Salivary Gland

5

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1. *What are the basic histologic components of the salivary gland, and how are they characterized?*

   Many salivary gland (SG) tumors are biphasic, composed of at least two cell types, ductal and myoepithelial cells. An understanding of how the different components of normal salivary gland express various immunohistochemical markers will help inform the pathologist of a specific tumor type and aid in the correct diagnosis. Not all of the markers expressed in normal tissue are present in its neoplastic counterpart. In addition, among the normal SG components, there are different types of ducts, acini, and supporting cells including serous and mucinous acini, intercalated ducts, striated ducts, excretory ducts, and two types of supporting cells (myoepithelial and basal cells). Figure 5.1 depicts the normal acinar-ductal unit. Table 5.1 shows the immunohistochemical profile of the different components and their variations.

   Reference: [1]

2. *How has the terminology of salivary gland tumors changed and what are the newest entities described in this group?*

   A handful of old and new tumors were either reclassified or added to the 4th edition of the *World Health Organization (WHO) Classification of Head and Neck Tumors* published in 2017. Some novel entities have been excluded, pending further studies, but are worthy of discussion here (Table 5.2). The questions that follow in this chapter will use the newer terminology and include older terms for clarification, when needed.

   References: [2, 3]

3. *What are some of the unusual morphologic changes that are seen in pleomorphic adenomas and what is their significance?*

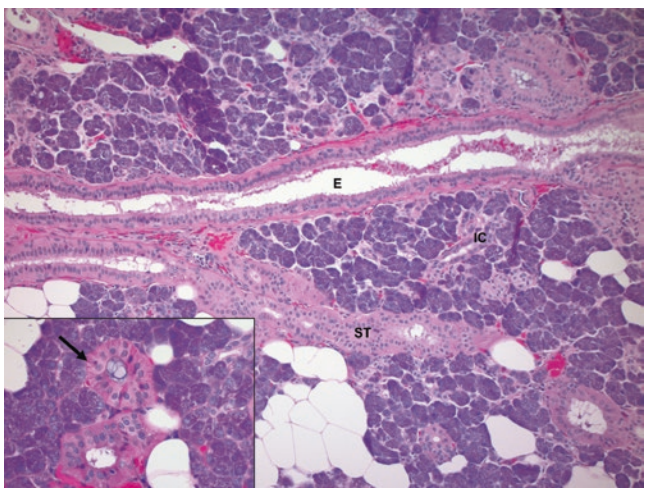

Fig. 5.1 Normal parotid gland. Serous acini predominate. A large interlobular excretory duct (E) with a second layer of abluminal basal cells (arrow) gives rise to striated ducts (ST) with cuboidal cells and subnuclear striations (inset, arrow). Smaller intercalated ducts (IC) are found among the acini

Table 5.1 Histology and immunoprofile of normal salivary gland cell types

Cell type	Morphology	Positive stains	Negative stains
Myoepithelial cell	Abluminal cells that support acini and intercalated ducts Spindled, elongated cells with oval nucleus	CK5/6 CK14 p63, p40 SMA MSA Calponin Caldesmon Sox-10	CK7 LMWCK weak, variable S100 variable
Basal cell	Abluminal cells that support excretory ducts Low cuboidal cells with central, round to oval nucleus	CK5/6 CK14 p63, p40 CK7 CK8/18 Sox-10	Negative muscle markers: SMA Calponin Caldesmon S100 variable
Serous acini	Triangular cells with round, basally located nucleus Basophilic, cytoplasmic, zymogen granules	GCDFP-15 CK8/18 Amylase Sox-10 PAS PAS-D DOG-1 CD117	Mucicarmine Alcian blue P63 CK7
Mucous acini	Triangular cells with round, basally located nucleus Pale, mucinous cytoplasm	Mucicarmine PAS PASD	CD117 CK7
Intercalated duct luminal cells	Luminal cells Cuboidal with scant cytoplasm, round nucleus	CK7 CK8/18 Cam5.2 CK19 CK14 Galectin 3 EMA CEA Sox-10 DOG-1 CD117 weak	S100 variable
Striated duct	Luminal, columnar cells Central, round nucleus; and subnuclear, cytoplasmic striations	CK7 CK8/18 Cam5.2 CK19 CK14 Galectin 3 Sox-10 AMA, PTAH	SMA Calponin Caldesmon S100
Apocrine cells	Abundant, eosinophilic vacuolated cytoplasm, apical snouting	AR GCDFP-15	
Oncocytic cells	Abundant, eosinophilic granular, cytoplasm, central, round nucleus	AMA, PTAH	

CK cytokeratin, *SMA* smooth muscle actin, *MSA* muscle-specific actin, *LMWCK* low molecular weight cytokeratin, *HMWCK* high molecular weight cytokeratin, *GCDFP* gross cystic disease fluid protein, *PAS(D)* periodic acid-Schiff (with diastase), *EMA* epithelial membrane antigen, *CEA* carcinoembryonic antigen, *AMA* anti-mitochondrial antibody, *PTAH* phosphotungstic acid hematoxylin, *AR* androgen receptors

Table 5.2 Changes in WHO terminology for salivary gland tumors

New/reclassified tumors	Previous or alternate name	Comments
Clear cell carcinoma (CCC)	Hyalinizing clear cell carcinoma Clear cell carcinoma, not otherwise specified (NOS)	A more encompassing term was favored since not all CCC are hyalinizing
Secretory carcinoma	Mammary analogue secretory carcinoma (MASC)	A new entity with a specific ETV6-NTRK3 translocation
Polymorphous adenocarcinoma (PAC)	Polymorphous low-grade adenocarcinoma[a] (PMLG)	The "low-grade" designation was removed to allow for flexibility in grading
Intraductal carcinoma	Low-grade intraductal carcinoma[a] Low-grade salivary duct carcinoma[a] Low-grade cribriform cystadenocarcinoma[a]	A broad term used to encompass old and new lesions that are *noninvasive* (or microinvasive) intraductal carcinomas
Poorly differentiated carcinoma	Large cell carcinoma[a] Now includes: large cell neuroendocrine carcinoma Small cell neuroendocrine carcinoma Undifferentiated carcinoma	Neuroendocrine carcinomas in this category may or may *not* have neuroendocrine differentiation
Ductal papillomas	Includes: Inverted ductal papilloma Intraductal papilloma Sialadenoma papilliferum	All three entities are papillomas of salivary duct origin
Adenocarcinoma, not otherwise specified	Includes: Mucinous adenocarcinoma Cystadenocarcinoma	A diagnosis of exclusion for tumors that do not fit under any other named entity
Cribriform adenocarcinoma of (tongue) minor salivary gland	Remains in the PAC (PMLG) category despite some differences in clinical presentation and behavior	Shares PRKD genetic alterations similar to those of PAC Shares some morphologic overlap with PAC
Metastasizing pleomorphic adenoma	Removed from the list of malignant tumors	Discussed in the section on pleomorphic adenomas, given their identical histologic appearance

[a]Indicates previous terminology

Conventional pleomorphic adenomas have an admixture of myoepithelial and ductal cells with varying amounts of chondromyxoid stroma. Metaplastic changes can display both epithelial and stromal differentiation.

- The most well-described epithelial change in PA is squamous metaplasia. The squamous cells show abundant, eosinophilic cytoplasm, and bland nuclear features, with or without keratin pearl formation (Fig. 5.2).
- Cystic change within the ducts and associated keratin is referred to as adnexal-like differentiation.
- On small biopsy material, mucoepidermoid carcinoma (MEC) enters the differential diagnosis. However, keratinization is not a feature of MEC and is rarely seen, even in its high-grade form.

Most stromal metaplasias seen in PA are due to the pluripotent differentiation of the myoepithelial cell.

- Fatty metaplasia is not an uncommon finding, and it usually comprises less than 20% of the tumor but may be as much as 80%. It is seen almost exclusively in the major salivary glands.
- Ultrastructural studies show myoepithelial cells with abundant intracellular lipid. Consequently, these fatty areas express cytokeratins and myoepithelial markers.
  - Sebaceous metaplasia is commonly seen alongside fatty metaplasia.

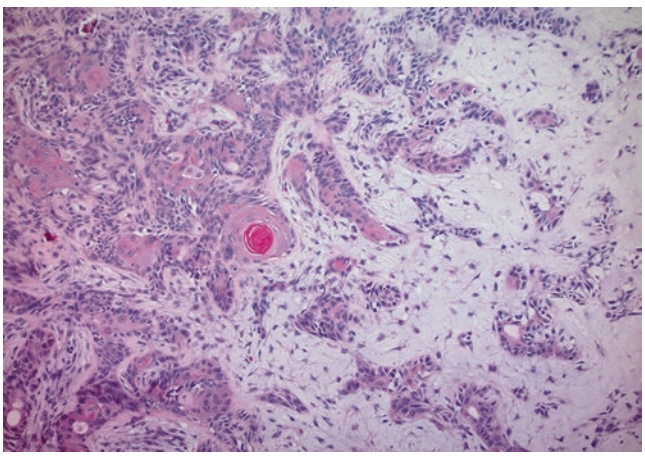

Fig. 5.2 Pleomorphic adenoma with squamous metaplasia. Chondromyxoid stroma (right) contains nests of hyperchromatic, small, angulated, myoepithelial cells surrounding eosinophilic ductal cells with squamous metaplasia and keratin pearl formation

- Other mesenchymal changes include bony metaplasia and schwannian change.
  - Such areas will demonstrate myoepithelial differentiation by immunohistochemistry.

