoma, and mucoepidermoid carcinoma, and metastatic tumors which may contain clear cells, in particular those from the kidney and thyroid. The clear cells of EMC are myoepithelial cells which contain glycogen and are PAS positive diastase sensitive and mucicarmine negative. The clear cells of clear cell myoepithelioma are also glycogen-containing myoepithelial cells with the same staining characteristics as those in EMC. Clear cell myoepitheliomas, however, lack ducts and may contain foci of other types of myoepithelial cells such as the plasmacytoid, hyaline, and epithelioid forms. Acinic cell carcinoma contains cells with PAS-positive diastase-resistant granules not seen in EMC. Mucoepidermoid carcinoma contains intracytoplasmic droplets of mucin which is PAS positive diastase resistant and mucicarmine positive. The clear cells in renal cell carcinoma contain both glycogen and lipid and will be PAS positive diastase sensitive and will also stain with lipid stains. Clear cell carcinoma of the thyroid is negative for both glycogen and lipid but will stain for thyroglobulin and thyroid transcription factor.

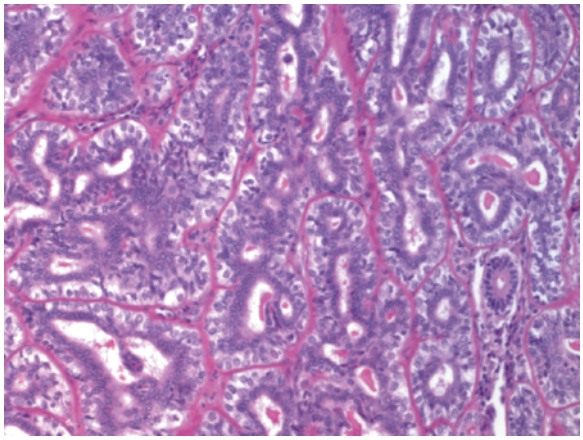

Fig. 3.16: Epithelial-myoepithelial carcinoma. The tumor forms tubules lined by a luminal layer of epithelial cells and an abluminal single or multiple cell layer of myoepithelial cells with clear cytoplasm. Prominent collars of basement membrane material surround the structures. Pleomorphism is absent or minimal (H&E, 200×)

Treatment and Prognosis

The treatment is complete surgical resection. Fonseca et al. found higher values of proliferative cell nuclear antigen in the myoepithelial cells as opposed to the epithelial cells and a higher recurrence rate in those tumors with a predominately solid myoepithelial growth pattern [124, 274]. A study by Tralongo et al. also found that higher proliferative activity occurred in tumors with a more aggressive clinical course [49, 274]. Other studies, however, failed to demonstrate a correlation between proliferative activity or histologic growth pattern and prognosis [124]. The majority of the tumors are diploid [49, 124, 129, 377, 516]. Some studies have found that those which were aneuploid pursued a more aggressive clinical course, however, 60% of those that were diploid also recurred or metastasized [49, 124, 129, 377, 516]. Local recurrence rates for EMC range from 30% to 50% [335, 395]. Regional lymph node metastases occur in 18% of patients and distant metastases in 7–25% [265, 317, 472]. The overall 5-year survival rate is 80%. This drops off to approximately 70% at 10 years.

Basal Cell Adenocarcinoma

Clinical Features

Basal cell adenocarcinoma is the malignant counterpart of basal cell adenoma. It is an uncommon low-grade malignancy first recognized by Klima et al. in 1978 [147, 317, 423]. It accounts for 1.6% of all salivary gland neoplasms and 2.9% of all salivary gland malignancies [423].

Most patients are in their sixth or seventh decade (mean age 60 years) although cases have been reported in individuals as young as 2 months and as old as 92 years [265, 317, 423, 436, 603]. Basal cell adenocarcinoma occurs with equal frequency in men and women [265]. Most of these tumors arise de novo. Origin in a pre-existing basal cell adenoma is uncommon and when it does occur it usually involves the membranous type of basal cell adenoma [15, 147, 265, 317]. Approximately 90% of the tumors arise in the major salivary glands with the vast majority involving the parotid gland [181]. Origin in minor salivary glands is uncommon [52, 423]. Patients usually present with an asymptomatic swelling which may be of weeks to years in duration. Pain and tenderness are uncommon [502]. In approximately 10–15% of cases basal cell adenocarcinoma of salivary glands occurs in conjunction with dermal cylindromas and trichoepitheliomas. This association, while significant, is lower than the 40% association of basal cell adenomas with these dermal tumors [603].

Pathologic Features

Basal cell adenocarcinomas are solid tan to gray tumors up to 7 cm in diameter. Infiltration into adjacent salivary gland parenchyma and soft tissue may be readily apparent or very subtle.

Microscopically there is a striking resemblance to basal cell adenomas both in growth pattern and cytology. Four growth patterns, identical to those in basal cell adenoma, occur. The tubular pattern is characterized by

multiple small ductal structures, the trabecular by anastomosing cords of cells, the solid by rounded nests or large sheets of cells, and the membranous by overproduction of basement membrane material which accumulates both around cell nests and intercellularly. While any combination of growth patterns may be seen in a single tumor, one usually predominates. Of the four patterns, the solid is the most common.

Cytologically two cell types similar to those in basal cell adenomas are present. One is a small round cell with a round dark staining nucleus and scant cytoplasm and the other a larger cell with a lighter staining nucleus and amphophilic cytoplasm. In most tumors the smaller cells are arranged peripherally and perpendicular alignment of their nuclei produces a palisading effect, which may, however, not be as conspicuous as in basal cell adenomas. Centrally located larger cells may produce swirls and squamous eddies.

Cellular and nuclear pleomorphism are minimal and necrosis, if present, is focal and not extensive. Mitoses are not frequent averaging two or less per 10 high power fields. Careful examination, however, will reveal invasive growth. In addition there is a 25–35% incidence of perineural and intravascular invasion [65, 265, 502, 616].

Immunohistochemically basal cell adenocarcinoma does not differ from basal cell adenoma [502]. Staining results support both epithelial and myoepithelial differentiation in both the small and large cells. While all tumors stain for cytokeratin, the majority are also at least focally positive for S-100, smooth muscle actin, vimentin, carcinoembryonic antigen, and epithelial membrane antigen [115, 181, 375].

Pleuro-potential ductal reserve cells are thought to give rise to this tumor [436]. The membranous variant of basal cell adenoma is the most common variant to give rise to basal cell adenocarcinoma, however, this is uncommon, most basal cell adenocarcinomas apparently arising de novo [423].

Differential Diagnosis

Included in the differential diagnosis of basal cell adenocarcinoma are basal cell adenoma, adenoid cystic carcinoma, cutaneous basal cell carcinoma, and small cell carcinoma. In some instances basal cell adenocarcinoma may only be differentiated from basal cell adenoma by identifying an infiltrative growth pattern and/or perineural and intravascular invasion. Some have found staining for Ki-67, p53, bcl-2, and epidermal growth factor receptor helpful in making this distinction [336, 580]. The membranous variant of basal cell adenoma is typically multifocal and care must be taken not to mistake multifocality for invasion.

Basal cell adenocarcinoma and adenoid cystic carcinoma both show perineural invasion and both produce hyalinized basement membrane material. Intercellular deposits of basement membrane material, squamous eddies, and peripheral palisading, however, are features associated with basal cell adenocarcinoma and not adenoid cystic carcinoma. A dual population of small and large cells is also characteristic of basal cell adenocarcinoma and not adenoid cystic carcinoma.

Perineural invasion and immunohistochemical evidence of myoepithelial differentiation would aid in distinguishing basal cell adenocarcinoma from cutaneous basal cell carcinoma. Clinical information as to the location of the tumor would also be invaluable.

Basal cell adenocarcinoma lacks the nuclear molding, brisk mitotic activity, and prominent necrosis of small cell carcinomas. Unlike small cell carcinoma, it is negative for synaptophysin and chromogranin.

Treatment and Prognosis

Treatment is complete surgical excision. Since it is a low-grade carcinoma, neck dissection is usually reserved for patients with clinically positive lymph nodes. In a recent review of a large series of basal cell adenocarcinomas Muller and Barnes found a local recurrence rate of 37%. Cervical lymph node metastases were present in 8% and distant metastases in 4%. There was a mean follow-up of 54 months on 45 patients. Of these patients, 37 were alive without disease, 4 were alive with disease, 1 died of disease, and 3 died of other causes [10, 35, 120, 437, 488, 495].

Myoepithelial Carcinoma

Clinical Features

Myoepithelial carcinoma (malignant myoepithelioma) is the malignant counterpart of myoepithelioma. By definition it is composed exclusively or almost exclusively of myoepithelial cells with an infiltrative growth pattern.

Myoepithelial carcinomas account for only 0.2% of all epithelial salivary gland tumors and 10% of all myoepi-

thelial salivary gland tumors [437, 495]. Approximately 84 cases have been reported to date [580]. Seventy-five percent occur in the parotid gland [10, 120, 336, 437, 488, 495, 580, 593]. When minor salivary glands are involved there is a distinct predilection for those in the palate [495]. The tumors are most common in the sixth and seventh decades (range 24–81 years) and occur with equal frequency in men and women [495]. A painless mass is usually the only clinical complaint. Approximately 50% of cases have arisen in a pre-existing benign tumor, usually a pleomorphic adenoma or a myoepithelioma.

Pathologic Features

Grossly myoepithelial carcinomas are unencapsulated soft to firm and often nodular. They vary in size from 2 to 10 cm. The cut surface is tan to gray-white and may show areas of necrosis and cystic degeneration. Glassy gelatinous areas may also be observed [303, 405, 495].

Microscopically there is infiltrative destructive growth into the adjacent salivary gland or soft tissues. These tumors frequently have a multinodular growth pattern. The nodules of tumor cells are separated by fibrous stroma and often have myxoid or necrotic centers. As in myoepitheliomas any of four cell types may be present and in any proportion. These cell types are: (1) epithelioid, (2) plasmacytoid (or hyaline), (3) spindle, and (4) clear cell. The epithelioid cells have a moderate amount of eosinophilic cytoplasm. The plasmacytoid or hyaline cells have eccentrically placed nuclei reminiscent of plasma cells and a glassy eosinophilic cytoplasm. They tend to be particularly numerous in palatal tumors. The spindle cells are elongated and resemble plump fibroblasts. The clear cells have clear cytoplasm due to the presence of glycogen. In some myoepithelial carcinomas the cytologic atypia is obvious whereas in others cytologic features of malignancy are very subtle and indeed the diagnosis of malignancy may rest solely on identifying areas of invasive destructive growth. In the 25 cases reported by Savera et al. 40% were classified as high grade and 60% as low grade [171, 174, 221].

The stromal component of these tumors is characterized by the presence of amphophilic to blue-gray myxoid material and or eosinophilic hyalinized material. The myxoid material is particularly characteristic and often accumulates around nests of plasmacytoid cells.

Results of immunoperoxidase stains are essentially the same as obtained with myoepitheliomas. Myoepithelial carcinomas are positive for AE1/3, vimentin, and S-100 in virtually all cases. Vimentin and S-100 are infrequently present in normal myoepithelial cells but are sensitive (although non-specific) markers of neoplastic myoepithelial cells. Reactivity for other myoepithelial cell markers such as muscle specific actin, GFAP, smooth muscle actin, and calponin is variable.

Differential Diagnosis

The differential diagnosis is lengthy and includes a number of other salivary gland tumors such as: polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, oncocytoma and hyalinizing clear cell carcinoma, benign and malignant spindle cell tumors, plasmacytomas, and metastatic renal cell carcinoma. Documentation of exclusive myoepithelial differentiation by immunohistochemistry will usually permit distinction of myoepithelial carcinomas from other neoplasms.

Treatment and Prognosis

The treatment is complete surgical excision. The clinical behavior of myoepithelial carcinomas is unpredictable. Although tumors showing cytologic pleomorphism, numerous mitoses and necrosis are usually associated with an adverse outcome, some with aggressive histologic features have been clinically indolent. In addition there have been reports of histologically low-grade tumors that have metastasized and resulted in death [221].

Cystadenocarcinoma

Clinical Features

Cystadenocarcinomas of the salivary glands are low-grade cystic neoplasms which have been reported in the past under a variety of names including malignant papillary cystadenoma, mucus-producing adenopapillary carcinoma, low-grade papillary adenocarcinoma, papillary adenocarcinoma, adenopapillary carcinoma, papillary cystadenocarcinoma, and papillary cystic adenocarcinoma [9, 27, 69, 112, 140, 171, 174, 185, 221, 320, 412, 422, 501, 510, 529, 543, 544, 615].

The tumor is twice as common in the major salivary glands as opposed to the minor salivary glands and most

frequently occurs in the parotid [221]. Cystadenocarcinomas have been reported over an age range of 20–86 years, however, 75% of patients are over the age of 50 years (mean age 58.8 years) [334].

Microscopically there are haphazardly arranged cystic spaces that vary in size and shape. Mucin released from ruptured cysts can produce an inflammatory response. The cystic spaces are separated by scant to abundant stroma. Solid cellular areas and ducts may be present between the cysts and at the periphery of tumor but they never comprise the major portion of the neoplasm. The cysts and ducts are lined by small and large cuboidal and columnar cells with eosinophilic, clear, or mucinous cytoplasm. In some tumors the columnar cells impart a decidedly enteric appearance. The epithelium lining the cystic spaces may form a single layer to multiple layers. In over three fourths of cases there is a prominent intracystic papillary growth. This may range from small collections of cells lacking a fibrovascular core to large elongated and branching structures supported by fibrovascular cores. A cribriform growth pattern may also be seen. Nuclei are typically bland and mitoses are infrequent. Although some tumors may show a moderate degree of nuclear pleomorphism this has not been predictive of a more aggressive course. In contrast, tumors composed predominately of columnar cells may prove to be more aggressive [314, 585].

Recognizing these tumors as carcinomas is predicated upon finding areas of infiltrative growth. Tumors arising in minor salivary glands infiltrate adjacent soft tissue and skeletal muscle and may even infiltrate bone. In major salivary glands the infiltrative growth may be limited to the gland parenchyma making it more difficult to appreciate. Perineural invasion is not a feature of this neoplasm.

Differential Diagnosis

Included in the differential diagnosis are cystadenomas and all other salivary gland neoplasms that may have a cystic component. Cystadenomas are the benign counterpart of cystadenocarcinomas and do not have the infiltrative growth pattern of the latter.

Low-grade mucoepidermoid carcinomas are predominately cystic and often papillary cystic but unlike cystadenocarcinomas contain a mixture of mucous, epidermoid, and intermediate cells. Epidermoid differentiation is uncommon in cystadenocarcinomas. Also the solid proliferative component is usually larger in mucoepidermoid carcinomas than in cystadenocarcinomas.

The cystic and papillary areas of polymorphous low-grade adenocarcinoma can also be confused with cystadenocarcinoma. Features of polymorphous low-grade adenocarcinoma which can aid in the distinction from cystadenocarcinoma include a more variable growth pattern, mucinous and hyalinized stroma, and perineural invasion.

The papillary cystic form of acinic cell carcinoma is distinguished from cystadenocarcinoma by its microcystic growth pattern and tumor cells with basophilic, PAS-positive diastase-resistant zymogen granules.

Treatment and Prognosis

Cystadenocarcinomas are low-grade tumors and complete surgical excision is usually curative.

These tumors are uncommon and the series by Foss et al. remains the largest to date [293]. They had follow-up on 40 of their 57 patients. Local recurrence occurred in three patients and four had regional lymph node metastasis, three at the time of diagnosis and one 4.5 years following initial surgery. Three patients developed local recurrences which were successfully treated. Of the 40 patients, 36 were alive and 4 died of other causes after a mean postsurgical interval of 59 months.

Salivary Duct Carcinoma

Clinical Features

First described by Kleinsasser et al. in 1968, salivary duct carcinoma is a rare high-grade tumor thought to arise from the large excretory ducts [314]. The name is somewhat misleading since essentially all salivary gland carcinomas are believed to arise from reserve cells of the ductal system.

The peak incidence of this tumor occurs in the sixth and seventh decades. It is more common in men than women by a ratio of 2.5:1. It occurs most commonly in the parotid gland (78%) followed by the submandibular gland (12%) and the minor salivary glands (10%) [293]. Salivary duct carcinoma comprises approximately 6–10% of all carcinomas of the parotid [13]. Many patients present with signs and symptoms reflecting the aggressive be-

havior of this tumor including a rapidly enlarging painful mass and facial nerve paresis or paralysis. In the series by Jaehne et al., approximately two thirds of the patients presented with T3 or T4 tumors [293]. Hosal et al. reported the presence of calcifications seen on CT scans in 5 of their 15 patients [84, 150, 272, 358, 425, 451, 533].

Pathologic Features

Grossly salivary duct carcinomas are firm and gray white. Tumor margins may be obviously infiltrating or, less frequently, may appear deceptively discrete. Central comedo-type necrosis may be apparent on cross-section.

Microscopically the tumor is very reminiscent of ductal carcinoma of the breast. An intraductal component is characterized by solid, papillary, cribriform, and comedo growth patterns similar to intraductal carcinoma of the breast. All four growth patterns may be present in the same tumor. The invasive component typically grows as ribbons and small clusters of cells in a desmoplastic often hyalinized stroma reminiscent of invasive ductal carcinoma of the breast. It should also be stressed that invasive disease may also produce growth patterns similar to intraductal disease. In these instances invasion is recognized by a lack of a smooth round contour to the nests of tumor cells and also by a lack of a peripheral layer of myoepithelial cells [136, 205, 244, 314, 358, 451, 528]. The tumor cells are moderately large with an increased nuclear cytoplasmic ratio, abundant eosinophilic cytoplasm, hyperchromatic pleomorphic nuclei with prominent nucleoli, and frequent and abnormal mitotic figures (Fig. 3.17a, b). Perineural invasion is present in approximately 80% of cases [37, 155, 358, 398, 451]. The tumor cells are typically positive for cytokeratin and epithelial membrane antigen. Immunoreactivity for CEA has varied from 0% to 72% while staining for S-100 has varied from 0% to 41% depending on the series [285, 433, 434, 460, 518]. Salivary duct carcinomas are also frequently positive for gross cystic disease fluid protein, androgen receptor, and HER2/neu [304, 433, 460]. They are seldom positive for estrogen and progesterone receptors [433, 460]. Proliferative activity as measured by Ki-67 is usually high.

Histologic variants of salivary duct carcinoma include sarcomatoid, micropapillary, and mucin-rich [434]. The sarcomatoid variant is biphasic consisting of both carcinomatous and sarcomatous areas histologically. The sarcomatous change is considered to be a dedifferentiated phenomenon and has also been seen in mucoepidermoid, acinic cell, adenoid cystic, squamous cell, and epithelial-myoepithelial salivary gland carcinomas [285, 518]. The sarcomatous component expresses cytokeratin and epithelial membrane antigen in addition to being positive for vimentin [316, 592]. The micropapillary variant has foci where the tumor produces morula-like papillary cell clusters which lack fibrovascular cores and are surrounded by clear spaces [13, 119]. Mucin-rich sal-

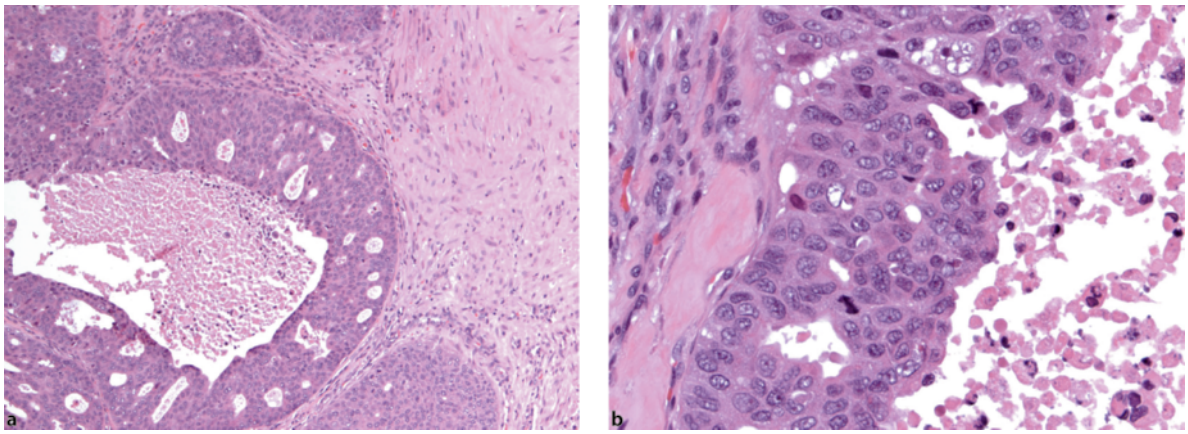

Fig. 3.17: Salivary duct carcinoma. **a** Cribriform and comedo growth patterns (H&E, 100×). **b** Higher magnification to show marked pleomorphism of tumor cells and abnormal mitotic figures (H&E, 400×)

ivary duct carcinoma is characterized by islands of tumor cells surrounded by pools of mucus which in turn are separated into compartments by bands of fibrous tissue [293].