Various case series and reports have described intravascular tumor in pleomorphic adenomas.

- Epithelium and stroma can be seen in small, thin-walled vessels and large, muscular vessels. The proposed mechanism is artifactual tumor spillage into the vasculature as a result of biopsy or surgical manipulation.
- None of the reported cases have been associated with tumor metastasis or aggressive behavior. The phenomenon is observed most commonly in major salivary glands and is characterized by:
  - An absence of platelet meshwork
  - Involvement of vessels at the tumor periphery
  - Involvement of more than one vessel

References: [4–13]

4. *What is the biologic behavior of "benign" metastasizing pleomorphic adenoma and are there any risk factors for its development?*
   - Metastasizing pleomorphic adenoma (MPA) is a rare entity with less than 100 cases reported in the English literature.
   - The old terminology of *benign* metastasizing PA has fallen out of favor, as estimated mortality rates are 20% and disease-free survival approaches 50%.
   - The latency period between diagnosis and metastasis averages 15 years (range: 3–51 years).
   - Knight et al. reported metastases most commonly in the bone (37%), lung (34%), and cervical lymph nodes (20%). There are also reports of MPA to the kidney, skin, and brain.
   - There are no definitive histopathologic features to distinguish MPA from conventional PA (Fig. 5.3). The morphology of the metastases is identical to the primary tumor and shows no cytologic atypia or malignant transformation. A few factors are associated with increased risk:
     - Repeated surgical manipulation – up to 80% are associated with at least one, though typically multiple, recurrences at the primary site. Recurrent tumors may show multiple nodules (Fig. 5.4).
     - Metastasis occurs only after resection of the primary tumor, raising the possibility of tumor spillage into the vasculature as a possible mechanism.

   References: [14–19]
5. *What are the malignant forms of pleomorphic adenoma and how are they diagnosed?*

   Up to 15% of untreated PA will undergo malignant transformation. The malignant forms of PA are carcinoma ex pleomorphic adenoma (CEXPA) and carcinosarcoma. CEXPA is a rare tumor primarily seen in the parotid gland with a minority of cases presenting in the submandibular gland and the palate. Patients present with rapid growth of a long-standing, preexisting mass. Regardless of histologic subtype, CEXPA is a high-grade tumor.
   - The type of carcinoma which arises in a CEXPA should always be specified and usually takes the form of adenocarcinoma, not otherwise specified (NOS) or salivary duct carcinoma (SDC).
   - Evidence of PA must be present either by histologic evaluation or clinical documentation of a previous PA at the same site. Extensive hyalinization or fibrosis in the tumor only suggests a previous PA (Fig. 5.5).
   - CEXPA is broadly divided into three categories: intracapsular, minimally invasive, and widely invasive.
     - Intracapsular carcinoma exhibits overt, cytologically malignant features (i.e., atypical mitoses, pleomorphism, necrosis) within the capsule of the PA. It can look like anything from ductal carcinoma in situ to an infiltrative carcinoma.
   - Random atypia or areas that resemble cytologically low-grade carcinomas (e.g., mucoepidermoid or

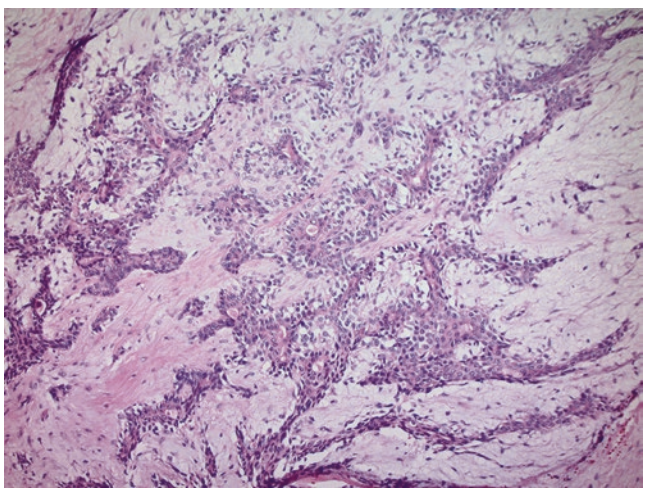

Fig. 5.3 Pleomorphic adenoma

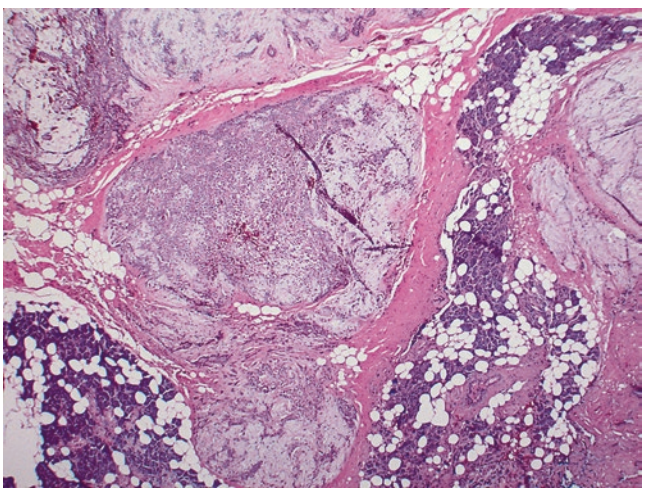

Fig. 5.4 Recurrent pleomorphic adenoma. Multiple nodules of predominantly chondromyxoid stroma are scattered within normal parotid gland parenchyma

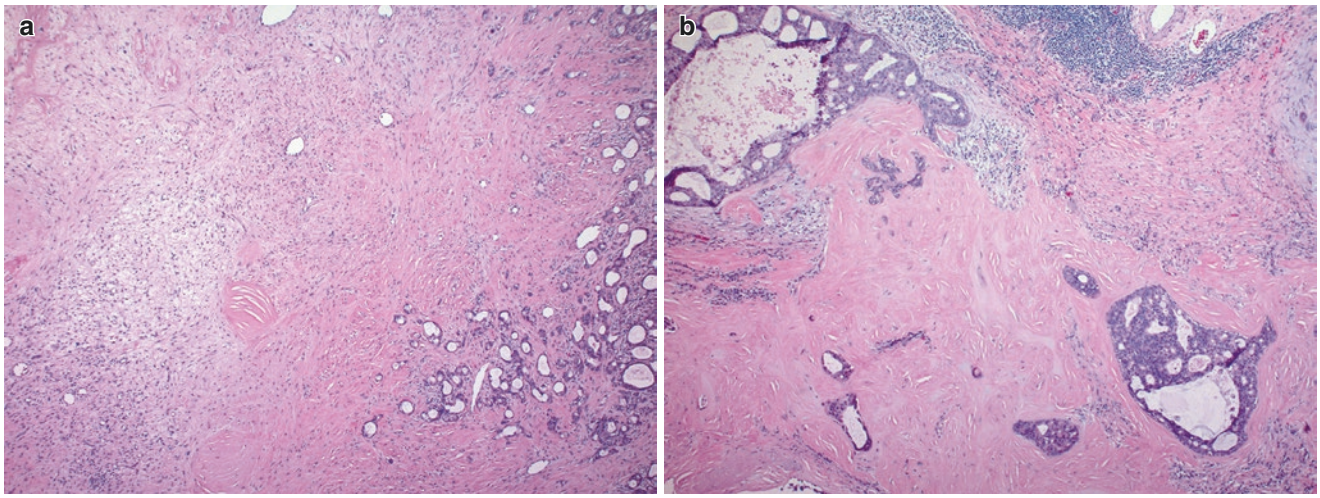

Fig. 5.5 Carcinoma ex pleomorphic adenoma. (**a**) Residual tubules of pleomorphic adenoma are seen at the periphery of a large, hyalinized, fibrotic nodule. (**b**) Salivary duct carcinoma arising in a pleomorphic adenoma shows cribriform glands with punched out lumens, Roman arches, and comedo necrosis

adenoid cystic carcinoma) are not sufficient for a diagnosis of intracapsular carcinoma.
  - Minimally invasive CEXPA shows invasion of the PA capsule. By definition, the distance of invasion beyond the capsule must be less than 1.5 mm.
  - Widely invasive CEXPA shows invasion ≥1.5 mm beyond the PA border with an associated mortality rate of 35–65%.
- Tumors with less than 1.5 mm of invasion show few or no recurrences, no distant metastases or tumor-associated deaths. Several studies that proposed a cut-off of 4–6 mm show similar outcomes.
- The proportion of carcinoma, type of carcinoma, tumor size, grade, and extent of invasion all have prognostic significance and should be reported.