Differential Diagnosis

The differential diagnosis includes metastatic adenocarcinoma from the prostate and metastatic ductal carcinoma of the breast. Immunoperoxidase staining for prostate-specific antigen aids in ruling out metastatic prostate carcinoma [38]. It is more difficult to exclude metastatic ductal carcinoma of the breast since, in rare instances, salivary duct carcinoma is positive for estrogen and progesterone receptors. Identifying areas of intraductal (in situ) tumor would serve to distinguish salivary duct carcinoma from both metastatic prostate and breast carcinoma [293]. Less frequently other primary salivary gland cancers, namely mucoepidermoid carcinoma and low-grade papillary adenocarcinoma, enter into the differential diagnosis. Mucoepidermoid carcinomas, unlike salivary duct carcinomas, are not characterized by papillary, cribriform, and comedo growth patterns. Moreover mucoepidermoid carcinomas have a more heterogeneous cell population consisting of intermediate, epidermoid, and mucin cells. This is in contradistinction to the single, albeit pleomorphic, cell type that comprises salivary duct carcinoma. Papillary growth in a low-grade adenocarcinoma should not cause confusion with salivary duct carcinoma since this is cytologically a low-grade tumor. In addition it is primarily a cancer of minor rather than major salivary glands.

Treatment and Prognosis

Because of its aggressive clinical behavior, salivary duct carcinoma is treated by complete surgical excision of the primary combined with neck dissection and adjuvant radiotherapy. Cervical lymph node metastases are present in 60–80% of cases. Hosal et al. found that 50% of patients with clinically negative (N0) lymph nodes had histologically positive lymph nodes [149]. The incidence of distant metastases ranges from 33% to 66%. Two thirds of patients die of their disease usually within 4 years of treatment [79, 149]. Death is usually from distant metastases which occur most commonly to the lungs and bone [79, 149].

Low-grade Cribriform Cystadenocarcinoma

Clinical Features

This tumor was first described by Delgado et al. in 1996 [79, 149]. The authors proposed the term low-grade salivary duct carcinoma. Currently the preferred term is low-grade cribriform cystadenocarcinoma (LGCC) which avoids confusion with conventional salivary duct carcinoma which is a high-grade tumor with a poor prognosis.

This is an uncommon tumor, less than 30 cases having been reported [221]. Patients have a median age of 64 years and the tumor occurs with equal frequency in men and women. In a combined series of 26 cases, 25 arose in the parotid gland and one in the submandibular gland [79, 149]. Most patients seek treatment because of the presence of an asymptomatic mass.

Pathologic Features

Tumors range in size from 0.7 to 4 cm. Grossly they are well circumscribed and typically have a cystic component which may be either focal or extensive.

Microscopically LGCC resembles atypical ductal hyperplasia of the breast or micropapillary/cribriform in situ ductal carcinoma of the breast. Single or multiple cystically dilated ducts and smaller ducts are filled by cells forming cribriform, micropapillary, and filigree papillary patterns. Areas showing a solid growth pattern may also be present. The tumor cells are cytologically bland ductal cells (Fig. 3.18a, b). Some may contain a golden brown lipofuscin-like pigment in the cytoplasm imparting an apocrine-like appearance to the cells. Immunoperoxidase stains for myoepithelial cells demonstrate that most of the tumors are in situ although some will show foci of microinvasion or small focal areas of limited invasive disease.

Low-grade cribriform cystadenocarcinomas are strongly and diffusely positive for S-100, however, they do not show evidence of myoepithelial differentiation. Stains for HER-2/neu and androgen are typically negative [170, 196, 299].

Differential Diagnosis

The differential diagnosis of LGCC centers around cystadenocarcinoma and the papillary cystic variant of acinic

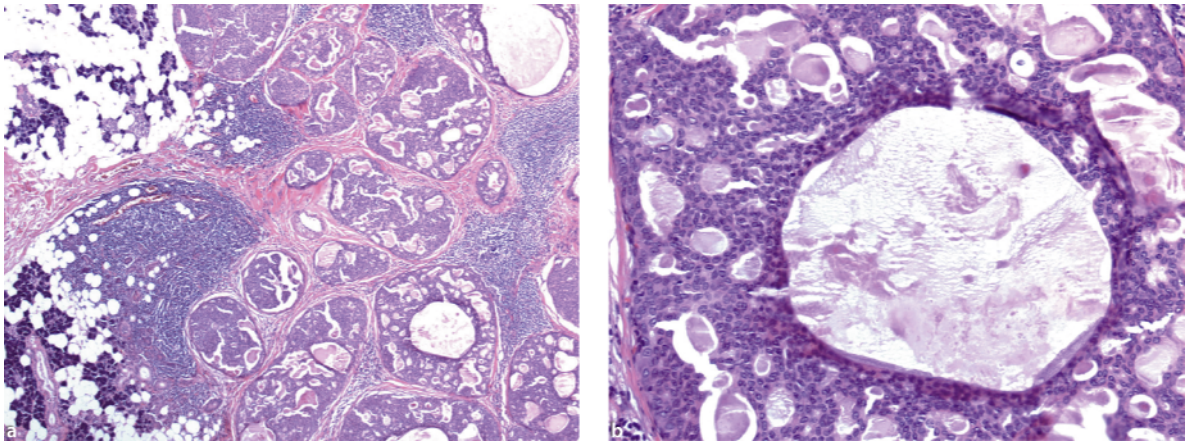

Fig. 3.18: Low-grade cribriform cystadenocarcinoma. **a** Infiltrating tumor with cribriform/micropapillary growth pattern (H&E, 40×). **b** Higher magnification to show that the tumor cells are cytologically bland. This is in marked contrast to the pleomorphism seen in salivary duct carcinomas (H&E, 200×)

cell carcinoma. Although cystadenocarcinomas often have a papillary component they lack the resemblance to atypical ductal hyperplasia and ductal carcinoma in situ of the breast which is so characteristic of LGCC. In addition cystadenocarcinomas tend to have a more obvious invasive component, while LGCCs are frequently entirely in situ carcinomas or only minimally invasive [299, 421, 430, 602].

The papillary cystic variant of acinic cell carcinoma will contain acinar cells with basophilic zymogen granules which are PAS positive diastase resistant. These are not present in LGCC. LGCC may, however, contain intracytoplasmic golden yellow granules of lipofuschin-like material.

Low-grade cribriform cystadenocarcinoma is strongly and diffusely positive for S-100 and negative for androgen receptor and HER-2/neu. This is exactly opposite to the staining pattern of salivary duct carcinoma and argues against LGCC being a low- grade form of salivary duct carcinoma.

Treatment and Prognosis

The treatment is complete surgical resection. Follow-up is limited because of the small number of reported cases, however, to date none have recurred [170, 196, 421, 602].

Large Cell Carcinoma

Clinical Features

Large cell carcinoma of the salivary glands is a rare high-grade neoplasm composed of large undifferentiated cells lacking any features of squamous cell carcinoma or adenocarcinoma. In some series it is two to three times less common than small cell carcinoma of salivary glands, however, in at least one series it was more common than small cell carcinoma of salivary glands [33, 280, 421].

These tumors are more common in the major than the minor salivary glands and most frequently occur in the parotid gland [348, 438]. They are rapidly growing and patients often present with involvement of adjacent soft tissue and skin. Cervical metastasis is also frequently present. Most patients are in their seventh decade when diagnosed and there is no sex bias with regard to incidence [53, 299].

Pathologic Features

Grossly the tumors tend to be large, averaging 3 cm at the time of surgery. Large cell carcinomas are poorly circumscribed firm gray-white tumors which may be solid and partially cystic. The cut surface frequently has areas of hemorrhage and necrosis. Infiltration into the salivary

gland parenchyma and frequently the surrounding soft tissues is obvious grossly in most cases.

Microscopically the tumor is composed of sheets, nests, and trabeculae of large undifferentiated cells which may be strikingly pleomorphic or relatively uniform (Fig. 3.19). The individual tumor cells are two to three times larger than those of small cell carcinoma and have abundant eosinophilic to amphophilic cytoplasm. Some cells may have clear cytoplasm due to the presence of glycogen. Mucin, however, is not present. Nuclei are large and pleomorphic with prominent single or multiple nucleoli. Some cells may be elongated and spindle shaped. A few large cell carcinomas have contained numerous osteoclast-like giant cells [59, 170, 253, 281, 302, 340, 426, 478, 482]. Mitotic figures are abundant and foci of necrosis are common as are perineural and angiolymphatic invasion. Some tumors may be positive for neuroendocrine markers such as synaptophysin and chromogranin A [170, 196, 251].

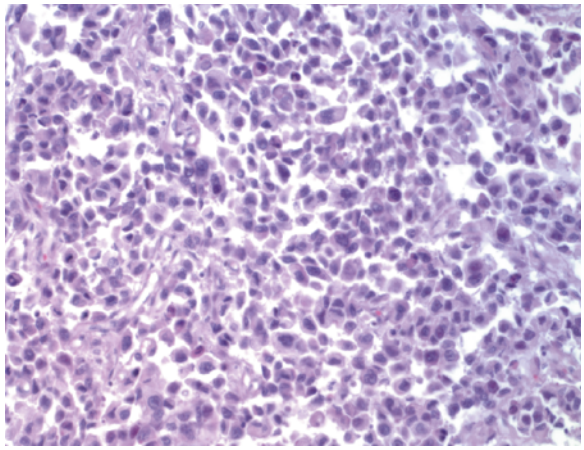

Fig. 3.19: Large cell carcinoma. The tumor is composed of sheets and nests of large pleomorphic cells. There is no evidence of squamous or glandular differentiation (H&E, 200×)

Differential Diagnosis

Metastatic undifferentiated or poorly differentiated carcinomas, large cell and anaplastic lymphomas, and metastatic melanomas must be considered in the differential diagnosis. A thorough history and physical examination are critical in excluding the possibility of a metastatic poorly differentiated or undifferentiated carcinoma.

Large cell carcinomas have a tendency to grow in a dyscohesive cell pattern which can closely mimic large cell and anaplastic lymphomas. Unlike large cell carcinomas, lymphomas will be negative for cytokeratin and positive for lymphoid markers with immunohistochemistry techniques.

Immunohistochemistry is also invaluable in separating amelanotic melanomas from large cell carcinomas. The melanomas will be negative for cytokeratin but positive for markers such as S-100, HMB45, and Melan A.

Treatment and Prognosis

Large cell carcinoma is a highly malignant tumor which requires aggressive treatment. This frequently entails radical surgery combined with radiation and chemotherapy. With undifferentiated carcinomas, cell size (large cell carcinoma versus small cell carcinoma) does not appear to alter the prognosis [170, 251, 427].

Small Cell Carcinoma

Clinical Features

Although most common in the lung, approximately 4% of small cell carcinomas arise from a variety of extrapulmonary sites including the head and neck where they have been reported in the larynx, pharynx, cervical esophagus, nose and paranasal sinuses, oral cavity, and salivary glands [281, 340, 366, 482]. The most common site in the head and neck is the larynx.

Small cell carcinoma accounts for less than 2% of salivary gland malignancies and less than 1% of all salivary gland neoplasms [170, 196, 482]. Over 80% arise in the parotid gland [170, 196, 251, 482]. Less frequently they arise in the submandibular gland or the minor salivary glands [427]. Approximately 60% occur in men although in some series the male to female ratio may be as high as 6:1 [251]. Patients are usually over the age of 50 years (mean 54 years) although rarely these cancers have been reported in children [483]. Most patients complain of a rapidly enlarging mass which may or may not be painful. Unlike pulmonary small cell carcinoma, there is no association between smoking and small cell carcinoma of the salivary gland [108, 432].

Pathologic Features

The tumors are gray to gray-white and firm. Infiltrative growth is usually obvious grossly.

Microscopically small cell carcinoma forms infiltrative sheets, nests, and trabeculae of cells supported by a fibrovascular stroma. Focal rosette-like formations, peripheral palisading, and ductal differentiation may be present [108]. Individual tumor cells are 1.5 to 2 times the diameter of a lymphocyte. They have round to fusiform hyperchromatic nuclei, small inconspicuous nucleoli, and scant cytoplasm. Nuclear molding and crush artifact are common. Mitoses are frequent and foci of tumor necrosis are commonly seen.

Some tumors are composed of cells which are slightly larger and have more cytoplasm corresponding to the intermediate type of small cell carcinoma of the lung. Foci of squamous differentiation may occasionally be seen [432].

Small cell carcinomas of salivary glands are typically positive for the cytokeratin stains AE1/3, CK20, and CAM5.2 frequently in a perinuclear dot-like pattern. CK7 is positive in addition to CK20 in approximately one third of cases [432]. These tumors are also positive for neuroendocrine markers, most commonly neuron-specific enolase, chromogranin, and synaptophysin.

Differential Diagnosis

Most frequently entertained in the differential diagnosis are metastatic small cell carcinoma of the lung, metastatic Merkel cell carcinoma of the skin, malignant lymphoma, and the solid variant of adenoid cystic carcinoma.

Small cell carcinoma of the lung and small cell carcinoma of the salivary gland are histologically identical. Knowledge of the clinical history and physical examination along with the results of special stains will usually lead to the correct diagnosis. Small cell carcinomas of the lung are positive for CK7 and negative for CK20. In addition the perinuclear dot-like staining pattern is not seen [251, 253]. They are also positive for thyroid transcription factor while small cell carcinomas of salivary glands are usually negative, although in one series of 15 cases of small cell carcinoma of salivary glands three were positive for thyroid transcription factor [432].

Merkel cell carcinoma and small cell carcinoma of salivary gland origin have an identical immunohistochemical staining pattern including a characteristic perinuclear dot-like pattern with cytokeratin stains. A detailed history and physical examination is critical in excluding a diagnosis of Merkel cell carcinoma.

Malignant lymphomas are negative for cytokeratin and neuroendocrine markers and positive for lymphocyte markers such as leukocyte common antigen. The exact opposite is true for small cell carcinomas.

Rarely the solid variant of adenoid cystic carcinoma may mimic small cell carcinoma on routine hematoxylin and eosin stained sections. Unlike small cell carcinoma, however, it does not show a perinuclear dot-like staining pattern with cytokeratin stains and neuroendocrine stains are negative.

Treatment and Prognosis

Although not as aggressive as small cell carcinoma of the lung or larynx, small cell carcinoma of the salivary glands is a high-grade malignancy and is treated aggressively. This frequently involves a combination of surgery, radiation, and chemotherapy [216, 513, 549]. Gnepp et al. reported 2- and 5-year survival rates of 70% and 46% for small cell carcinoma of salivary glands compared to 16% and 5% for those of the larynx [539]. Another series by Nagao et al. reported 2- and 5-year survival rates of 38% and 13% for small cell carcinoma of salivary glands [237, 513].

Primary Squamous Cell Carcinoma

Clinical Features

Primary squamous cell carcinomas of the salivary glands (PSSC) are rare, extremely aggressive neoplasms, the majority of patients presenting with advanced disease [384, 513]. In Spiro's review of 2,807 salivary gland tumors, PSSC accounted for only 1.9% [23, 513]. Nine percent of patients have a history of prior radiation exposure [23, 131, 237, 355, 389, 513].

In over two thirds of cases the cancer arises in the parotid gland and most of the remaining cases originate in the submandibular gland [513]. Rare cases probably arise in minor salivary glands although these may be difficult or impossible to distinguish from mucosal squamous cell carcinomas with extension into underlying minor salivary glands. PSSC is twice as common in men as women [365]. Although it has been reported in all decades of life,

it is most common in the seventh decade. It is extremely uncommon in individuals below the age of 20 years [435]. Signs and symptoms include a painful rapidly enlarging mass and facial nerve palsy, although up to 50% may present with an asymptomatic mass [42, 237, 355, 389, 513].

Pathologic Features

Primary squamous cell carcinomas are gray-white, firm, usually grossly infiltrative, and average 3 cm in diameter. The cut surface may show focal areas of necrosis.

Histologically the tumors are usually moderately differentiated squamous cell carcinomas. Keratin production, often with keratin pearl formation, and intercellular bridge formation are easily identified (Fig. 3.20). Less frequently the tumors are high grade. Perineural invasion is frequently present. The stroma typically show a desmoplastic response.

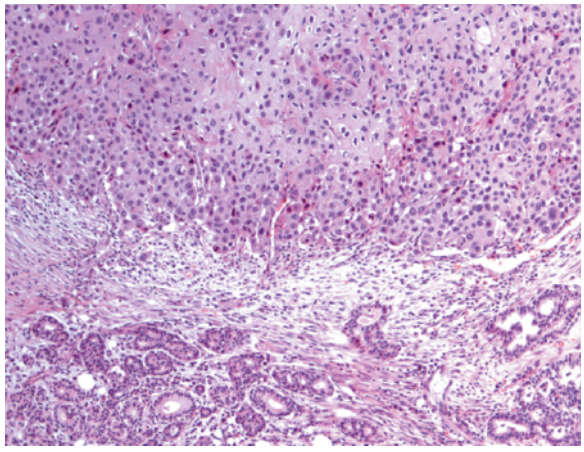

Fig. 3.20: Primary squamous cell carcinoma. Glassy cytoplasm and intercellular bridges identify this tumor as a squamous cell carcinoma (top half of figure). Residual salivary gland is present in the lower half of figure (H&E, 100×)

Differential Diagnosis

Squamous metaplasia, necrotizing sialometaplasia, keratocystoma, high-grade mucoepidermoid carcinoma, and metastatic squamous cell carcinoma all enter into the differential diagnosis.

Squamous metaplasia may occur in other neoplasms in response to inflammation and leakage of cyst contents such as may occur for example in Warthin's tumor. Prior fine-needle aspiration of benign tumors may also induce squamous metaplasia [216, 237, 355].

Preservation of normal lobular architecture and lack of invasion best serve to distinguish necrotizing sialometaplasia from PSSC. These features may, however, be difficult to appreciate in a small biopsy.

Keratocystoma is a benign cystic neoplasm in which cystic spaces are filled with keratin and lined by regularly oriented bland squamous cells. Although some solid squamous islands may be present there is no evidence of invasive, destructive growth [23, 216, 237, 355].

Mucoepidermoid carcinomas must, by definition, contain mucous cells. Mucous cells, however, are not numerous in high-grade tumors and indeed may not be recognized in some cases, unless the sections are stained with PAS-diastase or mucicarmine stains. While composed primarily of squamous (epidermoid cells), high-grade mucoepidermoid carcinomas do not show the extensive intracellular keratinization, keratin pearl formation, and intercellular bridge formation characteristic of PSSC.

Metastatic squamous cell carcinoma to salivary glands is more common than PSSC. This is particularly true in the parotid with its rich supply of both peri- and intraglandular lymph nodes [359]. The presence of a focus of squamous cell carcinoma in situ would serve to distinguish PSSC from metastatic squamous cell carcinoma. Such foci are seldom seen however because most PSSCs present at an advanced stage with obliteration of any foci of in situ disease. The clinical history and physical examination may provide valuable information. Squamous cell carcinoma metastatic to the parotid usually originates from skin lesions of the head and neck. The skin of the frontal and temporal areas, the periorbital region, the cheek, the pinna, the external ear canal, and the pre- and postauricular areas are favored sites. Tumors at these sites are usually clinically obvious long before metastases to the parotid.

Treatment and Prognosis

This is an aggressive tumor and radical resection with neck dissection is usually indicated. The facial nerve may be spared if not directly infiltrated by tumor. Up to 75% of patients have histologically positive cervical lymph nodes. There is a significant incidence of local-regional recurrence which has led to the use of postoperative radiation therapy in may instances. Distant metastases occur in 20–30% of patients. The 5-year survival rate is 25%.

Take Home Messages

- Salivary gland pathologic entities have a wide morphologic spectrum, and there may be considerable overlap between non-neoplastic, benign, and malignant entities.
- Non-neoplastic disease is often a manifestation of an underlying systemic disease. Necrotizing sialometaplasia is important to consider as it may histologically mimic malignancy. Marginal zone B-cell lymphoma may be a late complication of autoimmune MESA.
- Benign tumors are varied and named for their cell type. They have an appreciable recurrence rate if incompletely excised. Pleomorphic adenomas can behave aggressively after multiple recurrences without having malignant histologic features. Some tumors that are multifocal such as canalicular adenomas and Warthin's tumors, imply a field effect, while membranous type basal cell adenoma is multifocal often as a result of known mutations. Malignant transformation is extremely rare.
- Malignant tumors are as varied as their benign counterparts. Certain tumors are almost always low grade (i.e., polymorphous low-grade adenocarcinoma, acinic cell carcinoma, epithelial-myoepithelial carcinoma), while others are definitionally high grade (i.e., salivary duct carcinoma, large cell carcinoma, and small cell carcinoma). Malignant mixed tumor should be considered a category of disease with several clinicopathologic variants rather than a distinct entity. Histologic grading systems are most important in adenoid cystic carcinoma and mucoepidermoid carcinoma, while understanding of pathologic prognosticators in other malignant tumors is still not well established.

References

1. Abbondanzo SL (2001) *Extranodal marginal-zone B-cell lymphoma of the salivary gland*. Ann Diagn Pathol 5:246–254
2. Aberle AM, Abrams AM, Bowe R, et al. (1985) *Lobular (polymorphous low-grade) carcinoma of minor salivary glands. A clinicopathologic study of twenty cases*. Oral Surg Oral Med Oral Pathol 60:387–395
3. Abrams AM, Melrose RJ, Howell FV (1973) *Necrotizing sialometaplasia. A disease simulating malignancy*. Cancer 32:130–135
4. Aframian D, Milhem II, Kirsch G, et al. (1995) *Necrotizing Sialometaplasia after Silastic Ring Vertical Gastroplasty: Case Report and Review of Literature*. Obes Surg 5:179–182
5. Ahn MS, Hayashi GM, Hilsinger RL Jr., et al. (1999) *Familial mixed tumors of the parotid gland*. Head Neck 21:772–775
6. Albores-Saavedra J, Morris AW (1963) *Sebaceous adenoma of the submaxillary salivary gland. Report of a case*. Arch Otolaryngol 77:500–503
7. Alcedo JC, Fabrega JM, Arosemena JR, et al. (2004) *Imatinib mesylate as treatment for adenoid cystic carcinoma of the salivary glands: report of two successfully treated cases*. Head Neck 26:829–831
8. Alho OP, Kristo A, Luotonen J, et al. (1996) *Intraductal papilloma as a cause of a parotid duct cyst. A case report*. J Laryngol Otol 110:277–278
9. Allen MS Jr., Fitz-Hugh GS, Marsh WL Jr. (1974) *Low-grade papillary adenocarcinoma of the palate*. Cancer 33:153–158
10. Alos L, Cardesa A, Bombi JA, et al. (1996) *Myoepithelial tumors of salivary glands: a clinicopathologic, immunohistochemical, ultrastructural, and flow-cytometric study*. Semin Diagn Pathol 13:138–147
11. Alos L, Lujan B, Castillo M, et al. (2005) *Expression of membrane-bound mucins (MUC1 and MUC4) and secreted mucins (MUC2, MUC5AC, MUC5B, MUC6 and MUC7) in mucoepidermoid carcinomas of salivary glands*. Am J Surg Pathol 29:806–813
12. Alvarez-Canas C, Rodilla IG (1996) *True malignant mixed tumor (carcinosarcoma) of the parotid gland. Report of a case with immunohistochemical study*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81:454–458
13. Anderson C, Muller R, Piorkowski R, et al. (1992) *Intraductal carcinoma of major salivary gland*. Cancer 69:609–614
14. Andreadis D, Epivatianos A, Poulopoulos A, et al. (2006) *Detection of C-KIT (CD117) molecule in benign and malignant salivary gland tumours*. Oral Oncol 42:57–65

15. Andreadis D, Nomikos A, Epivatianos A, et al. (2005) *Basaloid squamous cell carcinoma versus basal cell adenocarcinoma of the oral cavity*. Pathology 37:560–563
16. Arafat A, Brannon RB, Ellis GL (1981) *Adenomatoid hyperplasia of mucous salivary glands*. Oral Surg Oral Med Oral Pathol 52:51–55
17. Arida M, Barnes EL, Hunt JL (2005) *Molecular assessment of allelic loss in Warthin tumors*. Mod Pathol 18:964–968
18. Aronsohn RS, Batsakis JG, Rice DH, et al. (1976) *Anomalies of the first branchial cleft*. Arch Otolaryngol 102:737–740
19. Arriaga MA, Myers EN (1990) *The surgical management of chronic parotitis*. Laryngoscope 100:1270–1275
20. Assor D (1970) *Sebaceous lymphadenoma of the parotid gland. A case report*. Am J Clin Pathol 53:100–103
21. Attie JN, Sciubba JJ (1981) *Tumors of major and minor salivary glands: clinical and pathologic features*. Curr Probl Surg 18:130–133
22. Auclair PL (1994) *Tumor-associated lymphoid proliferation in the parotid gland. A potential diagnostic pitfall*. Oral Surg Oral Med Oral Pathol 77:19–26
23. Auclair PL, Ellis GL (1991) *Primary squamous cell carcinoma* Surgical pathology of the salivary glands. Edited by Ellis GL, Auclair PL, Gnepp DR. Philadelphia, WB Saunders Co., pp 369–378
24. Auclair PL, Ellis GL (1996) *Atypical features in salivary gland mixed tumors: their relationship to malignant transformation*. Mod Pathol 9:652–657
25. Avitia S, Hamilton JS, Osborne RF (2005) *Epithelial-myoepithelial carcinoma*. Ear Nose Throat J 84:764, 767
26. Aydin O, Yilmaz T, Ozer F, et al. (2002) *Necrotizing sialometaplasia of parotid gland: a possible vasculitic cause*. Int J Pediatr Otorhinolaryngol 64:171–174
27. Aydm E, Turkoglu S, Ozen O, et al. (2005) *Mucinous cystadenocarcinoma of a minor salivary gland in the upper lip: Case report*. Auris Nasus Larynx 32:301–304
28. Ayoub OM, Bhatia K, Mal RK (2002) *Pleomorphic adenoma of the parotid gland: is long-term follow-up needed?* Auris Nasus Larynx 29:283–285
29. Azevedo LR, Damante JH, Lara VS, et al. (2005) *Age-related changes in human sublingual glands: a post mortem study*. Arch Oral Biol 50:565–574
30. Azumi N, Battifora H (1987) *The cellular composition of adenoid cystic carcinoma. An immunohistochemical study*. Cancer 60:1589–1598
31. Azzopardi JG, Evans DJ (1971) *Malignant lymphoma of parotid associated with Mikulicz disease (benign lymphoepithelial lesion)*. J Clin Pathol 24:744–752
32. Bahler DW, Swerdlow SH (1998) *Clonal salivary gland infiltrates associated with myoepithelial sialadenitis (Sjogren's syndrome) begin as nonmalignant antigen-selected expansions*. Blood 91:1864–1872
33. Balogh K, Wolbarsht RL, Federman M, et al. (1985) *Carcinoma of the parotid gland with osteoclastlike giant cells. Immunohistochemical and ultrastructural observations*. Arch Pathol Lab Med 109:756–761
34. Baratz M, Loewenthal M, Rozin M (1976) *Sebaceous lymphadenoma of the parotid gland*. Arch Pathol Lab Med 100:269–270
35. Barnes L, Appel B, Perez H, et al. (1985) *Myoepitheliomas of the head and neck: Case report and review.* J Surg Oncol 28:21–28
36. Barnes L, Appel BN, Perez H, et al. (1985) *Myoepithelioma of the head and neck: case report and review*. J Surg Oncol 28:21–28
37. Barnes L, Rao U, Contis L, et al. (1994) *Salivary duct carcinoma. Part II. Immunohistochemical evaluation of 13 cases for estrogen and progesterone receptors, cathepsin D, and c-erbB-2 protein*. Oral Surg Oral Med Oral Pathol 78:74–80
38. Barnes L, Rao U, Krause J, et al. (1994) *Salivary duct carcinoma. Part I. A clinicopathologic evaluation and DNA image analysis of 13 cases with review of the literature*. Oral Surg Oral Med Oral Pathol 78:64–73
39. Barrett AW, Speight PM (1995) *Adenomatoid hyperplasia of oral minor salivary glands*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79:482–487
40. Batsakis J (1979) *Tumors of the Head and Neck*. Clinical and Pathological Considerations, 2nd edition. Baltimore, Williams and Wilkins and Wilkins Co., pp 26–30
41. Batsakis JG (1982) *Malignant mixed tumor*. Ann Otol Rhinol Laryngol 91:342–343
42. Batsakis JG (1983) *Primary squamous cell carcinomas of major salivary glands*. Ann Otol Rhinol Laryngol 92:97–98
43. Batsakis JG (1991) *Sublingual gland*. Ann Otol Rhinol Laryngol 100:521–522
44. Batsakis JG, Bernacki EG, Rice DH, et al. (1975) *Malignancy and the benign lymphoepithelial lesion*. Laryngoscope 85:389–399
45. Batsakis JG, Bruner JM, Luna MA (1988) *Polycystic (dysgenetic) disease of the parotid glands*. Arch Otolaryngol Head Neck Surg 114:1146–1148
46. Batsakis JG, Chinn E, Regezi JA, et al. (1978) *The pathology of head and neck tumors: salivary glands, part 2*. Head Neck Surg 1:167–180
47. Batsakis JG, Chinn EK, Weimert TA, et al. (1979) *Acinic cell carcinoma: a clinicopathologic study of thirty-five cases*. J Laryngol Otol 93:325–340

48. Batsakis JG, el-Naggar AK (1991) *Terminal duct adenocarcinomas of salivary tissues*. Ann Otol Rhinol Laryngol 100:251–253
49. Batsakis JG, el-Naggar AK, Luna MA (1992) *Epithelial-myoepithelial carcinoma of salivary glands*. Ann Otol Rhinol Laryngol 101:540–542
50. Batsakis JG, Kraemer B, Sciubba JJ (1983) *The pathology of head and neck tumors: the myoepithelial cell and its participation in salivary gland neoplasia, Part 17*. Head Neck Surg 5:222–233
51. Batsakis JG, Luna MA (1990) *Histopathologic grading of salivary gland neoplasms: I. Mucoepidermoid carcinomas*. Ann Otol Rhinol Laryngol, 99:835–838
52. Batsakis JG, Luna MA (1991) *Basaloid salivary carcinoma*. Ann Otol Rhinol Laryngol 100:785–787
53. Batsakis JG, Luna MA (1991) *Undifferentiated carcinomas of salivary glands*. Ann Otol Rhinol Laryngol 100:82–84
54. Batsakis JG, Luna MA, el-Naggar A (1990) *Histopathologic grading of salivary gland neoplasms: III. Adenoid cystic carcinomas*. Ann Otol Rhinol Laryngol 99:1007–1009
55. Batsakis JG, Pinkston GR, Luna MA, et al. (1983) *Adenocarcinomas of the oral cavity: a clinicopathologic study of terminal duct carcinomas*. J Laryngol Otol 97:825–835
56. Batsakis JG, Raymond AK (1989) *Sialocysts of the parotid glands*. Ann Otol Rhinol Laryngol 98:487–489
57. Batsakis JG, Regezi JA (1978) *The pathology of head and neck tumors: salivary glands, part 1*. Head Neck Surg 1:59–68
58. Batsakis JG, Wozniak KJ, Regezi JA (1977) *Acinous cell carcinoma: a histogenetic hypothesis*. J Oral Surg 35:904–906
59. Baugh RF, Wolf GT, McClatchey KD (1986) *Small cell carcinoma of the head and neck*. Head Neck Surg 8:343–354
60. Baurmash HD (2004) *Chronic recurrent parotitis: a closer look at its origin, diagnosis, and management*. J Oral Maxillofac Surg 62:1010–1018
61. Beahrs OH, Woolner LB, Kirklin JW, et al. (1957) *Carcinomatous transformation of mixed tumors of the parotid gland*. AMA Arch Surg, 75:605–613; discussion 613–604
62. Begin LR, Black MJ (1993) *Salivary-type myxoid myoepithelioma of the sinonasal tract: a potential diagnostic pitfall*. Histopathology 23:283–285
63. Begin LR, Rochon L, Frenkiel S (1991) *Spindle cell myoepithelioma of the nasal cavity*. Am J Surg Pathol 15:184–190
64. Beltran D, Faquin WC, Gallagher G, et al. (2006) *Selective immunohistochemical comparison of polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma*. J Oral Maxillofac Surg 64:415–423
65. Berean KW, Watts MC, Mills SE (1995) *Basal cell adenocarcinoma of salivary glands*. Lab Invest 72:99A
66. Bhalla RK, Jones TM, Taylor W, et al. (2002) *Carcinosarcoma (malignant mixed tumor) of the submandibular gland: A case report and review of the literature*. J Oral Maxillofac Surg 60:1067–1069
67. Bharadwaj G, Nawroz I, O'Regan B (2007) *Sclerosing polycystic adenosis of the parotid gland*. Br J Oral Maxillofac Surg 45:74–76
68. Billroth T (1859) *Beobachtungen Uber Geschwulste der Speichisdrusen Virch*. Pathol Anat 17:357–375
69. Blanck C, Eneroth CM, Jakobsson PA (1971) *Mucus-producing adenopapillary (non-epidermoid) carcinoma of the parotid gland*. Cancer 28:676–685
70. Bleiweiss IJ, Huvos AG, Lara J, et al. (1992) *Carcinosarcoma of the submandibular salivary gland. Immunohistochemical findings*. Cancer 69:2031–2035
71. Boahene DK, Olsen KD, Lewis JE, et al. (2004) *Mucoepidermoid carcinoma of the parotid gland: the Mayo clinic experience*. Arch Otolaryngol Head Neck Surg 130:849–856
72. Boles R, Johns ME, Batsakis JG (1973) *Carcinoma in pleomorphic adenomas of salivary glands*. Ann Otol Rhinol Laryngol 82:684–690
73. Bombi JA, Alos L, Rey MJ, et al. (1996) *Myoepithelial carcinoma arising in a benign myoepithelioma: immunohistochemical, ultrastructural, and flow-cytometrical study*. Ultrastruct Pathol 20:145–154
74. Bos I, Meyer S, Merz H (2004) *[Lymphadenoma of the parotid gland without sebaceous differentiation. Immunohistochemical investigations]*. Pathologe 25:73–78
75. Bowman SJ (2002) *Collaborative research into outcome measures in Sjogren's syndrome. Update on disease assessment*. Scand J Rheumatol Suppl (116):23–27
76. Bradley P (2005) *Metastasizing pleomorphic salivary adenoma should now be considered a low grade malignancy with a lethal potential*. Otolaryngol Head Neck Surg 13:123–126
77. Bradley PJ (2004) *Adenoid cystic carcinoma of the head and neck: a review*. Curr Opin Otolaryngol Head Neck Surg 12:127–132
78. Bradley PJ (2005) *Metastasizing pleomorphic salivary adenoma should now be considered a low-grade malignancy with a lethal potential*. Curr Opin Otolaryngol Head Neck Surg 13:123–126
79. Brandwein-Gensler M, Hille J, Wang BY, et al. (2004) *Low-grade salivary duct carcinoma: description of 16 cases*. Am J Surg Pathol 28:1040–1044
80. Brandwein M, Huvos A (1995) *Laryngeal oncocytic cystadenomas. Eight cases and a literature review*. Arch Otolaryngol Head Neck Surg 121:1302–1305

81. Brandwein M, Huvos AG, Dardick I, et al. (1996) *Noninvasive and minimally invasive carcinoma ex mixed tumor: a clinicopathologic and ploidy study of 12 patients with major salivary tumors of low (or no?) malignant potential*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81:655–664
82. Brandwein MS, Huvos AG (1991) *Oncocytic tumors of major salivary glands. A study of 68 cases with follow-up of 44 patients*. Am J Surg Pathol 15:514–528
83. Brandwein MS, Ivanov K, Wallace DI, et al. (2001) *Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading*. Am J Surg Pathol 25:835–845
84. Brandwein MS, Jagirdar J, Patil J, et al. (1990) *Salivary duct carcinoma (cribriform salivary carcinoma of excretory ducts). A clinicopathologic and immunohistochemical study of 12 cases*. Cancer 65:2307–2314
85. Brannon RB, Fowler CB, Hartman KS (1991) *Necrotizing sialometaplasia. A clinicopathologic study of sixty-nine cases and review of the literature*. Oral Surg Oral Med Oral Pathol 72:317–325
86. Brannon RB, Houston GD, Meader CL (1985) *Adenomatoid hyperplasia of mucous salivary glands: a case involving the retromolar area*. Oral Surg Oral Med Oral Pathol 60:188–190
87. Brannon RB, Sciubba JJ, Giulani M (2001) *Ductal papillomas of salivary gland origin: A report of 19 cases and a review of the literature*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 92:68–77
88. Brannon RB, Willard CC (2003) *Oncocytic mucoepidermoid carcinoma of parotid gland origin*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96:727–733
89. Brauneis J, Laskawi R, Schroder M, et al. (1990) *[Squamous cell carcinoma in the area of the parotid gland. Metastasis or primary tumor?]*. HNO 38:292–294
90. Brehmer D, Hohbach M, Laubert A (1999) *[Intraductal papilloma of the parotid gland]*. Laryngorhinootologie 78:332–334
91. Brook I (2003) *Acute bacterial suppurative parotitis: microbiology and management*. J Craniofac Surg 14:37–40
92. Browand BC, Waldron CA (1975) *Central mucoepidermoid tumors of the jaws. Report of nine cases and review of the literature*. Oral Surg Oral Med Oral Pathol 40:631–643
93. Bruner JM, Cleary KR, Smith FB, et al. (1989) *Immunocytochemical identification of HIV (p24) antigen in parotid lymphoid lesions*. J Laryngol Otol 103:1063–1066
94. Buchholz TA, Shimotakahara SG, Weymuller EA Jr., et al. (1993) *Neutron radiotherapy for adenoid cystic carcinoma of the head and neck*. Arch Otolaryngol Head Neck Surg 119:747–752
95. Buchner A, Merrell PW, Carpenter WM, et al. (1991) *Adenomatoid hyperplasia of minor salivary glands*. Oral Surg Oral Med Oral Pathol 71:583–587
96. Buenting JE, Smith TL, Holmes DK (1998) *Giant pleomorphic adenoma of the parotid gland: case report and review of the literature*. Ear Nose Throat J 77:637–640
97. Bullerdiek J, Wobst G, Meyer-Bolte K, et al. (1993) *Cytogenetic subtyping of 220 salivary gland pleomorphic adenomas: correlation to occurrence, histological subtype, and in vitro cellular behavior*. Cancer Genet Cytogenet 65:27–31
98. Buxton RW, Maxwell JH, French AJ (1953) *Surgical treatment of epithelial tumors of the parotid gland.* Surg Gynecol Obstet 97:401–416
99. Cabov T, Macan D, Manojlovic S, et al. (2004) *Oral inverted ductal papilloma*. Br J Oral Maxillofac Surg 42:75–77
100. Capone RB, Ha PK, Westra WH, et al. (2002) *Oncocytic neoplasms of the parotid gland: a 16-year institutional review*. Otolaryngol Head Neck Surg 126:657–662
101. Cardesa A, Alos L (2005) *Myoepithelioma*. Pathology and Classification of Head and Neck Tumours. Edited by Barnes EL, Eveson JW, Reichart P, Sidransky D. Lyon, IARC, pp 259–260
102. Carew JF, Spiro RH, Singh B, et al. (1999) *Treatment of recurrent pleomorphic adenomas of the parotid gland*. Otolaryngol Head Neck Surg 121:539–542
103. Caselitz J, Schulze I, Seifert G (1986) *Adenoid cystic carcinoma of the salivary glands: an immunohistochemical study*. J Oral Pathol 15:308–318
104. Casler JD, Conley JJ (1992) *Surgical management of adenoid cystic carcinoma in the parotid gland*. Otolaryngol Head Neck Surg 106:332–338
105. Castle JT, Thompson LD, Frommelt RA, et al. (1999) *Polymorphous low grade adenocarcinoma: a clinicopathologic study of 164 cases*. Cancer 86:207–219
106. Castro WH, Drummond SN, Gomez RS (2002) *Subacute necrotizing sialadenitis in the buccal mucosa*. J Oral Maxillofac Surg 60:1494–1496
107. Chan JK, Saw D (1987) *Sclerosing mucoepidermoid tumour of the parotid gland: report of a case*. Histopathology 11:203–207
108. Chan JK, Suster S, Wenig BM, et al. (1997) *Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous neuroendocrine) carcinomas and salivary gland small cell carcinomas from small cell carcinomas of various sites*. Am J Surg Pathol 21:226–234
109. Chang A, Harawi SJ (1992) *Oncocytes, oncocytosis, and oncocytic tumors*. Pathol Annu 27 Pt 1:263–304
110. Chang JY, Hsiao CH (2004) *Lymphadenoma lacking sebaceous differentiation in the parotid gland*. J Formos Med Assoc 103:459–462