Carcinosarcoma is a biphasic tumor composed of malignant epithelial and mesenchymal components. It may arise de novo or from a preexisting PA (up to 30%). They account for less than 1% of all SG malignancies with less than 100 reported cases.

- Over 70% occur in the parotid gland; minor SG sites include palate and tongue.
- There is a male predominance and mean age at diagnosis is in the sixth decade.
- The carcinomatous component is usually a poorly differentiated adenocarcinoma, NOS or SDC.
- The sarcomatous portion is usually a high-grade chondrosarcoma. Osteosarcoma, fibrosarcoma, and unspecified spindle sarcoma are also seen.
- Carcinosarcomas have a poor prognosis with distant metastases and subsequent death in 60% of patients.
- Histologic grade and distance of invasion beyond the capsule of a preexisting PA strongly correlate with clinical behavior.

References: [13, 19–27]

6. *What are the grading systems for mucoepidermoid carcinoma and their correlation with clinical outcomes? Are there any independent histopathologic features that correlate with clinical outcomes?*
   - Mucoepidermoid carcinoma (MEC) is the most common malignancy of the salivary glands in adults and children.
   - MEC is characterized by a variably solid and cystic tumor with three cell types (Fig. 5.6):
     - Intermediate cell: most common cell type ranges from a small basaloid cell to a large cell with a moderate amount of eosinophilic cytoplasm, small, dark to slightly vesicular nucleus.
     - Squamous/epidermoid cell: large, polygonal cell with abundant eosinophilic cytoplasm scattered singly and in small nests.
     - Mucous cells: large cell with clear, mucinous cytoplasm and eccentric, dark nucleus.
   - Grading of MEC relies on several histomorphologic features. There are three popular grading systems, all with a three-tiered approach (Table 5.3).
     - Despite this lack of standardization, tumor grade significantly correlates with survival in each system, and it is an important determinant of therapy.
     - High-grade tumors are usually treated with surgery, radiation, and neck dissection.
     - The Brandwein system tends to bundle low and intermediate tumors together and upgrades individual tumors. The AFIP system does the opposite, generally downgrading tumors and bundling intermediate and high-grade tumors.

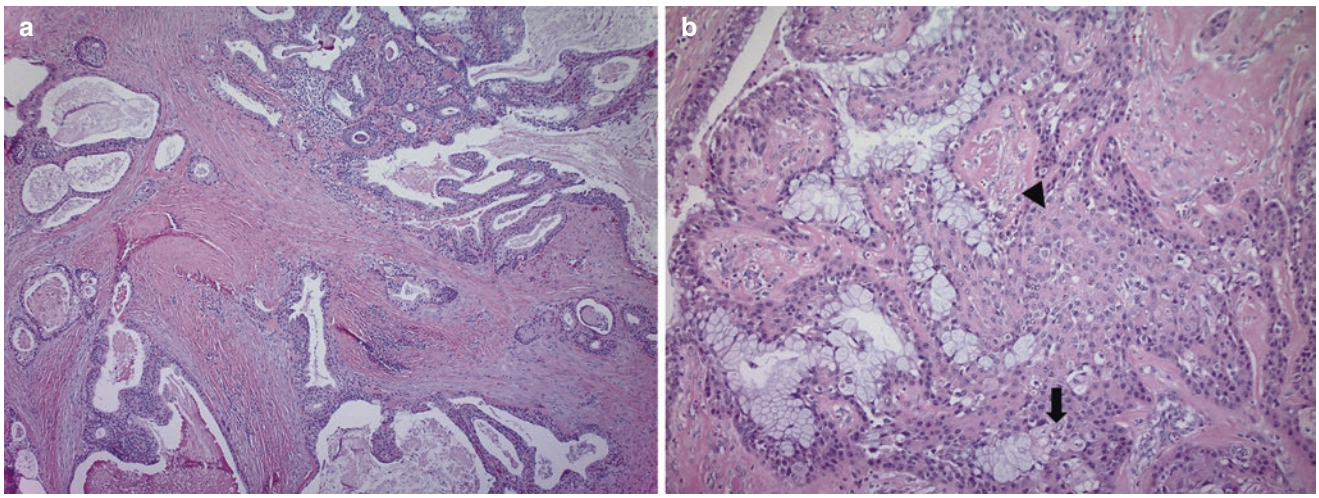

Fig. 5.6 Mucoepidermoid carcinoma. (**a**) Predominantly cystic tumor in a fibrotic stroma with smaller daughter cyst. (**b**) Sheets of eosinophilic intermediate cells (arrowhead) show minimal atypia. Rare squamous cells (arrow) and numerous mucous cells are present

Table 5.3 Comparison of grading systems for mucoepidermoid carcinoma

Modified Healy	**Brandwein**		**AFIP**	
	Feature	Points	Feature	Points
Low-grade: Micro- and macrocysts Mucus to squamoid cells 1:1 Minimal to moderate amount of intermediate cells Daughter cysts form from large cysts Minimal atypia Rare mitoses Circumscribed invasion Extravasated mucin pools with stromal reaction	Less than 25% cystic	2	Less than 20% cystic	2
	Perineural invasion	3	Perineural invasion	2
	Necrosis	3	Necrosis	3
Intermediate grade: No macrocysts Few microcysts Solid cellular nests Moderate pleomorphism Few mitoses Uncircumscribed invasion Fibrosis between cell nests Chronic inflammation at periphery	>4 mitoses/10 hpf	3	≥4 mitoses/10 hpf	3
	Pronounced atypia	2	Anaplasia	4
	Bone invasion	3		
	Lymphovascular invasion	3		
	Infiltrative border	2		
High-grade: No cysts, solid growth Considerable pleomorphism Frequent mitoses Soft tissue, perineural, or lymphovascular invasion Desmoplastic stroma Chronic inflammation less prominent	*Low-grade*	0	0–4 points	
	Intermediate grade	2–3	5–6	
	High-grade	4+	7–14	

hpf high-power field

  - 70–80% of MEC will be low or intermediate grade (LG, IG).
  - Population-based studies show no statistically significant difference in overall or disease-free survival between LG and IG tumors.
- Regardless of the grading system, a high tumor grade is an independent predictor of decreased survival. Other independent predictors of a worse prognosis include:
  - Advanced age
  - Tumor size
  - Positive lymph node metastases
  - Positive surgical margins
- 40–80% of LG and IG MECs are positive for the fusion product between the Mastermind-like 2 gene (MAML2) and the CREB-regulated transcription coactivator gene (CRTC), resulting in the t(11; 19)(q21; p13) translocation.
  - Several smaller studies have shown that the (MAML2) gene rearrangement partnered with

either CRTC1(MECT1) or CRTC3 conveys a favorable prognosis.
  - The specificity of the MAML2 rearrangements approaches 100% for MEC and may aid in the diagnosis of high-grade tumors.

References: [28–38]

7. *What are the three types of adenoid cystic carcinoma and how do they relate to tumor grade?*
   - Adenoid cystic carcinoma (AdCC) has a classic biphasic cellular composition of myoepithelial cells and ductal cells.
     - The predominant cells are small, uniform myoepithelial cells with scant, pale cytoplasm and bland, hyperchromatic, round to angulated nuclei. Ductal cells are low, cuboidal with regular, round nuclei, and a more dispersed chromatin.
     - Perineural invasion (PNI) is frequent.
   - AdCC has three growth patterns (in order of frequency):

1. Cribriform: nests of basaloid cells with sieve-like, punched out spaces containing pale, basophilic glycosaminoglycans or eosinophilic basement membrane material. Small ducts are scattered throughout the stroma and within the basaloid nests (Fig. 5.7).
2. Tubular: small duct proliferation with surrounding myoepithelial cells and dense, hyaline stroma.
3. Solid: large, solid nests and lobules of basaloid cells with minimal stroma. Nuclei are slightly larger than other types and more vesicular.

   - Histologic grading is based on type:
     - Low-grade: tubular, no solid component
     - Intermediate grade: cribriform (with or without minor solid component)
     - High-grade: at least 30% solid type
   - A higher percentage of solid type correlates with worse prognosis.
   - Some authors contend that any amount of a solid component will impact prognosis. As a result, this feature should be reported in clinical cases.
   - The MYB-NIFB translocation (t(6;9)) is present in approximately 30% of cases but has no impact on behavior.
     - Eighty percent of AdCC (including fusion negative cases) will express MYB by immunohistochemistry (IHC).
   - AdCC is a locally aggressive tumor characterized by a protracted clinical course of recurrences, late metastases, and death. Regardless of grade, most patients are treated with radiation therapy for local control. Lymph node metastases are seen in about 20% of patients. While 5-year survival rates approach 80%, 15-year survival rates are less than 20%.

References: [39–44]

8. *What are the histologic features of acinic cell carcinoma?*

Acinic cell carcinoma (AcCC) represents approximately 10% of all salivary gland carcinomas. It most commonly occurs in the parotid gland (85–90%) with a slight female predominance. AcCC is grossly well-circumscribed, non-infiltrative and may be lobulated.

- Morphologic subtypes include solid, microcystic/cystic, follicular, and papillo-cystic (Fig. 5.8). None of the morphologic variants correlate with clinical behavior.
- The non-acinar cells in AcCC are of intercalated duct origin and seen in the papillary, microcystic, and follicular types. These subtypes generally express CK7.