111. Chaplin AJ, Darke P, Patel S (1983) *Tyrosine-rich crystals in pleomorphic adenomas of parotid glands*. J Oral Pathol 12:342–346
112. Chaudhry AP, Vickers RA, Gorlin RJ (1961) *Intraoral minor salivary gland tumors: An analysis of 1,414 cases*. Oral Surg Oral Med Oral Path 14:1194–1226
113. Chen I, Tu H (2000) *Pleomorphic adenoma of the parotid gland metastasizing to the cervical lymph node*. Otolaryngol Head Neck Surg 122:455–457
114. Chen JC, Gnepp DR, Bedrossian CW (1988) *Adenoid cystic carcinoma of the salivary glands: an immunohistochemical analysis*. Oral Surg Oral Med Oral Pathol 65:316–326
115. Chen KT (1985) *Carcinoma arising in monomorphic adenoma of the salivary gland*. Am J Otolaryngol 6:39–41
116. Chen YK, Lin CC, Lin LM, et al. (1999) *Adenomatoid hyperplasia in the mandibular retromolar area. Case report*. Aust Dent J 44:135–136
117. Cheng J, Saku T, Okabe H, et al. (1992) *Basement membranes in adenoid cystic carcinoma. An immunohistochemical study*. Cancer 69:2631–2640
118. Chetty R (1998) *HIV-associated lymphoepithelial cysts and lesions: morphological and immunohistochemical study of the lymphoid cells*. Histopathology 33:222–229
119. Cheuk W, Miliauskas JR, Chan JKC (2004) *Intraductal carcinoma of the oral cavity: a case report and a reappraisal of the concept of pure ductal carcinoma in situ in salivary duct carcinoma.[see comment]*. Am J Surg Pathol 28:266–270
120. Chhieng DC, Paulino AF (2002) *Cytology of myoepithelial carcinoma of the salivary gland*. Cancer 96:32–36
121. Chilla R (1981) *Sialadenosis of the salivary glands of the head. Studies on the physiology and pathophysiology of parotid secretion*. Adv Otorhinolaryngol 26:1–38
122. Chilla R, Schroth R, Eysholdt U, et al. (1980) *Adenoid cystic carcinoma of the head and neck. Controllable and uncontrollable factors in treatment and prognosis*. ORL J Otorhinolaryngol Relat Spec 42:346–367
123. Chilla R, Witzemann V, Opaitz M, et al. (1981) *Possible involvement of parotid beta-adrenergic receptors in the etiology of sialadenosis*. Arch Otorhinolaryngol 230:113–120
124. Cho KJ, el-Naggar AK, Ordonez NG, et al. (1995) *Epithelial-myoepithelial carcinoma of salivary glands. A clinicopathologic, DNA flow cytometric, and immunohistochemical study of Ki-67 and HER-2/neu oncogene*. Am J Clin Pathol 103:432–437
125. Choi HR, Batsakis JG, Callender DL, et al. (2002) *Molecular analysis of chromosome 16q regions in dermal analogue tumors of salivary glands: a genetic link to dermal cylindroma?* Am J Surg Pathol 26:778–783
126. Chong GC, Beahrs OH, Woolner LB (1974) *Surgical management of acinic cell carcinoma of the parotid gland*. Surg Gynecol Obstet 138:65–68
127. Clark DB, Priddy RW, Swanson AE (1990) *Oral inverted ductal papilloma*. Oral Surg Oral Med Oral Pathol 69:487–490
128. Conley J, Dingman DL (1974) *Adenoid cystic carcinoma in the head and neck (cylindroma)*. Arch Otolaryngol 100:81–90
129. Corio RL, Sciubba JJ, Brannon RB, et al. (1982) *Epithelial-myoepithelial carcinoma of intercalated duct origin. A clinicopathologic and ultrastructural assessment of sixteen cases*. Oral Surg Oral Med Oral Pathol 53:280–287
130. Cornog J, Gray S (1976) *Surgical and clinical pathology of salivary gland tumors*. Diseases of the Salivary Glands. Edited by Rankow R, Polayes I. Philadelphia, WB Saunders Co., pp 130–142
131. Cornog JL (1970) *Surgical and clinical pathology of salivary gland tumors* Diseases of Salivary Glands Edited by Rankow R, Polayes I. Philadelphia, WB Saunders Co., pp 92–142
132. Corridan M (1956) *Glycogen-rich clear cell adenoma of the parotid*. J Pathol Bacteriol 72:623–627
133. Crumpler C, Scharfenberg JC, Reed RJ (1976) *Monomorphic adenomas of salivary glands. Trabecular-tubular, canalicular, and basaloid variants*. Cancer 38:193–200
134. Curran AE, White DK, Damm DD, et al. (2001) *Polymorphous low-grade adenocarcinoma versus pleomorphic adenoma of minor salivary glands: resolution of a diagnostic dilemma by immunohistochemical analysis with glial fibrillary acidic protein*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 91:194–199
135. da Cruz Perez DE, de Abreu Alves F, Nobuko Nishimoto I, et al. (2006) *Prognostic factors in head and neck adenoid cystic carcinoma*. Oral Oncol 42:139–146
136. Dagrada GP, Negri T, Tamborini E, et al. (2004) *Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry.[comment]*. Histopathology 44:301–302
137. Daley TD, Gardner DG, Smout MS (1984) *Canalicular adenoma: not a basal cell adenoma*. Oral Surg Oral Med Oral Pathol 57:181–188
138. Dalforno S, Donna A (1967) *[Sebaceous adenoma of the salivary gland]*. Cancro 20:667–673
139. Daniels TE (1984) *Labial salivary gland biopsy in Sjogren's syndrome. Assessment as a diagnostic criterion in 362 suspected cases*. Arthritis Rheum 27:147–156
140. Dardick I (1996) *Salivary Gland Tumor Pathology*. New York, Igaku-shoin, pp 235–239

141. Dardick I, Daley TD, van Nostrand AW (1986) *Basal cell adenoma with myoepithelial cell-derived stroma: a new major salivary gland tumor entity*. Head Neck Surg 8:257–267
142. Dardick I, Lytwyn A, Bourne AJ, et al. (1992) *Trabecular and solid-cribriform types of basal cell adenoma. A morphologic study of two cases of an unusual variant of monomorphic adenoma*. Oral Surg Oral Med Oral Pathol 73:75–83
143. Dardick I, Thomas MJ, van Nostrand AW (1989) *Myoepithelioma – new concepts of histology and classification: a light and electron microscopic study*. Ultrastruct Pathol 13:187–224
144. Darling MR, Schneider JW, Phillips VM (2002) *Polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma: a review and comparison of immunohistochemical markers*. Oral Oncol 38:641–645
145. de Araujo VC, de Sousa SO, Carvalho YR, et al. (2000) *Application of immunohistochemistry to the diagnosis of salivary gland tumors*. Appl Immunohistochem Mol Morphol 8:195–202
146. De la Maza LM, Schwartz MM, Soto EA (1971) *Sebaceous lymphadenoma of the parotid region*. Arch Pathol 92:294–295
147. de Sousa SO, Schwarzschild M, de Araujo NS, et al. (2000) *Basal cell adenocarcinoma of the palate with squamous metaplasia*. J Clin Pathol 53:153–156
148. de Sousa SO, Sesso A, de Araujo NS, et al. (1995) *Inverted ductal papilloma of minor salivary gland origin: morphological aspects and cytokeratin expression*. Eur Arch Otorhinolaryngol 252:370–373
149. Delgado R, Klimstra D, Albores-Saavedra J (1996) *Low grade salivary duct carcinoma. A distinctive variant with a low grade histology and a predominant intraductal growth pattern*. Cancer 78:958–967
150. Delgado R, Vuitch F, Albores-Saavedra J (1992) *High grade salivary duct carcinoma.* Mod Pathol 5:71A
151. Deysine M, Mann BF Jr. (1969) *Sebaceous lymphadenoma of the parotid gland: associated with a case of bilateral parotid gland tumors*. Ann Surg 169:437–443
152. Di Palma S, Corletto V, Lavarino C, et al. (1999) *Unilateral aneuploid dedifferentiated acinic cell carcinoma associated with bilateral-low grade diploid acinic cell carcinoma of the parotid gland*. Virchows Arch 434:361–365
153. Di Palma S, Simpson RH, Skalova A, et al. (1999) *Metaplastic (infarcted) Warthin's tumour of the parotid gland: a possible consequence of fine needle aspiration biopsy*. Histopathology 35:432–438
154. Di Palma S, Skalova A, Vanieek T, et al. (2005) *Non-invasive (intracapsular) carcinoma ex pleomorphic adenoma: recognition of focal carcinoma by HER-2/neu and MIB1 immunohistochemistry*. Histopathology 46:144–152
155. Dimery IW, Jones LA, Verjan RP, et al. (1987) *Estrogen receptors in normal salivary gland and salivary gland carcinoma*. Arch Otolaryngol Head Neck Surg 113:1082–1085
156. Dobson CM, Ellis HA (1987) *Polycystic disease of the parotid glands: case report of a rare entity and review of the literature*. Histopathology 11:953–961
157. Donath K (1976) *[Sialadenosis of the parotid gland. Ultrastructural, clinical and experimental findings in disturbances of secretion (author's transl)]*. Veroff Pathol (103):1–122
158. Donath K, Seifert G (1972) *[Ultrastructure and pathogenesis of myoepithelial sialadenitis. Occurrence of myoepithelial cells in the benign lymphoepithelial lesion (Sjogren's syndrome)]*. Virchows Arch A Pathol Anat 356:315–329
159. Donath K, Seifert G (1972) *Zur Diagnose and Ultrastruktur des tubularen Speichelgangcarcinoms. Epithelial-myoepitheliales Schaltstruckcarcinom*. Virchows Arch A Pathol Anat 356:16–31
160. Donath K, Seifert G (1975) *Ultrastructural studies of the parotid glands in sialadenosis*. Virchows Arch A Pathol Anat Histol 365:119–135
161. Donath K, Spillner M, Seifert G (1974) *The influence of the autonomic nervous system on the ultrastructure of the parotid acinar cells. Experimental contribution to the neurohormonal sialadenosis*. Virchows Arch A Pathol Anat Histol 364:15–33
162. Dreyer T, Battmann A, Silberzahn J, et al. (1993) *Unusual differentiation of a combination tumor of the parotid gland. A case report*. Pathol Res Pract 189:577–581; discussion 581–575
163. Edwards PC, Bhuiya T, Kelsch RD (2003) *C-kit expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and monomorphic adenoma*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 95:586–593
164. Edwards PC, Bhuiya T, Kelsch RD (2004) *Assessment of p63 expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and basal cell and canalicular adenomas*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 97:613–619
165. Eibling DE, Johnson JT, McCoy JP Jr., et al. (1991) *Flow cytometric evaluation of adenoid cystic carcinoma: correlation with histologic subtype and survival*. Am J Surg 162:367–372
166. el-Naggar AK, Batsakis JG, Luna MA, et al. (1990) *DNA flow cytometry of acinic cell carcinomas of major salivary glands*. J Laryngol Otol 104:410–416
167. el-Naggar AK, Lovell M, Callender DL, et al. (1999) *Cytogenetic analysis of a primary salivary gland myoepithelioma*. Cancer Genet Cytogenet 113:49–53

168. el-Naggar AK (2005) *Adenoid cystic carcinomas in Pathology and Genetics Head and Neck Tumors*. Edited by Barnes EL, Eveson JW, Reichart P, Sidransky D. Lyon, IARC Press, pp 221–222
169. Elliott JN, Oertel YC (1990) *Lymphoepithelial cysts of the salivary glands. Histologic and cytologic features*. Am J Clin Pathol 93:39–43
170. Ellis G, Auclair P *(1996) Tumors of the Salivary Glands, Atlas of Tumor Pathology, third series, fascicle 17*. Washington DC, Armed Forces Institute of Pathology, pp 296–369
171. Ellis G, Auclair P *(1996) Tumors of the Salivary Glands, Atlas of Tumor Pathology, third series, fascicle 17*. Washington DC, Armed Forces Institute of Pathology, pp 289–296
172. Ellis G, Simpson R *(2005) Acinic cell carcinoma in Pathology and Genetics Head and Neck Tumours (edited by Barnes L, Eveson J, Reichart P, Sidransky D) WHO, Lyon*. France, IARC Press, pp 216–218
173. Ellis GL (1998) *Clear cell neoplasms in salivary glands: clearly a diagnostic challenge*. Ann Diagn Pathol 2:61–78
174. Ellis GL, Auclair PL, Gnepp DR, et al. (1991) *Other malignant neoplasms in*. Surgical Pathology of the Salivary Glands. Philadelphia, WB Saunders, pp 455–488
175. Ellis GL, Auclair PL *(1991) Acinic cell adenocarcinoma in Surgical Pathology of the Salivary Glands (Ellis GL, Auclair PL, Gnepp DR, editors)*. Philadelphia, WB Saunders Co., pp 299–317
176. Ellis GL, Auclair PL *(1996) Acinic cell carcinoma in Tumors of the Salivary Glands, Atlas of Tumor Pathology, third series, fascicle 17*. Washington DC, Armed Forces Institute of Pathology, pp 183–203
177. Ellis GL, Auclair PL *(1996) Tumors of the Salivary Glands, Atlas of Tumor Pathology, third series, fascicle 17*. Washington DC, Armed Forces Institute of Pathology, pp 1–26
178. Ellis GL, Auclair PL (1991) *Ductal Papillomas*. Surgical pathology of the salivary glands. Philadelphia, W.B. Saunders, pp 238–252
179. Ellis GL, Auclair PL (1996) *Tumors of the salivary glands*. Washington D.C., Armed Forces Institute of Pathology, pp 268–281
180. Ellis GL, Corio RL (1983) *Acinic cell adenocarcinoma. A clinicopathologic analysis of 294 cases*. Cancer 52:542–549
181. Ellis GL, Wiscovitch JG (1990) *Basal cell adenocarcinomas of the major salivary glands*. Oral Surg Oral Med Oral Pathol 69:461–469
182. Emanuel P, Wang B, Wu M, et al. (2005) *p63 Immunohistochemistry in the distinction of adenoid cystic carcinoma from basaloid squamous cell carcinoma*. Mod Pathol 18:645–650
183. Enamorado I, Lakhani R, Korkmaz H, et al. (2004) *Correlation of histopathological variants, cellular DNA content, and clinical outcome in adenoid cystic carcinoma of the salivary glands*. Otolaryngol Head Neck Surg 131:646–650
184. Eneroth CM (1970) *Incidence and prognosis of salivary glands tumors at different sites. A study of parotid, submandibular and palatal tumors in 2632 patients.* Acta Otolaryngol Suppl 263:174–178
185. Eneroth CM (1971) *Salivary gland tumors in the parotid gland, submandibular gland, and the palate region*. Cancer 27:1415–1418
186. Eneroth CM, Blanck C, Jakobsson PA (1968) *Carcinoma in pleomorphic adenoma of the parotid gland*. Acta Otolaryngol 66:477–492
187. Eneroth CM, Hjertman L, Moberger G, et al. (1972) *Mucoepidermoid carcinomas of the salivary glands with special reference to the possible existence of a benign variety*. Acta Otolaryngol 73:68–74
188. Eneroth CM, Zetterberg A (1974) *Malignancy in pleomorphic adenoma. A clinical and microspectrophotometric study*. Acta Otolaryngol 77:426–432
189. Enlund F, Nordkvist A, Sahlin P, et al. (2002) *Expression of PLAG1 and HMGIC proteins and fusion transcripts in radiation-associated pleomorphic adenomas*. Int J Oncol 20:713–716
190. Epker BN, Henny FA (1971) *Intra-oral sebaceous gland adenoma*. Cancer 27:987–1000
191. Erlandson RA, Tandler B (1972) *Ultrastructure of acinic cell carcinoma of the parotid gland*. Arch Pathol Lab Med 93:130–140
192. Evans HL, Batsakis JG (1984) *Polymorphous low-grade adenocarcinoma of minor salivary glands. A study of 14 cases of a distinctive neoplasm*. Cancer 53:935–942
193. Evans HL, Luna MA (2000) *Polymorphous low-grade adenocarcinoma: a study of 40 cases with long-term follow up and an evaluation of the importance of papillary areas*. Am J Surg Pathol 24:1319–1328
194. Evans R, Cruickshank A (1970) *Epithelial Tumors of the Salivary Glands*. Philadelphia, W.B. Saunders Co., pp 226–241
195. Eversole L (2001) *Salivary gland pathology*. Head and neck pathology: with clinical correlations. Edited by Fu Y, Wenig BM, Abemayor E, Wenig BL. Philadelphia, Churchill-Livingstone, pp 242–291
196. Eversole LR, Gnepp DR, Eversole GM *(1991) Undifferentiated carcinoma in Surgical Pathology of the Salivary Glands, (Ellis GL, Auclair PL, Gnepp DR, editors)* Philadelphia, WB Saunders Co., pp 422–440