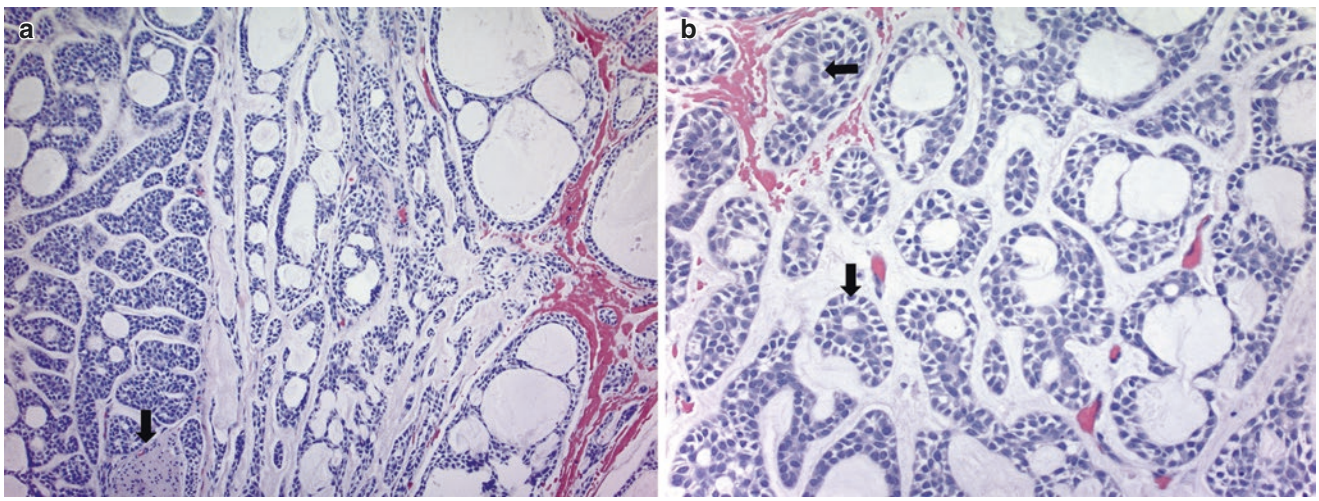

Fig. 5.7 Adenoid cystic carcinoma. (**a**) Areas of solid ACC have basaloid myoepithelial cells and demonstrate perineural invasion (arrow). Cribriform regions with lightly basophilic stroma are seen on the right. (**b**) Higher magnification shows the hyperchromatic, angulated myoepithelial cells, focally surrounding ductal structures (arrows)

  - The cells have a moderate amount of eosinophilic cytoplasm with variably sized, intracytoplasmic vacuoles that may coalesce to form lumina (Fig. 5.9a).
  - Cells show minimal atypia and may form sheets with small cystic spaces or large, thyroid-like, follicular spaces.
- The eosinophilic, luminal material reacts with PAS and may show weak mucicarmine staining.
- The solid type comprises sheets of acinar cells with granular, basophilic cytoplasm and intracytoplasmic, zymogen granules. Nuclei range from small, dark, dot-like to round with fine chromatin and conspicuous nucleoli (Fig. 5.9b). This subtype generally lacks duct differentiation and is negative for CK7.
- Cells may have a hobnail-type appearance; this should not be mistaken for apocrine-type, apical snouting.
- Strong cytoplasmic and canalicular staining for DOG-1 is a characteristic.
- AcCC is sometimes associated with a prominent lymphoid stroma.
- A small subset of cases occurs in minor salivary glands (5%), mainly the lip and buccal mucosa. Many of these, as well as zymogen granule-poor types, harbor the ETV6-NTRK3 translocation and have been reclassified as secretory carcinomas; see question 9.

References: [45–49]

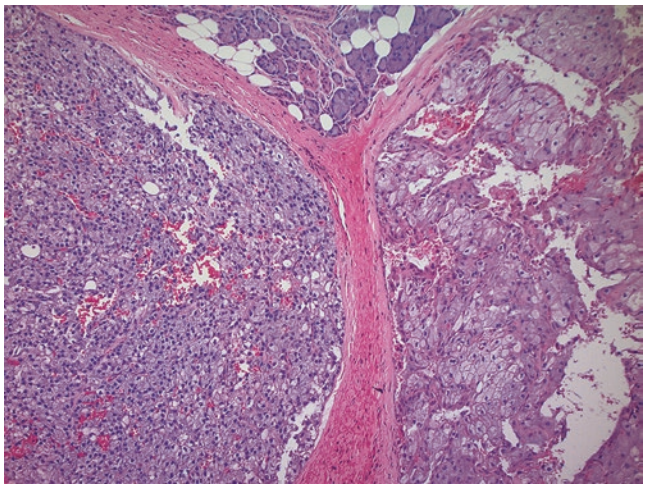

Fig. 5.8 Acinic cell carcinoma. Acinar cells are arranged in sheets and contain basophilic, granular cytoplasm (left) as well as finely reticulated, pale cytoplasm (right) with small, round, dark nuclei. In contrast, the normal parotid gland (top) shows small acini in a normal lobular architecture with intervening ducts

9. *What is mammary analogue secretory carcinoma and how is it characterized?*

Mammary analogue secretory carcinoma is a recently described tumor derived from intercalated duct epithelium that resembles secretory carcinoma of the breast. The 4th edition of the *WHO Classification of Head and Neck Tumors* uses the term secretory carcinoma (SC). It is primarily a tumor of the major salivary glands (80%). Patients are typically middle-aged with a slight male predominance.

- SC is circumscribed, unencapsulated tumors with invasive growth. The cells are arranged in tubular, papillary, microcystic, and solid growth patterns (Fig. 5.10). Fibrous septa separate the tumor lobules. The luminal pink, bubbly (colloid-like) material is positive for mucicarmine and PAS stains with and without diastase.
- The tumor cells are cuboidal with small, bland vesicular nuclei with conspicuous, central nucleoli, mild atypia, and vacuolated or granular, eosinophilic cyto-

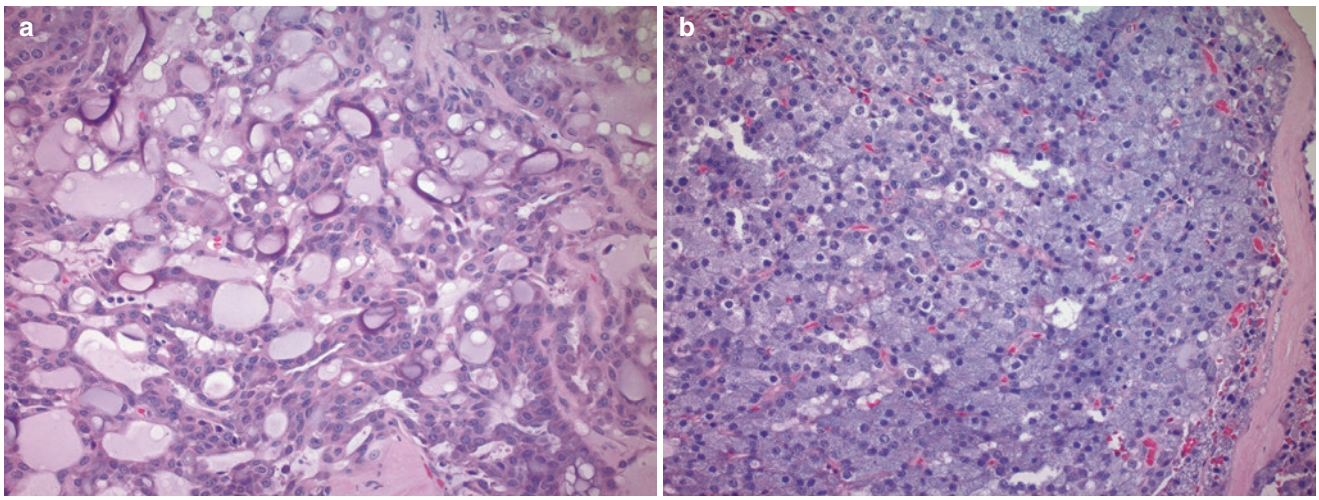

Fig. 5.9 Acinic cell carcinoma. (**a**) Microcystic pattern, with numerous small cysts, lined by cuboidal, intercalated duct-type cells. (**b**) Solid type with the "blue dot" appearance of small nuclei in acinar cells with deeply basophilic granules