197. Eveson JW, Auclair PL, Gnepp D, et al. (2005) *Tumors of Salivary Glands in Pathology and Genetics Head and Neck Tumors*. Edited by Barnes EL, Eveson JW, Reichart P, Sidransky D. Lyon, IARC Press, pp 212–215
198. Eveson JW, Cawson RA (1985) *Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution*. J Pathol 146:51–58
199. Eveson JW, Cawson RA (1985) *Tumours of the minor (oropharyngeal) salivary glands: a demographic study of 336 cases*. J Oral Pathol 14:500–509
200. Eveson JW, Cawson RA (1989) *Infarcted (infected) adenolymphomas. A clinicopathological study of 20 cases*. Clin Otolaryngol 14:205–210
201. Eveson JW, Kusafuka K, Stenman G, et al. (2005) *Pleomorphic adenoma*. Pathology and Classification of Head and Neck Tumours. Edited by Barnes EL, Eveson JW, Reichart P, Sidransky D. Lyon, IARC
202. Ezsias A, Sugar AW, Milling MA, et al. (1994) *Central mucoepidermoid carcinoma in a child*. J Oral Maxillofac Surg 52:512–515
203. Fadare O, Hileeto D, Gruddin YL, et al. (2004) *Sclerosing mucoepidermoid carcinoma of the parotid gland*. Arch Pathol Lab Med 128:1046–1049
204. Faivre S, Raymond E, Casiraghi D, et al. (2005) *Imatinib mesylate can induce objective response in progressing, highly expressing KIT adenoid cystic carcinoma of the salivary glands*. J Clin Oncol 23:6271–6273
205. Fan CY, Melhem MF, Hosal AS, et al. (2001) *Expression of androgen receptor, epidermal growth factor receptor, and transforming growth factor alpha in salivary duct carcinoma*. Arch Otolaryngol Head Neck Surg 127:1075–1079
206. Fauci AS, Haynes BF, Katz P, et al. (1983) *Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years*. Ann Intern Med 98:76–85
207. Felix A, Rosa-Santos J, Mendonca ME, et al. (2002) *Intracapsular carcinoma ex pleomorphic adenoma. Report of a case with unusual metastatic behaviour*. Oral Oncol 38:107–110
208. Ferguson JW, Geary CP, MacAlister AD (1987) *Sebaceous cell adenoma. Rare intra-oral occurrence of a tumour which is a frequent marker of Torre's syndrome*. Pathology 19:204–208
209. Ferreiro JA (1994) *Immunohistochemical analysis of salivary gland canalicular adenoma*. Oral Surg Oral Med Oral Pathol 78:761–765
210. Ferreiro JA (2005) *Canalicular adenoma*. Pathology and Classification of Head and Neck Tumours. Edited by Barnes EL, Eveson JW, Reichart P, Sidransky D. Lyon, IARC, pp 267
211. Ficarra G, Sapp JP, Christensen RE, et al. (1996) *Dysgenetic polycystic disease of the parotid gland: report of case*. J Oral Maxillofac Surg 54:1246–1249
212. Finn DG, Buchalter IH, Sarti E, et al. (1987) *First branchial cleft cysts: clinical update*. Laryngoscope 97:136–140
213. Firat P, Hosal S, Tutar E, et al. (2000) *Sebaceous lymphadenoma of the parotid gland*. J Otolaryngol 29:114–116
214. Fishleder A, Tubbs R, Hesse B, et al. (1987) *Uniform detection of immunoglobulin-gene rearrangement in benign lymphoepithelial lesions*. N Engl J Med 316:1118–1121
215. Fleming DA, Morrice I (1973) *Sebaceous lymphadenoma of the parotid gland: a report of a case*. J Pathol 110:259–261
216. Flynn MB, Maguire S, Martinez S, et al. (1999) *Primary squamous cell carcinoma of the parotid gland: the importance of correct histological diagnosis*. Ann Surg Oncol 6:768–770
217. Fonseca I, Soares J (1993) *Epithelial-myoepithelial carcinoma of the salivary glands. A study of 22 cases*. Virchows Arch A Pathol Anat Histopathol 422:389–396
218. Fonseca I, Soares J (1993) *Proliferating cell nuclear antigen immunohistochemistry in epithelial-myoepithelial carcinoma of the salivary glands*. Arch Pathol Lab Med 117:993–995
219. Foote FW Jr., Frazell EL (1953) *Tumors of the major salivary glands*. Cancer 6:1065–1133
220. Foschini MP, Gaiba A, Cocchi R, et al. (2005) *p63 expression in salivary gland tumors: role of DeltaNp73L in neoplastic transformation*. Int J Surg Pathol 13:329–335
221. Foss RD, Ellis GL, Auclair PL (1996) *Salivary gland cystadenocarcinomas. A clinicopathologic study of 57 cases*. Am J Surg Pathol 20:1440–1447
222. Fowler CB, Brannon RB (2000) *Subacute necrotizing sialadenitis: report of 7 cases and a review of the literature*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 89:600–609
223. Fowler MH, Fowler J, Ducatman B, et al. (2006) *Malignant mixed tumors of the salivary gland: a study of loss of heterozygosity in tumor suppressor genes*. Mod Pathol 19:350–355
224. Fox RI (2005) *Sjogren's syndrome*. Lancet 366:321–331
225. Franzen G, Klausen OG, Grenko RT, et al. (1991) *Adenoid cystic carcinoma: DNA as a prognostic indicator*. Laryngoscope 101:669–673
226. Franzen G, Nordgard S, Boysen M, et al. (1995) *DNA content in adenoid cystic carcinomas*. Head Neck 17:49–55
227. Freedman PD, Lumerman H (1983) *Lobular carcinoma of intraoral minor salivary gland origin. Report of twelve cases*. Oral Surg Oral Med Oral Pathol 56:157–166
228. Freeman SB, Kennedy KS, Parker GS, et al. (1990) *Metastasizing pleomorphic adenoma of the nasal septum*. Arch Otolaryngol Head Neck Surg 116:1331–1333

229. Freier K, Flechtenmacher C, Walch A, et al. (2005) *Differential KIT expression in histological subtypes of adenoid cystic carcinoma (ACC) of the salivary gland*. Oral Oncol 41:934–939
230. Fujibayashi T, Itoh H (1981) *Lymphoepithelial (so-called branchial) cyst within the parotid gland. Report of a case and review of the literature*. Int J Oral Surg 10:283–292
231. Furuse C, Sousa SO, Nunes FD, et al. (2005) *Myoepithelial cell markers in salivary gland neoplasms*. Int J Surg Pathol 13:57–65
232. Furuse C, Tucci R, Machado de Sousa SO, et al. (2003) *Comparative immunoprofile of polymorphous low-grade adenocarcinoma and canalicular adenoma*. Ann Diagn Pathol 7:278–280
233. Gallo O, Bocciolini C (1997) *Warthin's tumour associated with autoimmune diseases and tobacco use*. Acta Otolaryngol 117:623–627
234. Gandour-Edwards RF, Donald PJ, Vogt PJ, et al. (1994) *Carcinosarcoma (malignant mixed tumor) of the parotid: report of a case with a pure rhabdomyosarcoma component*. Head Neck 16:379–382
235. Garcia S, Martini F, Caces F, et al. (1998) *[Polycystic disease of the salivary glands: report of an attack of the submaxillary glands]*. Ann Pathol 18:58–60
236. Gardiner GW, Briant TD, Sheman L (1984) *Inverted ductal papilloma of the parotid gland*. J Otolaryngol 13:23–26
237. Gaughan RK, Olsen KD, Lewis JE (1992) *Primary squamous cell carcinoma of the parotid gland*. Arch Otolaryngol Head Neck Surg 118:798–801
238. George MK, Mansour P, Pahor AL (1991) *Terminal parotid duct carcinoma*. J Laryngol Otol 105:780–781
239. Gerughty RM, Scofield HH, Brown FM, et al. (1969) *Malignant mixed tumors of salivary gland origin*. Cancer 24:471–486
240. Geurts JM, Schoenmakers EF, Roijer E, et al. (1998) *Identification of NFIB as recurrent translocation partner gene of HMGIC in pleomorphic adenomas*. Oncogene 16:865–872
241. Geurts JM, Schoenmakers EF, Roijer E, et al. (1997) *Expression of reciprocal hybrid transcripts of HMGIC and FHIT in a pleomorphic adenoma of the parotid gland*. Cancer Res 57:13–17
242. Ghosh S, Panarese A, Bull PD, et al. (2003) *Marginally excised parotid pleomorphic salivary adenomas: risk factors for recurrence and management. A 12.5-year mean follow-up study of histologically marginal excisions*. Clin Otolaryngol 28:262–266
243. Gilcrease MZ, Nelson FS, Guzman-Paz M (1998) *Tyrosine-rich crystals associated with oncocytic salivary gland neoplasms*. Arch Pathol Lab Med 122:644–649
244. Glisson B, Colevas AD, Haddad R, et al. (2004) *HER2 expression in salivary gland carcinomas: dependence on histological subtype*. Clin Cancer Res 10:944–946
245. Gnepp DR (1993) *Malignant mixed tumors of the salivary glands: a review*. Pathol Annu 28 Pt 1:279–328
246. Gnepp DR (2003) *Sclerosing polycystic adenosis of the salivary gland: a lesion that may be associated with dysplasia and carcinoma in situ*. Adv Anat Pathol 10:218–222
247. Gnepp DR (2005) *Metastasizing pleomorphic adenoma*. Pathology and Classification of Head and Neck Tumours. Edited by Barnes EL, Eveson JW, Reichart P, Sidransky D. Lyon, IARC, p 245
248. Gnepp DR, Brannon R (1984) *Sebaceous neoplasms of salivary gland origin. Report of 21 cases*. Cancer 53:2155–2170
249. Gnepp DR, Chen JC, Warren C (1988) *Polymorphous low-grade adenocarcinoma of minor salivary gland. An immunohistochemical and clinicopathologic study*. Am J Surg Pathol 12:461–468
250. Gnepp DR, Chen JC, Warren C (1988) *Polymorphous low-grade adenocarcinoma of minor salivary gland. An immunohistochemical and clinicopathologic study*. Am J Surg Pathol 12:461–468
251. Gnepp DR, Corio RL, Brannon RB (1986) *Small cell carcinoma of the major salivary glands*. Cancer 58:705–714
252. Gnepp DR, el-Mofty S (1997) *Polymorphous low-grade adenocarcinoma: glial fibrillary acidic protein staining in the differential diagnosis with cellular mixed tumors*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 83:691–695
253. Gnepp DR, Ferlito A, Hyams V (1983) *Primary anaplastic small cell (oat cell) carcinoma of the larynx. Review of the literature and report of 18 cases*. Cancer 51:1731–1745
254. Gnepp DR, Wang LJ, Brandwein-Gensler M, et al. (2006) *Sclerosing polycystic adenosis of the salivary gland: a report of 16 cases*. Am J Surg Pathol 30:154–164
255. Goldfarb D, Mikaelian D, Keane WM (1994) *Mucoepidermoid carcinoma of the mandible*. Am J Otolaryngol 15:54–57
256. Goldman RL, Klein HZ (1972) *Glycogen-rich adenoma of the parotid gland. An uncommon benign clear-cell tumor resembling certain clear-cell carcinomas of salivary origin*. Cancer 30:749–754
257. Gomes AP, Sobral AP, Loducca SV, et al. (2004) *Sialadenoma papilliferum: immunohistochemical study*. Int J Oral Maxillofac Surg 33:621–624
258. Goode R, El-Nagger A (2005) *Mucoepidermoid carcinoma*. Pathology and Genetics Head and Neck Tumors. Edited by Barnes L, Eveson J, Reichart P, Sidransky D. Lyon, IARC Press, pp 219–220

259. Goode RK, Auclair PL, Ellis GL (1998) *Mucoepidermoid carcinoma of the major salivary glands: clinical and histopathologic analysis of 234 cases with evaluation of grading criteria*. Cancer 82:1217–1224
260. Goodisson DW, Burr RG, Creedon AJ, et al. (1999) *A case of metastasizing pleomorphic adenoma*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87:341–345
261. Gotte K, Riedel F, Coy JF, et al. (2000) *Salivary gland carcinosarcoma: immunohistochemical, molecular genetic and electron microscopic findings*. Oral Oncol 36:360–364
262. Gottesman RI, Som PM, Mester J, et al. (1996) *Observations on two cases of apparent submandibular gland cysts in HIV positive patients: MR and CT findings*. J Comput Assist Tomogr 20:444–447
263. Grage TB, Lober PH, Arhelger SW (1961) *Acinic cell carcinoma of the parotid gland.* Am J Surg 102:765–768
264. Greiner TC, Robinson RA, Maves MD (1989) *Adenoid cystic carcinoma. A clinicopathologic study with flow cytometric analysis*. Am J Clin Pathol 92:711–720
265. Gross M, Maly B, Goldfarb A, et al. (2004) *Basal cell adenocarcinoma in a buccal minor salivary gland*. Acta Otolaryngolog (Stockh) 124:213–216
266. Grotz KA, Wustenberg P, Kohnen R, et al. (2001) *Prophylaxis of radiogenic sialadenitis and mucositis by coumarin/troxerutine in patients with head and neck cancer – a prospective, randomized, placebo-controlled, double-blind study*. Br J Oral Maxillofac Surg 39:34–39
267. Gupta S, Sodhani P (1998) *Sialadenosis of parotid gland: a cytomorphologic and morphometric study of four cases*. Anal Quant Cytol Histol 20:225–228
268. Gurney TA, Eisele DW, Weinberg V, et al. (2005) *Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation*. Laryngoscope 115:1278–1282
269. Gustafsson H, Carlsoo B (1985) *Multiple acinic cell carcinoma. Some histological and ultrastructural features of a case*. J Laryngol Otol 99:1183–1193
270. Gustafsson H, Dahlqvist A, Anniko M, et al. (1987) *Mucoepidermoid carcinoma in a minor salivary gland in childhood*. J Laryngol Otol 101:1320–1323
271. Haberland-Carrodeguas C, Fornatora ML, Reich RF, et al. (2003) *Detection of human papillomavirus DNA in oral inverted ductal papillomas*. J Clin Pathol 56:910–913
272. Haines K, Murad T (1989) *Infiltrating salivary duct carcinoma of the parotid.* Lab Invest 60:36A
273. Hamed G, Shmookler BM, Ellis GL, et al. (1994) *Oncocytic mucoepidermoid carcinoma of the parotid gland*. Arch Pathol Lab Med 118:313–314
274. Hamper K, Brugmann M, Koppermann R, et al. (1989) *Epithelial-myoepithelial duct carcinoma of salivary glands: a follow-up and cytophotometric study of 21 cases*. J Oral Pathol Med 18:299–304
275. Hamper K, Lazar F, Dietel M, et al. (1990) *Prognostic factors for adenoid cystic carcinoma of the head and neck: a retrospective evaluation of 96 cases*. J Oral Pathol Med 19:101–107
276. Handra-Luca A, Lamas G, Bertrand JC, et al. (2005) *MUC1, MUC2, MUC4, and MUC5AC expression in salivary gland mucoepidermoid carcinoma: diagnostic and prognostic implications*. Am J Surg Pathol 29:881–889
277. Hansen A, Lipsky PE, Dorner T (2005) *Immunopathogenesis of primary Sjogren's syndrome: implications for disease management and therapy*. Curr Opin Rheumatol 17:558–565
278. Hanson TA (1975) *Acinic cell carcinoma of the parotid salivary gland presenting as a cyst. Report of two cases*. Cancer 36:570–575
279. Hara H, Oyama T, Omori K, et al. (1999) *Fine needle aspiration cytology of an intraductal papilloma originating in a sublingual gland. A case report*. Acta Cytol 43:457–463
280. Hayashi Y, Aoki N (1983) *Undifferentiated carcinoma of the parotid gland with bizarre giant cells. Clinicopathologic report with ultrastructural study*. Acta Pathol Jpn 33:169–176
281. Hayashi Y, Nagamine S, Yanagawa T, et al. (1987) *Small cell undifferentiated carcinoma of the minor salivary gland containing exocrine, neuroendocrine, and squamous cells*. Cancer 60:1583–1588
282. Hayes MM, Cameron RD, Jones EA (1993) *Sebaceous variant of mucoepidermoid carcinoma of the salivary gland. A case report with cytohistologic correlation*. Acta Cytol 37:237–241
283. Hegarty DJ, Hopper C, Speight PM (1994) *Inverted ductal papilloma of minor salivary glands*. J Oral Pathol Med 23:334–336
284. Hellquist HB, Sundelin K, Di Bacco A, et al. (1997) *Tumour growth fraction and apoptosis in salivary gland acinic cell carcinomas. Prognostic implications of Ki-67 and bcl-2 expression and of in situ end labelling (TUNEL)*. J Pathol 181:323–329
285. Henley J, Summerlin DJ, Potter D, et al. (2005) *Intraoral mucin-rich salivary duct carcinoma.[comment]*. Histopathology 47:436–437
286. Henley JD, Geary WA, Jackson CL, et al. (1997) *Dedifferentiated acinic cell carcinoma of the parotid gland: a distinct rarely described entity*. Hum Pathol 28:869–873

287. Henriksson G, Westrin KM, Carlsoo B, et al. (1998) *Recurrent primary pleomorphic adenomas of salivary gland origin: intrasurgical rupture, histopathologic features, and pseudopodia*. Cancer 82:617–620
288. Hiatt JL, Sank JJ (1991) *Embryology and anatomy of salivary glands*. Surgical Pathology of the Salivary Glands. Edited by Ellis GL AP, Gnepp DR. Philadelphia WB Saunders Co., pp 2–9
289. Hickman RE, Cawson RA, Duffy SW (1984) *The prognosis of specific types of salivary gland tumors*. Cancer 54:1620–1624
290. Honda K, Kashima K, Daa T, et al. (2000) *Clonal analysis of the epithelial component of Warthin's tumor*. Hum Pathol 31:1377–1380
291. Honda T, Yamamoto Y, Isago T, et al. (2005) *Giant pleomorphic adenoma of the parotid gland with malignant transformation*. Ann Plast Surg 55:524–527
292. Hoorweg JJ, Hilgers FJ, Keus RB, et al. (1998) *Metastasizing pleomorphic adenoma: a report of three cases*. Eur J Surg Oncol 24:452–455
293. Hosal AS, Fan C, Barnes L, et al. (2003) *Salivary duct carcinoma*. Otolaryngology – Head Neck Surg 129:720–725
294. Hotte SJ, Winquist EW, Lamont E, et al. (2005) *Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study*. J Clin Oncol 23:585–590
295. Howard DJ, Lund VJ (1985) *Reflections on the management of adenoid cystic carcinoma of the nasal cavity and paranasal sinuses*. Otolaryngol Head Neck Surg 93:338–341
296. Hrynchak M, White V, Berean K, et al. (1994) *Cytogenetic findings in seven lacrimal gland neoplasms*. Cancer Genet Cytogenet 75:133–138
297. Huang JW, Ming Z, Shrestha P, et al. (1996) *Immunohistochemical evaluation of the Ca(2+)-binding S-100 proteins S-100A1, S-100A2, S-100A4, S-100A6 and S-100B in salivary gland tumors*. J Oral Pathol Med 25:547–555
298. Hughes KV 3rd, Olsen KD, McCaffrey TV (1995) *Parapharyngeal space neoplasms*. Head Neck 17:124–130
299. Hui KK, Luna MA, Batsakis JG, et al. (1990) *Undifferentiated carcinomas of the major salivary glands*. Oral Surg Oral Med Oral Pathol 69:76–83
300. Hungermann D, Roeser K, Buerger H, et al. (2002) *Relative paucity of gross genetic alterations in myoepitheliomas and myoepithelial carcinomas of salivary glands*. J Pathol 198:487–494
301. Hyjek E, Smith WJ, Isaacson PG (1988) *Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialadenitis*. Hum Pathol 19:766–776
302. Ibrahim NB, Briggs JC, Corbishley CM (1984) *Extrapulmonary oat cell carcinoma*. Cancer 54:1645–1661
303. Ibrahim R, Bird DJ, Sieler MW (1991) *Malignant myoepithelioma of the larynx with massive metastatic spread to the liver: an ultrastructural and immunocytochemical study*. Ultrastruct Pathol 15:69–76
304. Ide F, Mishima K, Saito I (2003) *Sarcomatoid salivary duct carcinoma of the oral cavity*. Virchows Archiv 443:686–689
305. Ide F, Obara K, Enatsu K, et al. (2005) *Sclerosing mucoepidermoid carcinoma of the oral cavity*. J Oral Pathol Med 34:187–189
306. Iezzi G, Rubini C, Fioroni M, et al. (2002) *Sebaceous adenoma of the cheek*. Oral Oncol 38:111–113
307. Ihrler S, Steger W, Riederer A, et al. (1996) *[HIV-associated cysts of the parotid glands. An histomorphologic and magnetic resonance tomography study of formal pathogenesis]*. Laryngorhinootologie 75:671–676
308. Ihrler S, Zietz C, Riederer A, et al. (1996) *HIV-related parotid lymphoepithelial cysts. Immunohistochemistry and 3-D reconstruction of surgical and autopsy material with special reference to formal pathogenesis*. Virchows Arch 429:139–147
309. Ihrler S, Zietz C, Sendelhofert A, et al. (1999) *Lymphoepithelial duct lesions in Sjogren-type sialadenitis*. Virchows Arch 434:315–323
310. Imamura Y, Morishita T, Kawakami M, et al. (2004) *Sclerosing polycystic adenosis of the left parotid gland: report of a case with fine needle aspiration cytology*. Acta Cytol 48:569–573
311. Imbery TA, Edwards PA (1996) *Necrotizing sialometaplasia: literature review and case reports*. J Am Dent Assoc 127:1087–1092
312. Inoue Y, Nomura J, Hashimoto M, et al. (2001) *Epithelial-myoepithelial carcinoma of the palate: a case report*. J Oral Maxillofac Surg 59:1502–1505
313. Izutsu T, Kumamoto H, Kimizuka S, et al. (2003) *Sebaceous adenoma in the retromolar region: report of a case with a review of the English literature*. Int J Oral Maxillofac Surg 32:423–426
314. Jaehne M, Roeser K, Jaekel T, et al. (2005) *Clinical and immunohistologic typing of salivary duct carcinoma: a report of 50 cases*. Cancer 103:2526–2533
315. Jahan-Parwar B, Huberman RM, Donovan DT, et al. (1999) *Oncocytic mucoepidermoid carcinoma of the salivary glands*. Am J Surg Pathol 23:523–529
316. James GK, Pudek M, Berean KW, et al. (1996) *Salivary duct carcinoma secreting prostate-specific antigen*. Am J Clin Pathol 106:242–247

317. Jayakrishnan A, Elmalah I, Hussain K, et al. (2003) *Basal cell adenocarcinoma in minor salivary glands*. Histopathology 42:610–614
318. Jeng YM, Lin CY, Hsu HC (2000) *Expression of the c-kit protein is associated with certain subtypes of salivary gland carcinoma*. Cancer Lett 154:107–111
319. Jervis PN, Lee JA, Bull PD (2001) *Management of non-tuberculous mycobacterial peri-sialadenitis in children: the Sheffield otolaryngology experience*. Clin Otolaryngol 26:243–248
320. Johnston N, Rose D, Lutterloch M (2005) *Cystadenocarcinoma of salivary gland presenting as a cystic lesion in the mandible.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:201–204
321. Jurgens PE (2004) *Inverted ductal papilloma of the lower lip: a case report*. J Oral Maxillofac Surg 62:1158–1161
322. Kaminagakura E, Andrade CR, Rangel AL, et al. (2003) *Sebaceous adenoma of oral cavity: report of case and comparative proliferation study with sebaceous gland hyperplasia and Fordyce's granules*. Oral Dis 9:323–327
323. Kamisawa T, Nakajima H, Egawa N, et al. (2005) *IgG4-Related Sclerosing Disease Incorporating Sclerosing Pancreatitis, Cholangitis, Sialadenitis and Retroperitoneal Fibrosis with Lymphadenopathy*. Pancreatology 6:132–137
324. Kanazawa H, Furuya T, Murano A, et al. (2000) *Oncocytoma of an intraoral minor salivary gland: report of a case and review of literature*. J Oral Maxillofac Surg 58:894–897
325. Kas K, Voz ML, Roijer E, et al. (1997) *Promoter swapping between the genes for a novel zinc finger protein and beta-catenin in pleiomorphic adenomas with t(3;8)(p21;q12) translocations*. Nat Genet 15:170–174
326. Kasaboglu O, Er N, Tumer C, et al. (2004) *Micromorphology of sialoliths in submandibular salivary gland: a scanning electron microscope and X-ray diffraction analysis*. J Oral Maxillofac Surg 62:1253–1258
327. Kemp BL, Batsakis JG, el-Naggar AK, et al. (1995) *Terminal duct adenocarcinomas of the parotid gland*. J Laryngol Otol 109:466–468
328. Khullar SM, Best PV (1992) *Adenomatosis of minor salivary glands. Report of a case*. Oral Surg Oral Med Oral Pathol 74:783–787
329. Kici S, Peytral C (2001) *[Giant pleomorphic adenoma of the parotid gland: a case report and review of the literature]*. Ann Otolaryngol Chir Cervicofac 118:330–332
330. King OH Jr. (1967) *Carcinosarcoma of accessory salivary gland. First report of a case*. Oral Surg Oral Med Oral Pathol 23:651–659
331. Kirklin JW, Mc DJ, Harrington SW, et al. (1951) *Parotid tumors; histopathology, clinical behavior, and end results*. Surg Gynecol Obstet 92:721–733
332. Kitagawa S, Zen Y, Harada K, et al. (2005) *Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor)*. Am J Surg Pathol 29:783–791
333. Kjorell U, Ostberg Y (1984) *Distribution of intermediate filaments and actin microfilaments in parotid autoimmune sialoadenitis of Sjogren syndrome*. Histopathology 8:991–1011
334. Kleinsasser O, Klein HJ, Hubner G (1968) *Salivary duct carcinoma. A group of salivary gland tumors analogous to mammary duct carcinoma*. Arch Klin Exp Ohren- Nasen-Kehlkopfheilk 192:100–105
335. Klima M, Wolfe K, Johnson PE (1978) *Basal cell tumors of the parotid gland*. Arch Otolaryngol 104:111–116
336. Klumpp TR, Mohr RM, Silverman CL, et al. (1995) *Malignant myoepithelioma of the parotid gland: case report and review of the literature*. J Laryngol Otol 109:995–998
337. Knowles DM, Athan E, Ubriaco A, et al. (1989) *Extranodal noncutaneous lymphoid hyperplasias represent a continuous spectrum of B-cell neoplasia: demonstration by molecular genetic analysis*. Blood 73:1635–1645
338. Koka VN, Tiwari RM, van der Waal I, et al. (1989) *Adenoid cystic carcinoma of the salivary glands: clinicopathological survey of 51 patients*. J Laryngol Otol 103:675–679
339. Kokemueller H, Brueggemann N, Swennen G, et al. (2005) *Mucoepidermoid carcinoma of the salivary glands – clinical review of 42 cases*. Oral Oncol 41:3–10
340. Koss LG, Spiro RH, Hajdu S (1972) *Small cell (oat cell) carcinoma of minor salivary gland origin*. Cancer 30:737–741
341. Kotwall CA (1992) *Smoking as an etiologic factor in the development of Warthin's tumor of the parotid gland*. Am J Surg 164:646–647
342. Koutlas IG, Jessurun J, Iamaroon A (1994) *Immunohistochemical evaluation and in situ hybridization in a case of oral inverted ductal papilloma*. J Oral Maxillofac Surg 52:503–506
343. Krolls SO, Trodahl JN, Boyers RC (1972) *Salivary gland lesions in children. A survey of 430 cases*. Cancer 30:459–469
344. Kunze P (1979) *[Sebaceous lymphadenoma of the parotid gland (author's transl)]*. Zentralbl Allg Pathol 123:210–213
345. Kwon GY, Kim EJ, Go JH (2002) *Lymphadenoma arising in the parotid gland: a case report*. Yonsei Med J 43:536–538
346. Kwon MY, Gu M (2001) *True malignant mixed tumor (carcinosarcoma) of parotid gland with unusual mesenchymal component: a case report and review of the literature*. Arch Pathol Lab Med 125:812–815
347. Labouyrie E, Merlio JP, Beylot-Barry M, et al. (1993) *Human immunodeficiency virus type 1 replication within cystic lymphoepithelial lesion of the salivary gland*. Am J Clin Pathol 100:41–46

348. Larsson LG, Donner LR (1999) *Large cell neuroendocrine carcinoma of the parotid gland: fine needle aspiration, and light microscopic and ultrastructural study*. Acta Cytol 43:534–536
349. Leafstedt SW, Gaeta JF, Sako K, et al. (1971) *Adenoid cystic carcinoma of major and minor salivary glands*. Am J Surg 122:756–762
350. Lebsack JP, Marrogi AJ, Martin SA (1990) *Central mucoepidermoid carcinoma of the jaw with distant metastasis: a case report and review of the literature*. J Oral Maxillofac Surg 48:518–522
351. Lee DJ, Smith RR, Spaziani JT, et al. (1985) *Adenoid cystic carcinoma of the nasopharynx. Case reports and literature review*. Ann Otol Rhinol Laryngol 94:269–272
352. Lee IK, Liu JW (2005) *Tuberculous parotitis: case report and literature review*. Ann Otol Rhinol Laryngol 114:547–551
353. Lee JH, Lee JH, Kim A, et al. (2005) *Unique expression of MUC3, MUC5AC and cytokeratins in salivary gland carcinomas*. Pathol Int 55:386–390
354. Lee KC, Chan JK, Chong YW (1992) *Ossifying pleomorphic adenoma of the maxillary antrum*. J Laryngol Otol 106:50–52
355. Lee S, Kim GE, Park CS, et al. (2001) *Primary squamous cell carcinoma of the parotid gland*. Am J Otolaryngol 22:400–406
356. Leverstein H, van der Wal JE, Tiwari RM, et al. (1997) *Surgical management of 246 previously untreated pleomorphic adenomas of the parotid gland*. Br J Surg 84:399–403
357. Levin JM, Robinson DW, Lin F (1975) *Acinic cell carcinoma*. Arch Surg 110:64–68
358. Lewis JE, McKinney BC, Weiland LH, et al. (1996) *Salivary duct carcinoma. Clinicopathologic and immunohistochemical review of 26 cases*. Cancer 77:223–230
359. Lewis JE, Olsen KD (2005) *Tumors of Salivary Glands*. Pathology and Genetics Head and Neck Tumors. Edited by Barnes EL, Eveson J, Reichart P, Sidransky D. Lyon, IARC, pp 245–246
360. Lewis JE, Olsen KD, Sebo TJ (2001) *Carcinoma ex pleomorphic adenoma: pathologic analysis of 73 cases*. Hum Pathol 32:596–604
361. Lewis JE, Olsen KD, Weiland LH (1991) *Acinic cell carcinoma. Clinicopathologic review*. Cancer 67:172–179
362. Lewis PD, Baxter P, Paul Griffiths A, et al. (2000) *Detection of damage to the mitochondrial genome in the oncocytic cells of Warthin's tumour*. J Pathol 191:274–281
363. Lewis PD, Fradley SR, Griffiths AP, et al. (2002) *Mitochondrial DNA mutations in the parotid gland of cigarette smokers and non-smokers*. Mutat Res 518:47–54
364. Li S, Baloch ZW, Tomaszewski JE, et al. (2000) *Worrisome histologic alterations following fine-needle aspiration of benign parotid lesions*. Arch Pathol Lab Med 124:87–91
365. Li S, Baloch ZW, Tomaszewski JE, et al. (2000) *Worrisome histologic alterations following fine-needle aspiration of benign parotid lesions*. Arch Pathol Lab Med 124:87–91
366. Lin Y, Wu H, Tzeng J (2005) *Small-cell undifferentiated carcinoma of the submandibular gland: An extremely rare extrapulmonary site.* Am J Otolaryngol 26:60–63
367. Lins JE, Gnepp DR (1986) *Myoepithelioma of the palate in a child*. Int J Pediatr Otorhinolaryngol 11:5–13
368. Lipani C, Woytash JJ, Greene GW Jr. (1983) *Sebaceous adenoma of the oral cavity*. J Oral Maxillofac Surg 41:56–60
369. Littman CD, Alguacil-Garcia A (1987) *Clear cell carcinoma arising in pleomorphic adenoma of the salivary gland*. Am J Clin Pathol 88:239–243
370. LiVolsi VA, Perzin KH (1977) *Malignant mixed tumors arising in salivary glands. I. Carcinomas arising in benign mixed tumors: a clinicopathologic study*. Cancer 39:2209–2230
371. Lombardi T, Samson J, Kuffer R (2003) *Subacute necrotizing sialadenitis: a form of necrotizing sialometaplasia?* Arch Otolaryngol Head Neck Surg 129:972–975
372. Love GL, Sarma DP (1986) *Spindle cell mucoepidermoid carcinoma of submandibular gland*. J Surg Oncol 31:66–68
373. Loy TS, McLaughlin R, Odom LF, et al. (1989) *Mucoepidermoid carcinoma of the parotid as a second malignant neoplasm in children*. Cancer 64:2174–2177
374. Lucarini JW, Sciubba JJ, Khettry U, et al. (1994) *Terminal duct carcinoma. Recognition of a low-grade salivary adenocarcinoma.[see comment]*. Arch Otolaryngol Head Neck Surg 120:1010–1015
375. Luna MA, Batsakis JG, Tortoledo ME, et al. (1989) *Carcinomas ex monomorphic adenoma of salivary glands*. J Laryngol Otol 103:756–759
376. Luna MA, el-Naggar A, Batsakis JG, et al. (1990) *Flow cytometric DNA content of adenoid cystic carcinoma of submandibular gland. Correlation of histologic features and prognosis*. Arch Otolaryngol Head Neck Surg 116:1291–1296
377. Luna MA, Ordonez NG, Mackay B, et al. (1985) *Salivary epithelial-myoepithelial carcinomas of intercalated ducts: a clinical, electron microscopic, and immunocytochemical study*. Oral Surg Oral Med Oral Pathol 59:482–490
378. Luna MA, Tortoledo ME, Allen M (1987) *Salivary dermal analogue tumors arising in lymph nodes*. Cancer 59:1165–1169
379. Ma J, Chan JK, Chow CW, et al. (2002) *Lymphadenoma: a report of three cases of an uncommon salivary gland neoplasm*. Histopathology 41:342–350

380. Maisel RH, Johnston WH, Anderson HA, et al. (1977) *Necrotizing sialometaplasia involving the nasal cavity*. Laryngoscope 87:429–434
381. Mandel L, Carrao V (2005) *Bilateral parotid diffuse hyperplastic oncocytosis: case report*. J Oral Maxillofac Surg 63:560–562
382. Mandel L, Kim D, Uy C (1998) *Parotid gland swelling in HIV diffuse infiltrative CD8 lymphocytosis syndrome*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 85:565–568
383. Mandel L, Surattanont F (2002) *Bilateral parotid swelling: a review*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 93:221–237
384. Marciani RD, Trodahl JN, Dauchess VG, et al. (1976) *Squamous cell carcinoma of the submandibular gland*. J Oral Surg 34:646–650
385. Mariappan MR, Fadare O, Jain D (2004) *Sebaceous differentiation in salivary glands*. Arch Pathol Lab Med 128:245–246
386. Marie B, Labouyrie E, Scheid P, et al. (1997) *Human immunodeficiency virus type 1 in an unusual cystic lymphoepithelial lesion of the lung*. Histopathology 31:83–86
387. Marioni G, Marino F, Stramare R, et al. (2003) *Benign metastasizing pleomorphic adenoma of the parotid gland: a clinicopathologic puzzle*. Head Neck 25:1071–1076
388. Mark J, Dahlenfors R, Wedell B (1997) *Impact of the in vitro technique used on the cytogenetic patterns in pleomorphic adenomas*. Cancer Genet Cytogenet 95:9–15
389. Marks MW, Ryan RF, Litwin MS, et al. (1987) *Squamous cell carcinoma of the parotid gland*. Plast Reconstr Surg 79:550–554
390. Marmary Y, Gomori JM, Nitzan DW (1990) *Lymphoepithelial parotid cysts as presenting symptom of immunodeficiency virus infection: clinical, sialographic, and magnetic resonance imaging findings*. J Oral Maxillofac Surg 48:981–984
391. Martinez-Madrigal F, Micheau C (1989) *Histology of the major salivary glands*. Am J Surg Pathol 13:879–899
392. Martins C, Fonseca I, Roque L, et al. (1997) *Cytogenetic characterisation of Warthin's tumour*. Oral Oncol 33:344–347
393. Matsuba HM, Simpson JR, Mauney M, et al. (1986) *Adenoid cystic salivary gland carcinoma: a clinicopathologic correlation*. Head Neck Surg 8:200–204
394. McAdams RM, Mair EA, Rajnik M (2005) *Neonatal suppurative submandibular sialadenitis: case report and literature review*. Int J Pediatr Otorhinolaryngol 69:993–997
395. McCluggage G, Sloan J, Cameron S, et al. (1995) *Basal cell adenocarcinoma of the submandibular gland*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79:342–350
396. McFerran DJ, Ingrams DR, Gallimore AP, et al. (1995) *Polycystic disease of salivary glands*. J Laryngol Otol 109:165–167
397. McGavran MH, Bauer WC, Ackerman LV (1960) *Sebaceous lymphadenoma of the parotid salivary gland*. Cancer 13:1185–1187
398. McKinney B, Lewis J, Weiland L, et al. (1994) *Salivary duct carcinoma. Clinicopathologic and immunohistochemical review of 26 cases*. Lab Invest 70:100A
399. McQuone SJ (1999) *Acute viral and bacterial infections of the salivary glands*. Otolaryngol Clin North Am 32:793–811
400. Mehta RP, Faquin WC, Deschler DG (2004) *Pathology quiz case 1. Acinic cell carcinoma of the parotid gland with ductal extension*. Arch Otolaryngol Head Neck Surg 130:790, 792–793
401. Mentzel T (2004) *[Skin adnexal and salivary gland neoplasms. Similarities and differences of selected patients]*. Pathologe 25:79–88
402. Merchant WJ, Cook MG, Eveson JW (1996) *Polymorphous low-grade adenocarcinoma of parotid gland*. Br J Oral Maxillofac Surg 34:328–330
403. Merwin WH Jr., Barnes L, Myers EN (1985) *Unilocular cystic sebaceous lymphadenoma of the parotid gland*. Arch Otolaryngol 111:273–275
404. Michal M, Skalova A, Simpson RH, et al. (1997) *Well-differentiated acinic cell carcinoma of salivary glands associated with lymphoid stroma*. Hum Pathol 28:595–600
405. Michal M, Skalova A, Simpson RH, et al. (1996) *Clear cell malignant myoepithelioma of the salivary glands*. Histopathology 28:309–315
406. Miettinen M, Lasota J (2005) *KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation*. Appl Immunohistochem Mol Morphol 13:205–220
407. Miglianico L, Eschwege F, Marandas P, et al. (1987) *Cervico-facial adenoid cystic carcinoma: study of 102 cases. Influence of radiation therapy*. Int J Radiat Oncol Biol Phys 13:673–678
408. Mignogna MD, Fedele S, Lo Russo L (2004) *Anorexia/bulimia-related sialadenosis of palatal minor salivary glands*. J Oral Pathol Med 33:441–442
409. Miki H, Masuda E, Ohata S, et al. (1999) *Late recurrence of acinic cell carcinoma of the parotid gland*. J Med Invest 46:213–216
410. Milford CA, Mugliston TA, O'Flynn P, et al. (1989) *Carcinoma arising in a pleomorphic adenoma of the epiglottis*. J Laryngol Otol 103:324–327
411. Miliauskas JR (1991) *Polymorphous low-grade (terminal duct) adenocarcinoma of the parotid gland*. Histopathology 19:555–557