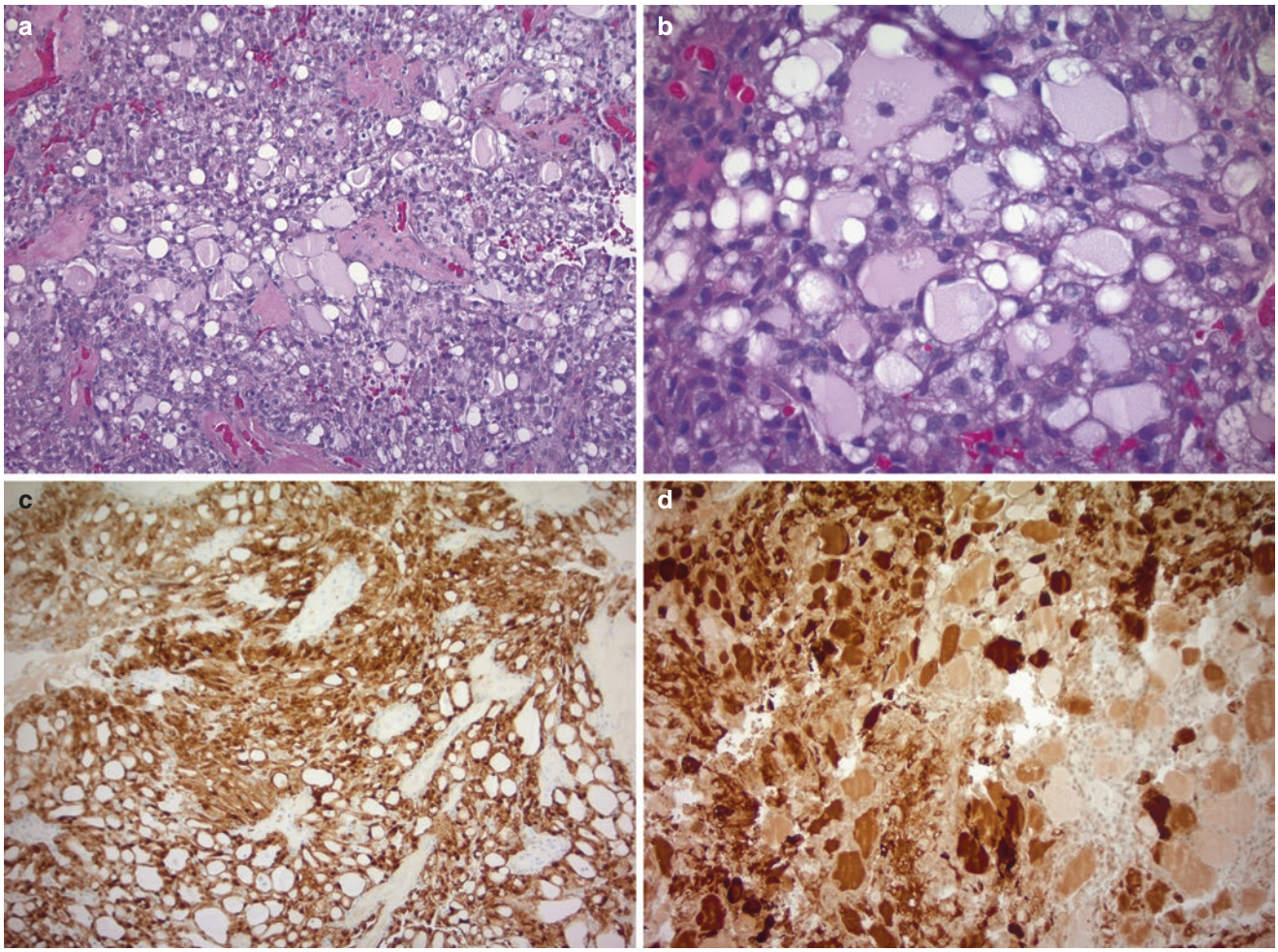

Fig. 5.10 Secretory carcinoma. (**a**) Microcystic pattern with variably sized spaces and pale eosinophilic secretions. (**b**) Tumor cytoplasm is finely vacuolated and lacks basophilic zymogen granules. (**c**) The tumor is strongly positive for S100 and (**d**) mammaglobin

plasm. Mitoses, necrosis, and lymphovascular invasion are rare.

- SC is characterized by the ETV6-NTRK3, t(12;15)(p13;q25) translocation, identical to that seen in mammary secretory carcinoma. Other translocation partners include t(12;XX).
- The primary differential diagnostic consideration with SC is acinic cell carcinoma. Table 5.4 summarizes the differences between SC and AcCC.
  - A subset of zymogen granule-poor AcCC and those in minor SG have been retrospectively reclassified as SC based on molecular findings.
  - The clinical significance of this distinction is unclear given the limited number of cases. However, SC may have a slightly higher rate of lymph node metastases (20%).
- SC can undergo high-grade transformation. High-grade tumors express p53 and membranous beta-catenin.

References: [46, 49–57]

10. *What are the clues to the diagnosis of polymorphous adenocarcinoma (polymorphous low-grade adenocarcinoma) and which entities are in the differential diagnosis?*

Polymorphous adenocarcinoma (PAC) is a monotypic tumor comprising cells of terminal/intercalated duct origin. It is classically described as cytologically uniform but architecturally diverse. It shows a relatively even distribution among intraoral and major salivary gland sites. There is twofold female predominance with a mean age of 60 years old.

- PAC is the second most common intraoral salivary gland carcinoma after adenoid cystic carcinoma.
- The palate is the most common location (approximately 60%).
- The different growth patterns include solid, lobular, papillary, ductal, and tubular; cribriform and papillary growth are less common.
- PAC is usually unencapsulated with a more solid, lobular center and small nests and cords of single cells radiating toward the tumor periphery in an infiltrative

Table 5.4 Contrasting features between secretory carcinoma and acinic cell carcinoma

	Secretory carcinoma	Acinic cell carcinoma
Gender predominance	Male	Female
Location	Minor and major SG	90% parotid
Predominant growth pattern	Solid, tubular Papillae common	Solid, microcystic Papillae rare
Infiltrative growth	Yes	No
Cell morphology	Monotonous Eosinophilic, vacuolated, granular	Varied Eosinophilic to basophilic, granular, clear, oncocytic
Hobnail cells	Yes	No
PAS+ cytoplasmic granules	No	Yes
DOG-1 IHC	Negative	Positive
S100 IHC	Positive	Negative
Mammaglobin IHC	Positive	Negative

pattern. This arrangement creates the classic, concentric, targetoid appearance (Figs. 5.11 and 5.12).

- The cells are small to intermediate in size with bland, oval nuclei, delicate nuclear membranes and pale chromatin.
- Perineural invasion is common and necrosis is rare.
- Mutations in PRKD1 E710D are present in up to 70% of cases.
- Overall 5- and 10-year survival rates are 91% and 73%, respectively. Distant metastases and deaths due to disease are rare.
- Locoregional recurrences, including cervical lymph node metastases, approach 30% and can have long latency periods in excess of 15 years. For this reason, and because of reports of occasional high-grade transformation, the "low-grade" moniker has been removed from the name in the 4th edition of WHO classification system.