412. Mills SE, Garland TA, Allen MS Jr. (1984) *Low-grade papillary adenocarcinoma of palatal salivary gland origin*. Am J Surg Pathol 8:367–374
413. Mino M, Pilch BZ, Faquin WC (2003) *Expression of KIT (CD117) in neoplasms of the head and neck: an ancillary marker for adenoid cystic carcinoma*. Mod Pathol 16:1224–1231
414. Mitchell DA, Eveson JW, Ord RA (1989) *Polymorphous low-grade adenocarcinoma of minor salivary glands – a report of three cases*. Br J Oral Maxillofac Surg 27:494–500
415. Moberger JG, Eneroth CM (1968) *Malignant mixed tumors of the major salivary glands. Special reference to the histologic structure in metastases*. Cancer 21:1198–1211
416. Mohamed AH (1976) *Ultrastructure of glycogen-rich clear cell carcinoma of the palate*. J Oral Pathol 5:103–121
417. Mohamed AH, Cherrick HM (1975) *Glycogen-rich adenocarcinoma of minor salivary glands. A light and electron microscopic study*. Cancer 36:1057–1066
418. Mohammed BS, Liu Z, Tang W, et al. (2006) *BCL-2, Ki67 and P53 expression in oral necrotizing sialometaplasia and squamous cell carcinoma*. Mod Pathol 19:105A
419. Molina CP, Chaljub G, Campbell GA (2003) *Pathologic quiz case: a 37-year-old man with spinal cord compression*. Arch Pathol Lab Med 127:887–889
420. Monk JS Jr., Church JS (1992) *Warthin's tumor. A high incidence and no sex predominance in central Pennsylvania*. Arch Otolaryngol Head Neck Surg 118:477–478
421. Moore JG, Bocklage T (1998) *Fine-needle aspiration biopsy of large-cell undifferentiated carcinoma of the salivary glands: presentation of two cases, literature review, and differential cytodiagnosis of high-grade salivary gland malignancies*. Diagn Cytopathol 19:44–50
422. Mostofi R, Wood RS, Christison W, et al. (1992) *Low-grade papillary adenocarcinoma of minor salivary glands. Case report and literature review*. Oral Surg Oral Med Oral Pathol 73:591–595
423. Muller S, Barnes L (1996) *Basal cell adenocarcinoma of the salivary glands. Report of seven cases and review of the literature*. Cancer 78:2471–2477
424. Muller S, Barnes L, Goodurn WJ Jr. (1997) *Sclerosing mucoepidermoid carcinoma of the parotid*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 83:685–690
425. Murrah VA, Batsakis JG (1994) *Salivary duct carcinoma*. Ann Otol Rhinol Laryngol 103:244–247
426. Myerowitz RL, Barnes EL, Myers E (1978) *Small cell anaplastic (oat cell) carcinoma of the larynx: report of a case and review of the literature*. Laryngoscope 88:1697–1702
427. Nadiminti H, Thomas GR, Regalado J (2004) *Pathology quiz case 1. Small cell carcinoma (SmCC) of the parotid gland*. Arch Otolaryngol Head Neck Surg 130:474–477
428. Nagao K, Matsuzaki O, Saiga H, et al. (1983) *A histopathologic study of benign and malignant lymphoepithelial lesions of the parotid gland*. Cancer 52:1044–1052
429. Nagao K, Matsuzaki O, Saiga H, et al. (1982) *Histopathologic studies of basal cell adenoma of the parotid gland*. Cancer 50:736–745
430. Nagao K, Matsuzaki O, Saiga H, et al. (1982) *Histopathologic studies of undifferentiated carcinoma of the parotid gland*. Cancer 50:1572–1579
431. Nagao T, Gaffey TA, Kay PA, et al. (2003) *Dedifferentiation in low-grade mucoepidermoid carcinoma of the parotid gland*. Hum Pathol 34:1068–1072
432. Nagao T, Gaffey TA, Olsen KD, et al. (2004) *Small cell carcinoma of the major salivary glands: clinicopathologic study with emphasis on cytokeratin 20 immunoreactivity and clinical outcome*. Am J Surg Pathol 28:762–770
433. Nagao T, Gaffey TA, Serizawa H, et al. (2004) *Sarcomatoid variant of salivary duct carcinoma: clinicopathologic and immunohistochemical study of eight cases with review of the literature*. Am J Clin Pathol 122:222–231
434. Nagao T, Gaffey TA, Visscher DW, et al. (2004) *Invasive micropapillary salivary duct carcinoma: a distinct histologic variant with biologic significance*. Am J Surg Pathol 28:319–326
435. Nagao T, Serizawa H, Iwaya K, et al. (2002) *Keratocystoma of the parotid gland: a report of two cases of an unusual pathologic entity.* Mod Pathol 15(9):1005–1010.
436. Nagao T, Sugano I, Ishida Y, et al. (1998) *Basal cell adenocarcinoma of the salivary glands: comparison with basal cell adenoma through assessment of cell proliferation, apoptosis, and expression of p53 and bcl-2*. Cancer 82:439–447
437. Nagao T, Sugano I, Ishida Y, et al. (1998) *Salivary gland malignant myoepithelioma: a clinicopathologic and immunohistochemical study of ten cases*. Cancer 83:1292–1299
438. Nagao T, Sugano I, Ishida Y, et al. (2000) *Primary large-cell neuroendocrine carcinoma of the parotid gland: immunohistochemical and molecular analysis of two cases*. Mod Pathol 13:554–561
439. Nagao T, Sugano I, Matsuzaki O, et al. (2000) *Intraductal papillary tumors of the major salivary glands: case reports of benign and malignant variants*. Arch Pathol Lab Med 124:291–295
440. Namin AK, Moshref M, Shahoon H, et al. (2005) *Intraosseous mucoepidermoid carcinoma of the maxilla in a teenager: a case report and review of literature*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 100:e93–96
441. Nasse D (1892) *Die Geschwulste der Speicheldrusen und verwandte Tumoren des Kopfes*. Langenbecks Arch Klin Chir 44:233–302

442. Nessan VJ, Jacoway JR (1979) *Biopsy of minor salivary glands in the diagnosis of sarcoidosis*. N Engl J Med 301:922–924
443. Neto AG, Pineda-Daboin K, Spencer ML, et al. (2005) *Sinonasal acinic cell carcinoma: a clinicopathologic study of four cases*. Head Neck 27:603–607
444. Nguyen LH, Black MJ, Hier M, et al. (2003) *HER2/neu and Ki-67 as prognostic indicators in mucoepidermoid carcinoma of salivary glands*. J Otolaryngol 32:328–331
445. Nishimura T, Furukawa M, Kawahara E, et al. (1991) *Differential diagnosis of pleomorphic adenoma by immunohistochemical means*. J Laryngol Otol 105:1057–1060
446. Nistal M, Garcia-Viera M, Martinez-Garcia C, et al. (1994) *Epithelial-myoepithelial tumor of the bronchus*. Am J Surg Pathol 18:421–425
447. Nordkvist A, Mark J, Dahlenfors R, et al. (1994) *Cytogenetic observations in 13 cystadenolymphomas (Warthin's tumors)*. Cancer Genet Cytogenet 76:129–135
448. Nordkvist A, Roijer E, Bang G, et al. (2000) *Expression and mutation patterns of p53 in benign and malignant salivary gland tumors*. Int J Oncol 16:477–483
449. Norlin R (1965) *Bilateral mixed tumor of the parotid initially regarded as pharyngeal neoplasm*. Pract Otorhinolaryngol (Basel) 27:298–301
450. Ochel HJ, Gademann G, Rocken C, et al. (2005) *Effects of imatinib mesylate on adenoid cystic carcinomas*. Anticancer Res 25:3659–3664
451. Ockner DM, Mills SE, Swanson PE, et al. (1994) *Salivary duct carcinoma: An immunohistologic comparison with invasive ductal carcinoma of the breast.* Lab Invest 70:100A
452. Ogawa I, Nikai H, Takata T, et al. (1992) *Clear-cell variant of mucoepidermoid carcinoma: report of a case with immunohistochemical and ultrastructural observations*. J Oral Maxillofac Surg 50:906–910
453. Olsen KD, Lewis JE (2001) *Carcinoma ex pleomorphic adenoma: a clinicopathologic review*. Head Neck 23:705–712
454. Olsen KD, Maragos NE, Weiland LH (1980) *First branchial cleft anomalies*. Laryngoscope 90:423–436
455. Orlian AI, Salman L, Reddi T, et al. (1987) *Sebaceous adenoma of the oral mucosa*. J Oral Med 42:38–39
456. Ortiz-Hidalgo C, Cervantes J, de la Vega G (1995) *Unilateral polycystic (dysgenetic) disease of the parotid gland*. South Med J 88:1173–1175
457. Orvidas LJ, Kasperbauer JL, Lewis JE, et al. (2000) *Pediatric parotid masses.* Arch Otolaryngol Head Neck Surg 126:177–184
458. Osial TA Jr., Whiteside TL, Buckingham RB, et al. (1983) *Clinical and serologic study of Sjogren's syndrome in patients with progressive systemic sclerosis*. Arthritis Rheum 26:500–508
459. Ozolek JA, Bastacky SI, Myers EN, et al. (2005) *Immunophenotypic comparison of salivary gland oncocytoma and metastatic renal cell carcinoma*. Laryngoscope 115:1097–1100
460. Padberg B-C, Sasse B, Huber A, et al. (2005) *Sarcomatoid salivary duct carcinoma*. Ann Diagn Pathol 9:86–92
461. Pai RR, Bharathi S, Naik R, et al. (1994) *Unilocular cystic sebaceous lymphadenoma of the parotid gland*. Indian J Pathol Microbiol 37:327–330
462. Peel R (2001) *Diseases of the salivary gland*. Surgical pathology of the head and neck. Edited by Barnes L. New York, Marcel-Dekker, pp 634–690
463. Penner CR, Folpe AL, Budnick SD (2002) *C-kit expression distinguishes salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma*. Mod Pathol 15:687–691
464. Perez-Ordonez B, Linkov I, Huvos AG (1998) *Polymorphous low-grade adenocarcinoma of minor salivary glands: a study of 17 cases with emphasis on cell differentiation*. Histopathology 32:521–529
465. Perzin KH, LiVolsi VA (1979) *Acinic cell carcinomas arising in salivary glands: a clinicopathologic study*. Cancer 44:1434–1457
466. Pesavento G, Ferlito A, Recher G (1980) *Primary clear cell carcinoma of the larynx*. J Clin Pathol 33:1160–1164
467. Piattelli A, Tete S (1995) *Lymphoepithelial cyst of the parotid gland*. Acta Stomatol Belg 92:137–138
468. Pinkston JA, Cole P (1996) *Cigarette smoking and Warthin's tumor*. Am J Epidemiol 144:183–187
469. Pires FR, da Cruz Perez DE, de Almeida OP, et al. (2004) *Estrogen receptor expression in salivary gland mucoepidermoid carcinoma and adenoid cystic carcinoma*. Pathol Oncol Res 10:166–168
470. Pires FR, de Almeida OP, de Araujo VC, et al. (2004) *Prognostic factors in head and neck mucoepidermoid carcinoma*. Arch Otolaryngol Head Neck Surg 130:174–180
471. Puxeddu R, Puxeddu P, Parodo G, et al. (1998) *Polymorphous low-grade adenocarcinoma of the parotid gland*. Eur J Morphol 36(suppl):262–266
472. Quddus MR, Henley JD, Affify AM, et al. (1999) *Basal cell adenocarcinoma of the salivary gland: an ultrastructural and immunohistochemical study*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87:485–492
473. Raad, II, Sabbagh MF, Caranasos GJ (1990) *Acute bacterial sialadenitis: a study of 29 cases and review*. Rev Infect Dis 12:591–601
474. Rapidis AD, Givalos N, Gakiopoulou H, et al. (2005) *Adenoid cystic carcinoma of the head and neck. Clinicopathological analysis of 23 patients and review of the literature.* Oral Oncol 41:328–335

475. Raslan WF, Sawyer DR, Mercuri LG (1998) *Central mucoepidermoid carcinoma*. J Can Dent Assoc 64:420–424
476. Reis-Filho JS, Schmitt FC (2002) *Taking advantage of basic research: p63 is a reliable myoepithelial and stem cell marker*. Adv Anat Pathol 9:280–289
477. Renehan A, Gleave EN, McGurk M (1996) *An analysis of the treatment of 114 patients with recurrent pleomorphic adenomas of the parotid gland*. Am J Surg 172:710–714
478. Richardson RL, Weiland LH (1982) *Undifferentiated small cell carcinomas in extrapulmonary sites*. Semin Oncol 9:484–496
479. Righi PD, Li YQ, Deutsch M, et al. (1994) *The role of the p53 gene in the malignant transformation of pleomorphic adenomas of the parotid gland*. Anticancer Res 14:2253–2257
480. Ritland F, Lubensky I, LiVolsi VA (1993) *Polymorphous low-grade adenocarcinoma of the parotid salivary gland*. Arch Pathol Lab Med 117:1261–1263
481. Robin C, Laboulbene A (1853) *Memoire sur trois productions morbides non decrites*. C R Soc Biol 5:185–196
482. Rodriguez J, Forcelledo M, Gutierrez L, et al. (2004) *Small cell undifferentiated carcinoma of the submandibular gland with neurosecretory features*. Ann Otol Rhinol Laryngol 113:55–59
483. Rollins CE, Yost BA, Costa MJ, et al. (1995) *Squamous differentiation in small-cell carcinoma of the parotid gland*. Arch Pathol Lab Med 119:183–185
484. Romagosa V, Bella MR, Truchero C, et al. (1992) *Necrotizing sialometaplasia (adenometaplasia) of the trachea*. Histopathology 21:280–282
485. Rosai J (1996) *Major and minor salivary glands*. Ackerman's surgical pathology. Edited by Rosai J. St. Louis, Mosby, pp 834–835
486. Rousseau A, Mock D, Dover DG, et al. (1999) *Multiple canalicular adenomas: a case report and review of the literature*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87:346–350
487. Rye LA, Calhoun NR, Redman RS (1980) *Necrotizing sialometaplasia in a patient with Buerger's disease and Raynaud's phenomenon*. Oral Surg Oral Med Oral Pathol 49:233–236
488. Said S, Compana J (2005) *Myoepithelial carcinoma ex-pleomorphic adenoma of salivary glands: A problematic diagnosis*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99:196–201
489. Sakorafas GH, Sarr MG, van de Velde CJ, et al. (2005) *Intraductal papillary mucinous neoplasms of the pancreas: A surgical perspective*. Surg Oncol 14:155–178
490. Saksela E, Tarkkanen J, Kohonen A (1970) *The malignancy of mixed tumors of the parotid gland. A clinicopathological analysis of 70 cases*. Acta Otolaryngol 70:62–70
491. Saksela E, Tarkkanen J, Wartiovaara J (1972) *Parotid clear-cell adenoma of possible myoepithelial origin*. Cancer 30:742–748
492. Santucci L, Smorlesi L (1954) *[I tumori misti, benigni e maligni, di tipo salivare, in sede extra-macro-salivare con particolare riguardo alle localizzazioni eccezionali.]*. Arch De Vecchi Anat Patol 22:623–692
493. Santucci M, Gallo O, Calzolari A, et al. (1993) *Detection of Epstein-Barr viral genome in tumor cells of Warthin's tumor of parotid gland*. Am J Clin Pathol 100:662–665
494. Sato T, Kamata SE, Kawabata K, et al. (2005) *Acinic cell carcinoma of the parotid gland in a child*. Pediatr Surg Int 21:377–380
495. Savera AT, Sloman A, Huvos AG, et al. (2000) *Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 25 patients*. Am J Surg Pathol 24:761–774
496. Schoning H, Emshoff R, Kreczy A (1998) *Necrotizing sialometaplasia in two patients with bulimia and chronic vomiting*. Int J Oral Maxillofac Surg 27:463–465
497. Schultz AM, Thomas AB, Henley JD, et al. (2004) *Pathologic quiz case: a 42-year-old man with right facial swelling and weakness. Dedifferentiated acinic cell carcinoma of the parotid gland*. Arch Pathol Lab Med 128:e52–53
498. Sciubba JJ, Brannon RB (1982) *Myoepithelioma of salivary glands: report of 23 cases*. Cancer 49:562–572
499. Seaver PR Jr., Kuehn PG (1979) *Adenoid cystic carcinoma of the salivary glands. A study of ninety-three cases*. Am J Surg 137:449–455
500. Seethala RR, LiVolsi VA, Zhang PJ, et al. (2005) *Comparison of p63 and p73 expression in benign and malignant salivary gland lesions*. Head Neck 27:696–702
501. Seifert G (1991) *Histologic Typing of Salivary Gland Tumors*. Springer, New York p 26
502. Seifert G (1996) *Classification and differential diagnosis of clear and basal cell tumors of the salivary glands*. Semin Diagn Pathol 13:95–103
503. Seifert G (1997) *Aetiological and histological classification of sialadenitis*. Pathologica 89:7–17
504. Seifert G (1997) *[Carcinoma in pre-existing Warthin tumors (cystadenolymphoma) of the parotid gland. Classification, pathogenesis and differential diagnosis]*. Pathologe 18:359–367
505. Seifert G (1998) *Are adenomyoepithelioma of the breast and epithelial-myoepithelial carcinoma of the salivary glands identical tumours?* Virchows Arch 433:285–288
506. Seifert G, Bull HG, Donath K (1980) *Histologic subclassification of the cystadenolymphoma of the parotid gland. Analysis of 275 cases*. Virchows Arch A Pathol Anat Histol 388:13–38

507. Seifert G, Donath K (1976) *Classification of the pathohistology of diseases of the salivary glands – review of 2,600 cases in the Salivary Gland Register*. Beitr Pathol 159:1–32
508. Seifert G, Donath K (1996) *Multiple tumours of the salivary glands – terminology and nomenclature*. Eur J Cancer B Oral Oncol 32B:3–7
509. Seifert G, Donath K, Schafer R (1999) *Lipomatous pleomorphic adenoma of the parotid gland. Classification of lipomatous tissue in salivary glands*. Pathol Res Pract 195:247–252
510. Seifert G, Miehlke A, Haubrich J, et al. (1986) *Diseases of the Salivary Glands: Diagnosis, Pathology, Treatment, Facial Nerve Surgery*, Stuttgart, Georg Theime Verlag, pp 248–252
511. Seifert G, Thomsen S, Donath K (1981) *Bilateral dysgenetic polycystic parotid glands. Morphological analysis and differential diagnosis of a rare disease of the salivary glands*. Virchows Arch A Pathol Anat Histol 390:273–288
512. Selva D, Davis GJ, Dodd T, et al. (2004) *Polymorphous low-grade adenocarcinoma of the lacrimal gland*. Arch Ophthalmol 122:915–917
513. Shemen LJ, Huvos AG, Spiro RH (1987) *Squamous cell carcinoma of salivary gland origin*. Head Neck Surg 9:235–240
514. Shimoda M, Kameyama K, Morinaga S, et al. (2004) *Malignant transformation of sialadenoma papilliferum of the palate: a case report*. Virchows Arch 445:641–646
515. Silvers AR, Som PM (1998) *Salivary glands*. Radiol Clin North Am 36:941–966, vi
516. Simpson RH, Clarke TJ, Sarsfield PT, et al. (1991) *Epithelial-myoepithelial carcinoma of salivary glands*. J Clin Pathol 44:419–423
517. Simpson RHW, Eveson JW (2005) *Warthin tumor*. Pathology and Classification of Head and Neck Tumours. Edited by Barnes EL, Eveson JW, Sidransky D. Lyons, IARC, pp 263–265
518. Simpson RHW, Prasad AR, Lewis JE, et al. (2003) *Mucin-rich variant of salivary duct carcinoma: a clinicopathologic and immunohistochemical study of four cases.* Am J Surg Pathol 27:1070–1079
519. Sjogren H, Dahlenfors R, Stenman G, et al. (2003) *Observations by G-banding and multicolor spectral karyotyping in a salivary gland basal cell adenoma*. Virchows Arch 442:86–87
520. Skalova A, Gnepp DR, Simpson RH, et al. (2006) *Clonal Nature of Sclerosing Polycystic Adenosis of Salivary Glands Demonstrated by Using the Polymorphism of the Human Androgen Receptor Locus (HUMARA) as a Marker*. Mod Pathol 19:105A
521. Skalova A, Leivo I, Von Boguslawsky K, et al. (1994) *Cell proliferation correlates with prognosis in acinic cell carcinomas of salivary gland origin. Immunohistochemical study of 30 cases using the MIB 1 antibody in formalin-fixed paraffin sections*. J Pathol 173:13–21
522. Skalova A, Leivo I, Wolf H, et al. (2000) *Oncocytic cystadenoma of the parotid gland with tyrosine-rich crystals*. Pathol Res Pract 196:849–851
523. Skalova A, Michal M (2005) *Cystadenoma*. Pathology and Classification of Head and Neck Tumours. Edited by Barnes EL, Eveson JW, Sidransky D. Lyons, IARC, pp 273–274
524. Skalova A, Michal M, Ryska A, et al. (1999) *Oncocytic myoepithelioma and pleomorphic adenoma of the salivary glands*. Virchows Arch 434:537–546
525. Skalova A, Michal M, Simpson RH, et al. (2002) *Sclerosing polycystic adenosis of parotid gland with dysplasia and ductal carcinoma in situ. Report of three cases with immunohistochemical and ultrastructural examination*. Virchows Arch 440:29–35
526. Skalova A, Simpson RH, Lehtonen H, et al. (1997) *Assessment of proliferative activity using the MIB1 antibody help to distinguish polymorphous low grade adenocarcinoma from adenoid cystic carcinoma of salivary glands*. Pathol Res Pract 193:695–703
527. Skalova A, Starek I, Simpson RH, et al. (2001) *Spindle cell myoepithelial tumours of the parotid gland with extensive lipomatous metaplasia. A report of four cases with immunohistochemical and ultrastructural findings*. Virchows Arch 439:762–767
528. Skalova A, Starek I, Vanecek T, et al. (2003) *Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry.[see comment]*. Histopathology 42:348–356
529. Slootweg PJ (1993) *Low-grade adenocarcinoma of the oral cavity: polymorphous or papillary?* J Oral Pathol Med 22:327–330
530. Slootweg PJ, Muller H (1987) *Low-grade adenocarcinoma of the oral cavity. A comparison between the terminal duct and the papillary type*. J Craniomaxillofac Surg 15:359–364
531. Smith A, Winkler B, Perzin KH, et al. (1985) *Mucoepidermoid carcinoma arising in an intraparotid lymph node*. Cancer 55:400–403
532. Smith BC, Ellis GL, Slater LJ, et al. (1996) *Sclerosing polycystic adenosis of major salivary glands. A clinicopathologic analysis of nine cases*. Am J Surg Pathol 20:161–170
533. Smith JA, Warhol MJ, Brodsky GL (1983) *An immunohistochemical study of a carcinoma of the parotid gland exhibiting both ductal and acinic cell differentiation*. Oral Surg Oral Med Oral Pathol 55:267–273

534. Smyth AG, Ward-Booth RP, High AS (1993) *Polycystic disease of the parotid glands: two familial cases*. Br J Oral Maxillofac Surg 31:38–40
535. Snyderman C, Johnson JT, Barnes EL (1986) *Extraparotid Warthin's tumor*. Otolaryngol Head Neck Surg 94:169–175
536. Som PM, Biller HF (1992) *Kimura disease involving parotid gland and cervical nodes: CT and MR findings*. J Comput Assist Tomogr 16:320–322
537. Soofer SB, Tabbara S (1999) *Intraductal papilloma of the salivary gland. A report of two cases with diagnosis by fine needle aspiration biopsy*. Acta Cytol 43:1142–1146
538. Spies JW (1930) *Adenoid cystic carcinoma*. Arch Surg 21:365–404
539. Spiro RH (1986) *Salivary neoplasms: overview of a 35-year experience with 2,807 patients*. Head Neck Surg 8:177–184
540. Spiro RH, Huvos AG, Strong EW (1977) *Malignant mixed tumor of salivary origin: a clinicopathologic study of 146 cases*. Cancer 39:388–396
541. Spiro RH, Huvos AG, Strong EW (1978) *Acinic cell carcinoma of salivary origin. A clinicopathologic study of 67 cases*. Cancer 41:924–935
542. Spiro RH, Huvos AG, Strong EW (1979) *Adenoid cystic carcinoma: factors influencing survival*. Am J Surg 138:579–583
543. Spiro RH, Huvos AG, Strong EW (1982) *Adenocarcinoma of salivary origin. Clinicopathologic study of 204 patients*. Am J Surg 144:423–431
544. Spiro RH, Koss LG, Hajdu SI, et al. (1973) *Tumors of minor salivary origin. A clinicopathologic study of 492 cases*. Cancer 31:117–129
545. Stanley RJ, Weiland LH, Olsen KD, et al. (1988) *Dedifferentiated acinic cell (acinous) carcinoma of the parotid gland*. Otolaryngol Head Neck Surg 98:155–161
546. Stell PM (1986) *Adenoid cystic carcinoma*. Clin Otolaryngol 11:267–291
547. Stephen J, Batsakis JG, Luna MA, et al. (1986) *True malignant mixed tumors (carcinosarcoma) of salivary glands*. Oral Surg Oral Med Oral Pathol 61:597–602
548. Stephen J, Luna MA, Batsakis J (1985) *Malignant mixed (heterologous) tumors of salivary glands*. Lab Invest 52:65A
549. Sterman BM, Kraus DH, Sebek BA, et al. (1990) *Primary squamous cell carcinoma of the parotid gland*. Laryngoscope 100:146–148
550. Stewart FW, Foote FW, Becker WF (1945) *Mucoepidermoid tumors of salivary glands*. Ann Surg 122:820–844
551. Stewart S, Levy R, Karpel J, et al. (1974) *Lymphoepithelial (branchial) cyst of the parotid gland*. J Oral Surg 32:100–106
552. Streubel B, Simonitsch-Klupp I, Mullauer L, et al. (2004) *Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites*. Leukemia 18:1722–1726
553. Suarez P, Hammond HL, Luna MA, et al. (1998) *Palatal canalicular adenoma: report of 12 cases and review of the literature*. Ann Diagn Pathol 2:224–228
554. Szanto PA, Luna MA, Tortoledo ME, et al. (1984) *Histologic grading of adenoid cystic carcinoma of the salivary glands*. Cancer 54:1062–1069
555. Tabak LA (1995) *In defense of the oral cavity: structure, biosynthesis, and function of salivary mucins*. Annu Rev Physiol 57:547–564
556. Tabak LA, Levine MJ, Mandel ID, et al. (1982) *Role of salivary mucins in the protection of the oral cavity*. J Oral Pathol 11:1–17
557. Takai Y, Dardick I, Mackay A, et al. (1995) *Diagnostic criteria for neoplastic myoepithelial cells in pleomorphic adenomas and myoepitheliomas. Immunocytochemical detection of muscle-specific actin, cytokeratin 14, vimentin, and glial fibrillary acidic protein*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79:330–341
558. Takai Y, Mori M, Dardick I, et al. (1994) *Myofilament localization and immunoelectron microscopic detection of muscle-specific actin in neoplastic myoepithelial cells in pleomorphic adenomas and myoepitheliomas*. Ultrastruct Pathol 18:575–591
559. Takeda Y, Shimono M (1999) *Pleomorphic adenoma with nuclear palisading arrangement of modified myoepithelial cells: histopathologic and immunohistochemical study*. Bull Tokyo Dent Coll 40:27–34
560. Tauxe WN, Mc DJ, Devine KD (1962) *A century of cylindromas. Short review and report of 27 adenoid cystic carcinomas arising in the upper respiratory passages*. Arch Otolaryngol 75:364–376
561. Tavassoli FA (1991) *Myoepithelial lesions of the breast. Myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma*. Am J Surg Pathol 15:554–568
562. Tay HL, Reilly PG, Akosa AB (1992) *Salivary terminal duct carcinoma*. J Laryngol Otol 106:649–651
563. Terada T, Ikeuchi S, Inomoto C, et al. (2004) *Mucoepidermoid carcinoma of the palate composed exclusively of clear cells (clear cell variant)*. Virchows Arch 445:541–543
564. Terry JH, Loree TR, Thomas MD, et al. (1991) *Major salivary gland lymphoepithelial lesions and the acquired immunodeficiency syndrome*. Am J Surg 162:324–329
565. Teymoortash A, Simolka N, Schrader C, et al. (2005) *Lymphocyte subsets in irradiation-induced sialadenitis of the submandibular gland*. Histopathology 47:493–500

566. Teymoortash A, Werner JA (2005) *Tissue that has lost its track: Warthin's tumour*. Virchows Arch 446:585–588
567. Thackray A, Lucas R (1974) *Tumors of the Major Salivary Glands*. Atlas of Tumor Pathology, Series 2, Fascicle 10. Washington, DC, Armed Forces Institute of Pathology, pp 107–117
568. Thompson AS, Bryant HC Jr. (1950) *Histogenesis of papillary cystadenoma lymphomatosum (Warthin's tumor) of the parotid salivary gland*. Am J Pathol 26:807–849
569. Tortoledo ME, Luna MA, Batsakis JG (1984) *Carcinomas ex pleomorphic adenoma and malignant mixed tumors. Histomorphologic indexes*. Arch Otolaryngol 110:172–176
570. Toynton S, Wilkins M, Cook H, et al. (1994) *True malignant mixed tumor of a minor salivary gland*. J Laryngol Otol 108:76–79
571. Tralongo V, Becchina G, Genovese F, et al. (2002) *Polymorphous low-grade adenocarcinoma of the salivary glands: clinicopathological and immunohistochemical study of a case*. Anticancer Res 22:1347–1352
572. Tralongo V, Daniele E (1998) *Epithelial-myoepithelial carcinoma of the salivary glands: a review of literature*. Anticancer Res 18:603–608
573. Tralongo V, Rodolico V, Nagar C, et al. (1997) *Epithelial-myoepithelial carcinoma of the salivary glands: a clinicopathologic, immunohistochemical and DNA flow cytometric study of three cases*. Anticancer Res 17:761–768
574. Tran PT, Cunningham CJ, Baughman RA (2004) *Glandular odontogenic cyst*. J Endod 30:182–184
575. Triglia JM, Nicollas R, Ducroz V, et al. (1998) *First branchial cleft anomalies: a study of 39 cases and a review of the literature*. Arch Otolaryngol Head Neck Surg 124:291–295
576. Trompouki E, Hatzivassiliou E, Tsichritzis T, et al. (2003) *CYLD is a deubiquitinating enzyme that negatively regulates NF-kappaB activation by TNFR family members*. Nature 424:793–796
577. Tsang YW, Tung Y, Chan JK (1991) *Polymorphous low grade adenocarcinoma of the palate in a child*. J Laryngol Otol 105:309–311
578. Tschen JA, McGavran MH (1979) *Sebaceous lymphadenoma: ultrastructural observations and lipid analysis*. Cancer 44:1388–1392
579. Tucci FM, Bianchi PM, Bottero S, et al. (1993) *Acinic cell carcinoma of the parotid gland in childhood*. Int J Pediatr Otorhinolaryngol 27:187–191
580. Tuncel U, Ergul G, Ozlugedik S, et al. (2004) *Myoepithelial carcinoma in the nasopharynx: an unusual localization*. Yonsei Med J 45:161–165
581. Tytor M, Gemryd P, Grenko R, et al. (1995) *Adenoid cystic carcinoma: significance of DNA ploidy*. Head Neck 17:319–327
582. Ubaidat MA, Robinson RA, Belding PJ, et al. (2001) *Sialadenoma papilliferum of the hard palate: report of 2 cases and immunohistochemical evaluation*. Arch Pathol Lab Med 125:1595–1597
583. Uccini S, Riva E, Antonelli G, et al. (1999) *The benign cystic lymphoepithelial lesion of the parotid gland is a viral reservoir in HIV type 1-infected patients*. AIDS Res Hum Retroviruses 15:1339–1344
584. Urano M, Abe M, Horibe Y, et al. (2002) *Sclerosing mucoepidermoid carcinoma with eosinophilia of the salivary glands*. Pathol Res Pract 198:305–310
585. Urban SD, Hall JM, Bentkover SH, et al. (2002) *Salivary duct carcinoma of minor salivary gland origin: report of a case involving the cavernous sinus*. J Oral Maxillofac Surg 60:958–962
586. van der Schans EJ, Knegt P, de Jong PC, et al. (1985) *Adenoid cystic carcinoma of the upper digestive and respiratory tracts. A retrospective study of 59 cases*. Clin Otolaryngol 10:63–67
587. van der Wal JE, Davids JJ, van der Waal I (1993) *Extraparotid Warthin's tumours – report of 10 cases*. Br J Oral Maxillofac Surg 31:43–44
588. van der Wal JE, Kraaijenhagen HA, van der Waal I (1995) *Subacute necrotising sialadenitis: a new entity?* Br J Oral Maxillofac Surg 33:302–303
589. van der Wal JE, Snow GB, van der Waal I (1990) *Intraoral adenoid cystic carcinoma. The presence of perineural spread in relation to site, size, local extension, and metastatic spread in 22 cases*. Cancer 66:2031–2033
590. van der Walt JD, Leake J (1987) *Granulomatous sialadenitis of the major salivary glands. A clinicopathological study of 57 cases*. Histopathology 11:131–144
591. Van Heerden WF, Raubenheimer EJ, Dreyer L (2005) *The role of DNA ploidy and Ki-67 in the grading of mucoepidermoid carcinomas*. Anticancer Res 25:2589–2592
592. Van Krieken JH (1993) *Prostate marker immunoreactivity in salivary gland neoplasms. A rare pitfall in immunohistoch emistry.[see comment]*. Am J Surg Pathol 17:410–414
593. Van Roggen G, Baatenburg-De J, Verschuur B, et al. (1998) *Myoepithelial carcinoma (malignant myoepithelioma): First report of an occurrence in the maxillary sinus*. Histopathology 32:239–241
594. Verghese S, Lalitha MK (1975) *Sebaceous lymphadenoma of the parotid region report of a case*. Indian J Pathol Bacteriol 18:46–48
595. Vicandi B, Jimenez-Heffernan JA, Lopez-Ferrer P, et al. (1999) *HIV-1 (p24)-positive multinucleated giant cells in HIV-associated lymphoepithelial lesion of the parotid gland. A report of two cases*. Acta Cytol 43:247–251

596. Vincent SD, Hammond HL, Finkelstein MW (1994) *Clinical and therapeutic features of polymorphous low-grade adenocarcinoma*. Oral Surg Oral Med Oral Pathol 77:41–47
597. Voz ML, Agten NS, Van de Ven WJ, et al. (2000) *PLAG1, the main translocation target in pleomorphic adenoma of the salivary glands, is a positive regulator of IGF-II*. Cancer Res 60:106–113
598. Voz ML, Astrom AK, Kas K, et al. (1998) *The recurrent translocation t(5;8)(p13;q12) in pleomorphic adenomas results in upregulation of PLAG1 gene expression under control of the LIFR promoter*. Oncogene 16:1409–1416
599. Vrielinck LJ, Ostyn F, van Damme B, et al. (1988) *The significance of perineural spread in adenoid cystic carcinoma of the major and minor salivary glands*. Int J Oral Maxillofac Surg 17:190–193
600. Waldron CA, el-Mofty SK, Gnepp DR (1988) *Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases*. Oral Surg Oral Med Oral Pathol 66:323–333
601. Waldron CA, Koh ML (1990) *Central mucoepidermoid carcinoma of the jaws: report of four cases with analysis of the literature and discussion of the relationship to mucoepidermoid, sialodontogenic, and glandular odontogenic cysts*. J Oral Maxillofac Surg 48:871–877
602. Wang C-P, Chang Y-L, Ko J-Y, et al. (2004) *Lymphoepithelial carcinoma versus large cell undifferentiated carcinoma of the major salivary glands*. Cancer 101:2020–2027
603. Warrick PD, Irish JC, Mancer K, et al. (2000) *Basal cell adenocarcinoma: a rare malignancy of the salivary glands*. J Otolaryngol 29:102–109
604. Warthin AS (1929) *Papillary cystadenoma lymphomatosum. A rare teratoid of the parotid*. J Cancer Res 13:116–125
605. Wasan SM (1971) *Sebaceous lymphadenoma of the parotid gland*. Cancer 28:1019–1022
606. Weber A, Langhanki L, Schutz A, et al. (2002) *Expression profiles of p53, p63, and p73 in benign salivary gland tumors*. Virchows Arch 441:428–436
607. Weed D, Gomez-Fernancez C, Pacheo J, et al. (2004) *MUC4 and ERBB2 expression in major and minor salivary gland mucoepidermoid carcinoma*. Head Neck 26:353–364
608. Weitzner S (1973) *Lymphoepithelial (branchial) cyst of parotid gland*. Oral Surg Oral Med Oral Pathol 35:85–88
609. Wenig BM, Harpaz N, DelBridge C (1989) *Polymorphous low-grade adenocarcinoma of seromucous glands of the nasopharynx. A report of a case and a discussion of the morphologic and immunohistochemical features*. Am J Clin Pathol 92:104–109
610. Wenig BM, Hitchcock CL, Ellis GL, et al. (1992) *Metastasizing mixed tumor of salivary glands. A clinicopathologic and flow cytometric analysis*. Am J Surg Pathol 16:845–858
611. Wermuth DJ, Mann CH, Odere F (1988) *Metastasizing pleomorphic adenoma arising in the soft palate*. Otolaryngol Head Neck Surg 99:505–508
612. Werning JT, Waterhouse JP, Mooney JW (1990) *Subacute necrotizing sialadenitis*. Oral Surg Oral Med Oral Pathol 70:756–759
613. Whitaker SB, Vigneswaran N, Singh BB (1997) *Androgen receptor status of the oral sebaceous glands*. Am J Dermatopathol 19:415–418
614. White DK, Miller AS, McDaniel RK, et al. (1982) *Inverted ductal papilloma: a distinctive lesion of minor salivary gland*. Cancer 49:519–524
615. Whittaker JS, Turner EP (1976) *Papillary tumours of the minor salivary glands*. J Clin Pathol 29:795–805
616. Williams SB, Ellis GL, Auclair PL (1993) *Immunohistochemical analysis of basal cell adenocarcinoma*. Oral Surg Oral Med Oral Pathol 75:64–69
617. Williamson JD, Simmons BH, el-Naggar A, et al. (2000) *Mucoepidermoid carcinoma involving Warthin tumor. A report of five cases and review of the literature*. Am J Clin Pathol 114:564–570
618. Wilson DF, Robinson BW (1984) *Oral inverted ductal papilloma*. Oral Surg Oral Med Oral Pathol 57:520–523
619. Winkle MR, Harrington PC, Maronian N (1999) *Central mucoepidermoid carcinoma of the mandible*. Am J Otolaryngol 20:169–171
620. Wu LY, Cheng J, Lu Y, et al. (2004) *[Epstein-Barr virus infection in benign lymphoepithelial lesions with malignant transformation of salivary glands]*. Zhonghua Kou Qiang Yi Xue Za Zhi 39:291–293
621. Wuketich S, Kittinger G (1966) *[Sebaceous lymphadenoma of the parotid]*. Arch Klin Exp Ohren Nasen Kehlkopfheilkd 187:836–844
622. Yu G, Ussmueller J, Donath K (2000) *[A clinicopathologic study on membranous basal cell adenoma]*. Zhonghua Kou Qiang Yi Xue Za Zhi 35:88–90
623. Yu G, Ussmueller J, Donath K (2000) *[Histogenesis and development of membranous basal cell adenoma of the salivary gland]*. Zhonghua Kou Qiang Yi Xue Za Zhi 35:31–33
624. Yu GY, Ma DQ, Zhang Y, et al. (2004) *Multiple primary tumours of the parotid gland*. Int J Oral Maxillofac Surg 33:531–534
625. Yu GY, Ubmuller J, Donath K (1998) *Membranous basal cell adenoma of the salivary gland: a clinicopathologic study of 12 cases*. Acta Otolaryngol 118:588–593

626. Zarbo RJ (2002) *Salivary gland neoplasia: a review for the practicing pathologist*. Mod Pathol 15:298–323
627. Zarbo RJ, Prasad AR, Regezi JA, et al. (2000) *Salivary gland basal cell and canalicular adenomas: immunohistochemical demonstration of myoepithelial cell participation and morphogenetic considerations*. Arch Pathol Lab Med 124:401–405
628. Zarbo RJ, Regezi JA, Lloyd RV, et al. (1987) *HLA-DR antigens in normal, inflammatory, and neoplastic salivary glands*. Oral Surg Oral Med Oral Pathol 64:577–584
629. Zhao M, Takata T, Ogawa I, et al. (1998) *Immunohistochemical demonstration of bone morphogenetic protein-2 and type II collagen in pleomorphic adenoma of salivary glands*. J Oral Pathol Med 27:293–296
630. Zschoch H (1992) *[Mucus gland infarct with squamous epithelial metaplasia in the lung. A rare site of so-called necrotizing sialometaplasia]*. Pathologe 13:45–48