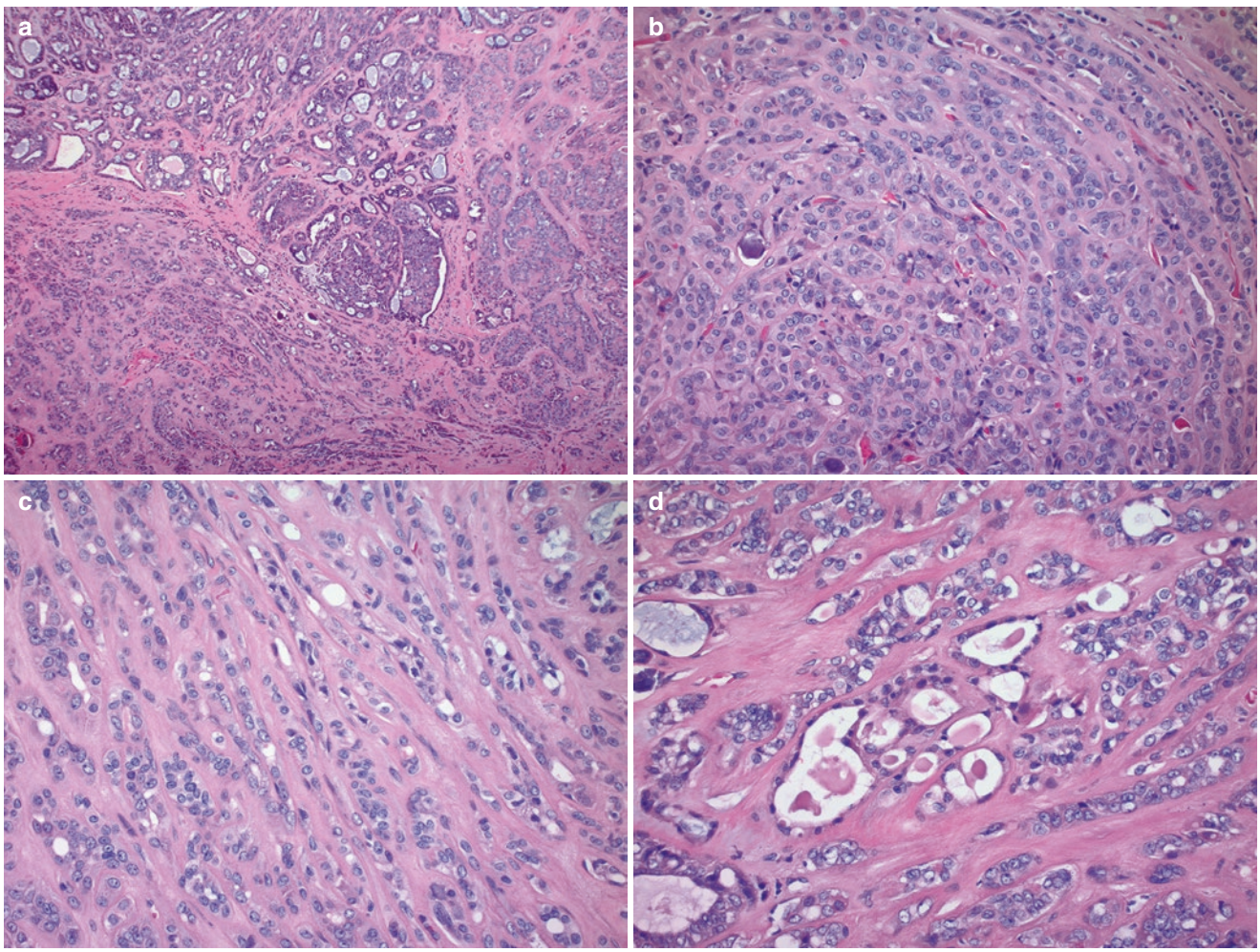

Fig. 5.11 Polymorphous adenocarcinoma. (**a**) Low magnification shows a variegated architecture with papillary structures toward the center and small tubules (top), single cells (bottom left), and lobules (right) at the periphery. (**b**) A tumor lobule shows a concentric targetoid arrangement and nuclear monotony with oval, bland, pale nuclei. (**c**) Tumor cells are arranged in single files and (**d**) tubules

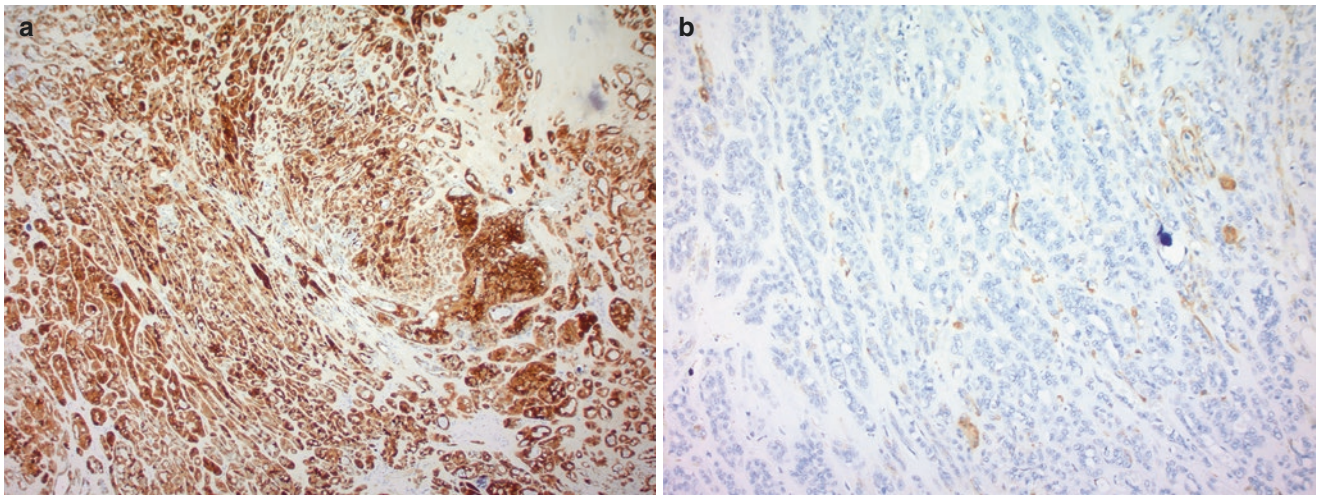

Fig. 5.12 Polymorphous adenocarcinoma. (**a**) S100 is strongly and diffusely positive. (**b**) SMA shows rare, scattered positive cells

Table 5.5 Tumors in the differential diagnosis of polymorphous adenocarcinoma

	Polymorphous adenocarcinoma	Adenoid cystic carcinoma	Pleomorphic adenoma	Cribriform adenocarcinoma of SG
Biphasic	No	Yes	Yes	Yes
Predominant cell	Ductal Monotonous, oval, fine to vesicular, pale chromatin	Myoepithelial Basaloid, small, hyperchromatic, angulated	Variable cell types Small dark myoepithelial cells, cuboidal ductal cells, ±squamous cells	Ductal PTC-like nuclei, oval, overlapping, irregular membranes, fine, pale chromatin
Cytoplasm	Appreciable, eosinophilic	Scant, pale		Abundant, clear to eosinophilic
Patterns	Classic single file, cell growth Variable: tubular, lobular, rarely cribriform, or papillary	Cribriform, tubular, solid	Variable sheets and nests of myoepithelial cells, scattered duct proliferation	Fibrous septa, lined by basal cells, retract from tumor nodules, creating glomeruloid effect Solid, cribriform, papillary
Stroma	Not prominent, variable Collagenous, mucoid, hyaline	Prominent in areas Hyaline or basophilic	Chondromyxoid	Collagenous, vague palisading of small, dark nuclei at edges of nodules
PNI	Frequent	Frequent	None	Not prominent
Myoepithelial markers	Negative	Positive	Positive	Positive at edges of tumor nodules
Ductal markers	Diffusely positive, LMWCK	Focal positive	Positive	Diffusely positive, LMWCK
p63/p40	Positive/Negative	Positive/Positive	Positive/Positive	Positive/na
S100 IHC	Strong, diffuse	Weak	Variable	Strong, diffuse
Molecular	PRKD1 E710D mutation	NIFB-MYB	PLAG1, HMGA2	PRKD1-3 translocation

SG salivary gland, *PTC* papillary thyroid carcinoma, *PNI* perineural invasion, *LMWCK* low molecular weight cytokeratins, *na* data not available

The major differential diagnoses with PAC arise primarily because the diagnosis is made on limited biopsy samples typically from the oral cavity (Table 5.5). Its polymorphous architecture has many mimics that are greatly reduced on excision specimens.

- Cribriform adenocarcinoma of (minor) salivary gland (CASG) shows significant morphologic overlap with PAC but a distinct clinical picture. Less than 100 cases have been reported in the literature. It occurs primarily in the minor salivary glands, and patients typically present with cervical lymph node metastases. However, the tumor has an excellent prognosis with no reported distant metastasis or deaths due to disease.
- CASG (Fig. 5.13) is not currently classified by the WHO but is probably best regarded as a cribriform variant of PAC. A subset harbor translocations of PRKD1-3 with ARID1A and DDX3X.

References: [2, 58–66]

11. *What are the morphologic subtypes of basal cell adenomas, their clinical relevance, and differential diagnosis?*

Basal cell adenomas are rare, accounting for 1–3% of all salivary gland tumors. They present primarily in the parotid gland, with a minority of cases in intraoral sites (upper lip) and submandibular gland. There is a slight female predominance with a wide age range and a peak incidence in the seventh decade.

- BCA is a well-circumscribed, encapsulated tumor composed of bland, basaloid cells that show some degree of nuclear palisading. Mitoses are rare, and necrosis is absent.

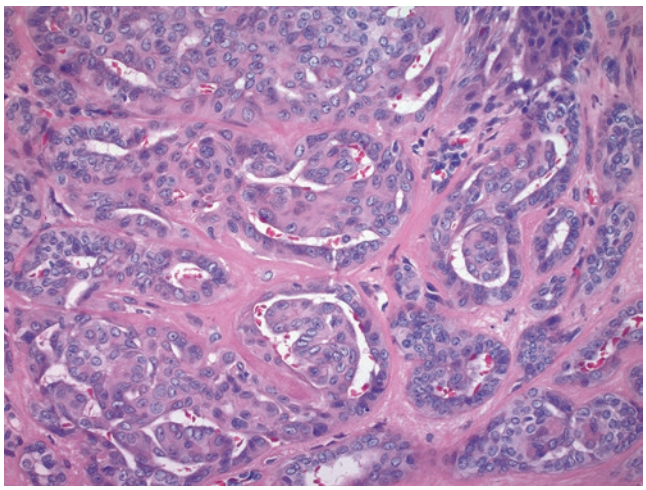

Fig. 5.13 Cribriform adenocarcinoma of the salivary gland. Tumor cell aggregates retract from basal cells at the stromal interface and form glomeruloid structures. Nuclei are oval, pale, and grooved reminiscent of papillary thyroid carcinoma

- There are four morphologic types (Table 5.6) of BCA; most tumors will show at least two types (Fig. 5.14).
- The two main cell types are abluminal with varying amounts of ductal cells:
  - Myoepithelial cells: small, dark cells with round to oval, hyperchromatic nuclei and scant cytoplasm.
    - Muscle markers: positive
    - Basal markers: positive (p63, CK5/6, CK14)
  - Basal cells: larger, abluminal cells with oval, more pale nuclei and more abundant, eosinophilic cytoplasm. They typically align at the epithelial-stromal interface and demonstrate palisading.
    - Muscle markers: negative
    - Basal markers: positive (p63, CK5/6, and CK14)

Basal cell adenocarcinoma (BCAC) poses the most significant diagnostic challenge with BCA. BCAC only differs from BCA by demonstrating infiltrative growth, including capsular, vascular or perineural invasion. Increased mitotic activity, pleomorphism, and necrosis may be seen but are not prominent features.

- Some authors suggest that a BCA with mitoses in excess of three per ten high-power fields should be carefully examined and completely submitted for histologic evaluation to exclude BCAC.
- The solid variant is the most common type of BCAC, and palate is the most common intraoral site.
- The differential diagnosis of BCAC depends on type and location. Immunohistochemical stains and morphologic features can help make the correct diagnosis.

Table 5.6 Clinicopathologic features of the morphologic types of basal cell adenoma

	Tubulo-trabecular	Solid	Membranous	Cribriform
Morphology	Interlacing network of tumor cords of varying thickness Tubules lined by duct epithelium and surrounded by abluminal cells	Large, irregularly shaped sheets and nodules separated by stroma ±Squamous eddies	Solid nests and nodules rimmed by dense, eosinophilic stroma Multinodular growth with "jigsaw" puzzle arrangement ±Squamous eddies	Cribriform nests of variable size Nests have light cells in the center, dark cells at the periphery
Stroma	Cellular, collagenous S100 IHC positive	Collagenous	Hyalinized, basement membrane material	Homogeneous pale blue/gray or pink
Molecular	CTNNB1 mutations β-catenin IHC positive	None	Cyclin-D1 mutations β-catenin IHC negative	None
Comments	DDX: canalicular adenoma – exclusive to the lip, edematous stroma, uniform, 2-cell thick cords	DDX: basaloid squamous cell carcinoma – abrupt keratin, necrosis	May be multifocal Up to 25% recur Associated with Brooke-Spiegler syndrome	DDX: adenoid cystic carcinoma – absence of palisading and only one abluminal cell type

DDX differential diagnosis

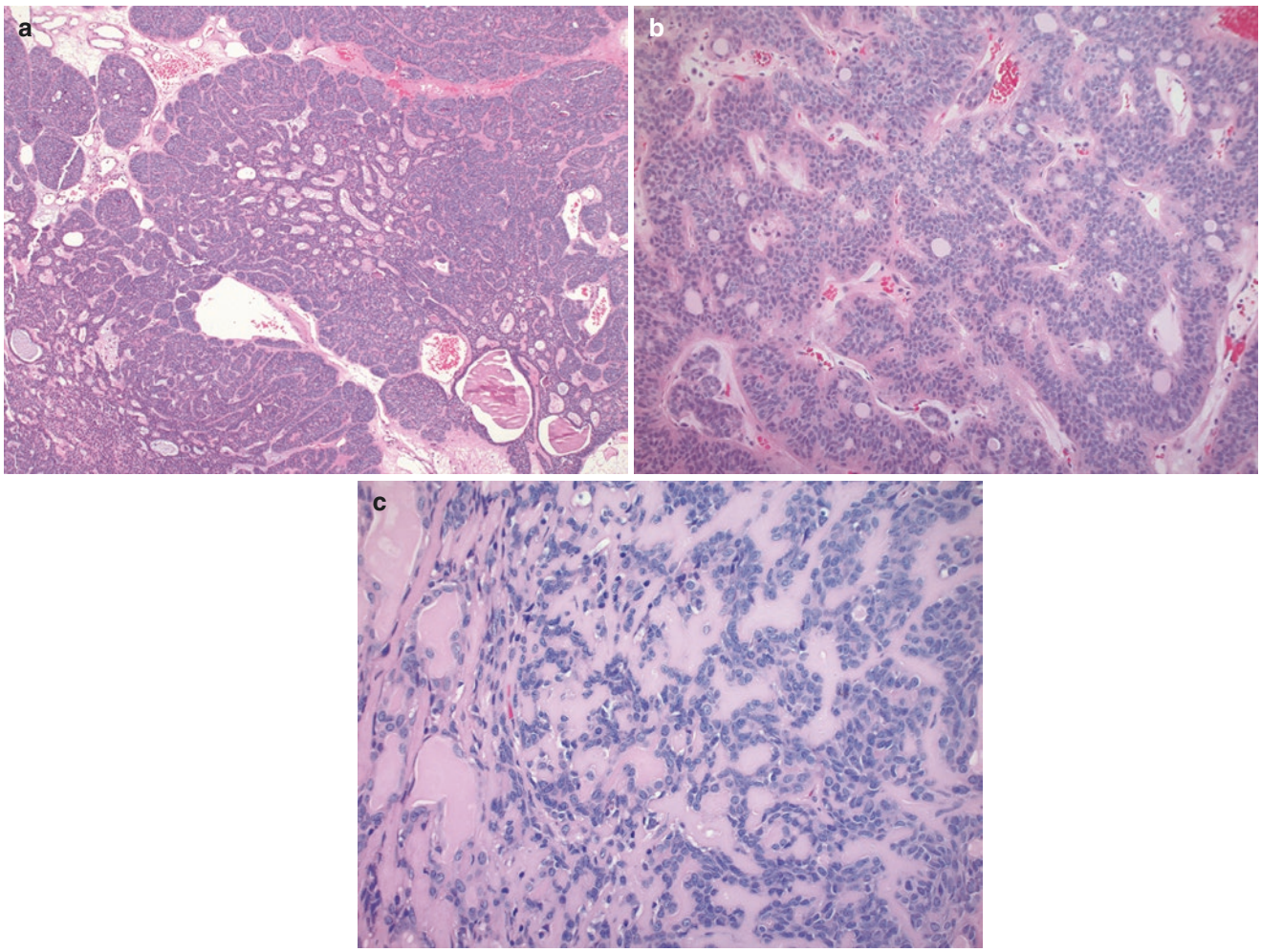

Fig. 5.14 Basal cell adenoma. (**a**) Solid type with tumor nests arranged in lobules. (**b**) Tubulo-trabecular pattern with ribbons of tumor cells and scattered tubular lumens. (**c**) Membranous type, cells are surrounded by hyalinized, eosinophilic basement membrane material

  - Adenoid cystic carcinoma
  - Basaloid squamous cell carcinoma
  - Basal cell carcinoma

References: [67–72]

12. *What are the criteria used to diagnose myoepithelial tumors, their subtypes, and the differential diagnoses?*

Myoepithelial tumors are rare tumors accounting for less than 2% of all salivary gland neoplasms. The parotid gland is the most common site (40–60%) with up to 20% of cases presenting in minor salivary gland, usually palate. Myoepitheliomas and myoepithelial carcinomas (MyEC) present as a slow-growing, painless masses.

- Myoepithelial tumors are encapsulated and composed almost exclusively of myoepithelial cells. Some authors do not accept any ductal elements, while others will allow for as much as 10% duct formation. Given the morphologic overlap with so many SG tumors, we prefer the former, more stringent criteria.
- There are five different cell types: epithelioid, spindled (Fig. 5.15), plasmacytoid or hyaline (Fig. 5.16), clear cell, and mucinous. Tumor variants generally comprise at least 75% of one cell type, but a mixed pattern is the rule.
  - The cell type is not clinically significant, but awareness of the different morphologies and their mimics is important in making an accurate diagnosis (Table 5.7).
  - The stroma can be positive for Alcian blue but usually negative for mucicarmine.
- The diagnosis of myoepithelial tumors requires demonstration of myoepithelial lineage by immunohistochemistry or ultrastructural analysis.
- Myoepithelial tumors co-express keratins and muscle markers to varying degrees:

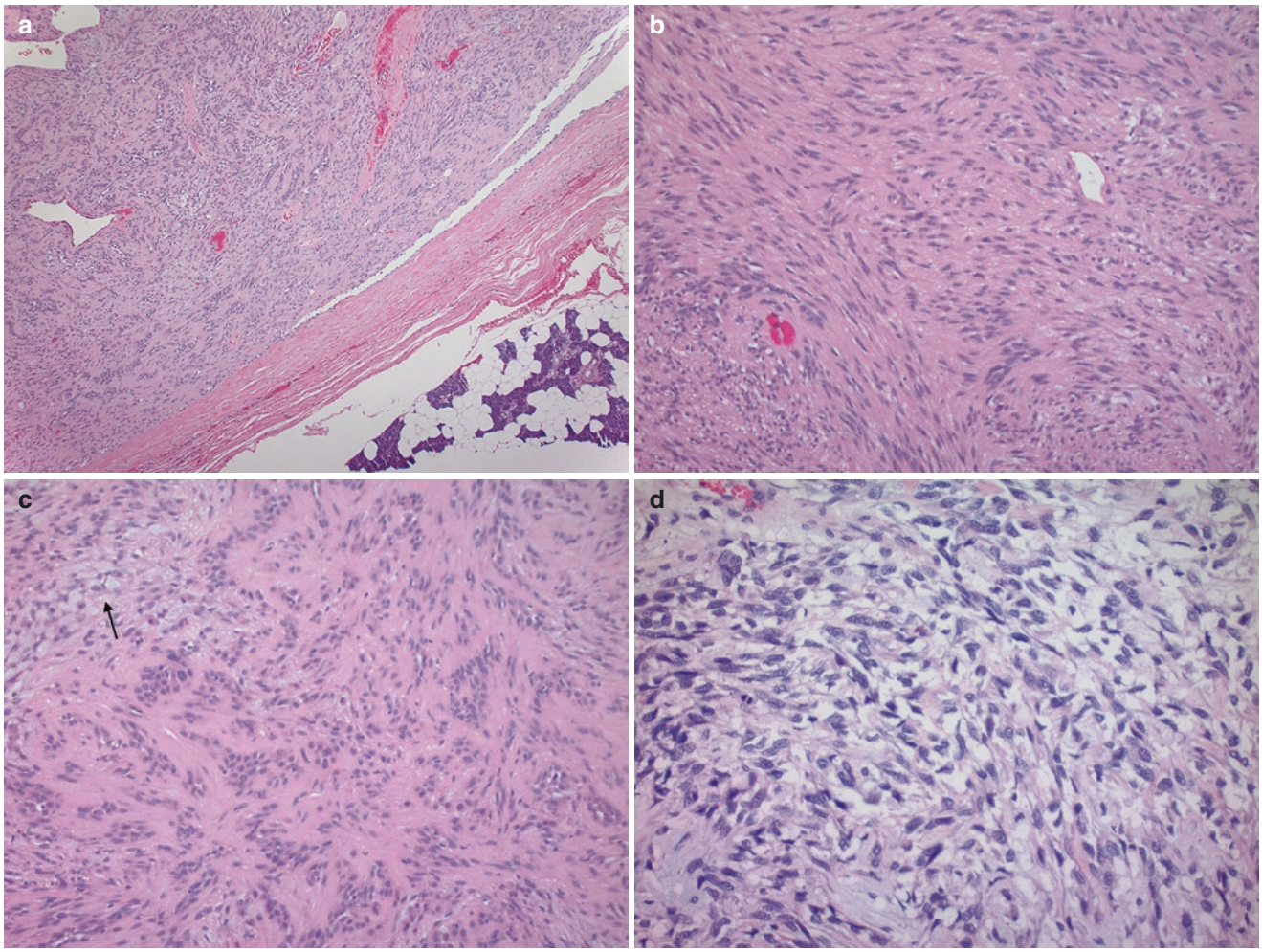

Fig. 5.15 Spindled myoepithelial tumors. (**a**–**c**) Myoepithelioma. A well-circumscribed spindle cell tumor composed of bland spindle cells arranged in intersecting fascicles with vague palisading similar to a schwannoma. Foci of tumor cell cords (**c** arrow) in a mucoid stroma offer a clue to the diagnosis. (**d**) Spindled myoepithelial carcinoma, in contrast, shows increased nuclear atypia and mitoses

  - Keratins: AE1/3, 34BetaE12, Cam5.2, CK14
  - Muscle markers: calponin, smooth muscle actin, SMA, MSA, calponin
  - Other positive markers: vimentin, S100, p63, GFAP
  - Negative markers: CK7
- A few notable exceptions to the classic immunoprofile:
  - Spindle variant is negative for pan-cytokeratin.
  - Mucinous variant expresses CK7, mucicarmine, with variable p63 and calponin.
  - Plasmacytoid variant may only weakly express muscle markers.
- Myoepithelial carcinoma (MyEC) is distinguished from myoepitheliomas by:
  - An infiltrative border, multinodular growth
  - Frequent or atypical mitoses (see Fig. 5.15d)
  - Tumor nodules with a hypercellular periphery and a necrotic center (see Fig. 5.16c, d)
- Histologic parameters such as grade, cell type, mitotic rate, the presence of necrosis, nerve or vascular invasion do not consistently correlate with prognosis.
- Clinically, MyEC has high metastatic rates, averaging 40–50% and frequent recurrences. Common sites of metastases are the lungs and cervical lymph nodes.

References: [1, 73–80]

13. *What is the differential diagnosis of oncocytic lesions of salivary gland?*

The three principal oncocytic lesions of the salivary gland are oncocytoma (Fig. 5.17), nodular oncocytic hyperplasia (or oncocytosis), and oncocytic carcinoma (Fig. 5.18). Among these, less than 10% represent oncocytic carcinomas. Table 5.8 summarizes the features of each.

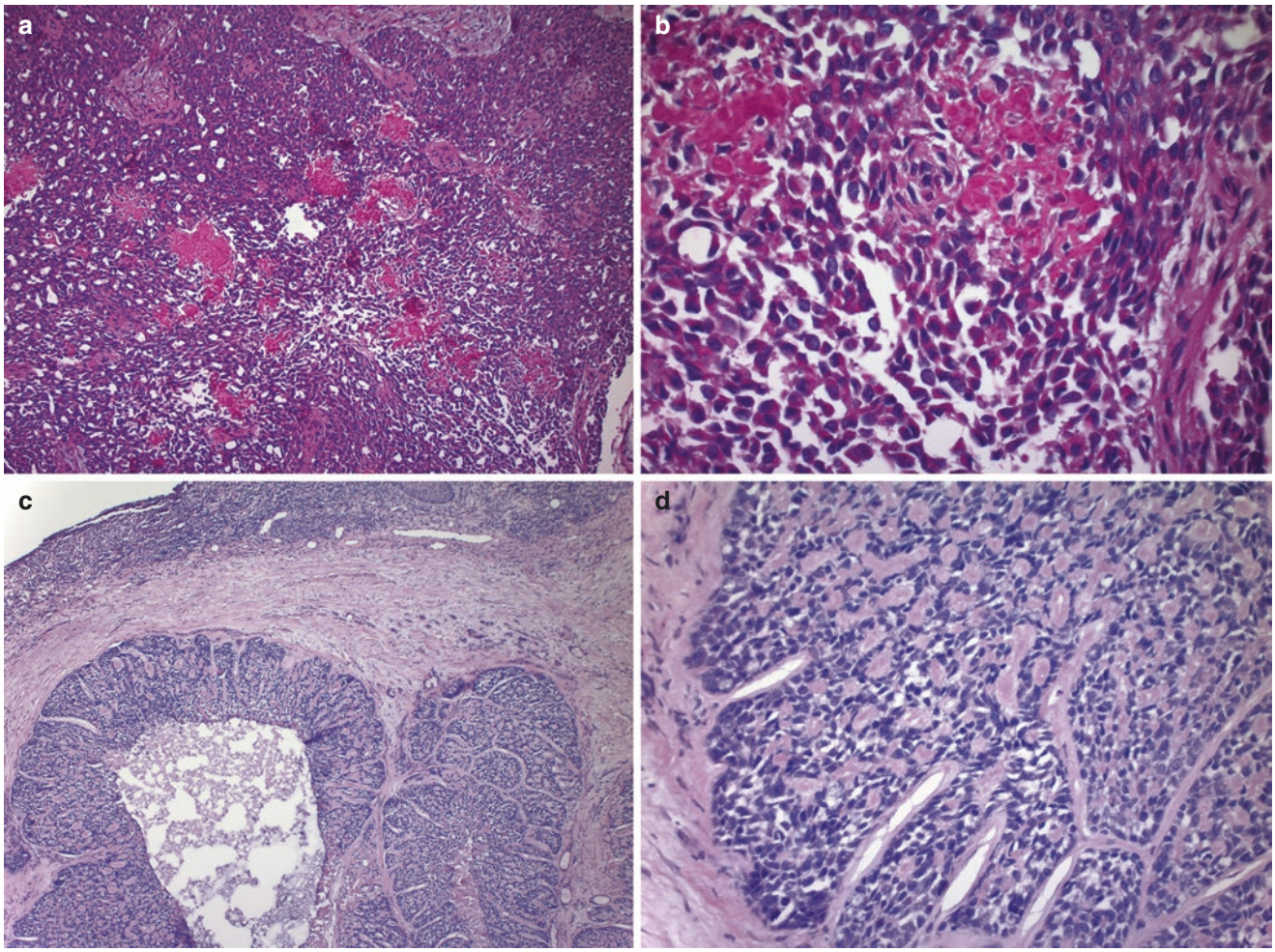

Fig. 5.16 Hyaline type myoepithelial tumors. (**a**, **b**) Myoepithelioma. Sheets of monotonous tumor cells with brightly eosinophilic, plasmacytoid cytoplasm and tufts of hyaline, basement membrane material (**b** center). (**c**, **d**) Myoepithelial carcinoma. Submucosal tumor lobules with necrotic centers and tumor cells surrounded by hyaline, basement material

- All three lesions occur in older patients (sixth to seventh decades) with no gender preference.
- Care should be taken to distinguish the clear cell variant of oncocytoma from other primary *and* secondary clear cell tumors (see question 14).
- The infiltrative growth pattern of oncocytic carcinoma is a key feature in the diagnosis, as pleomorphism and atypia may be focal.

Oncocytic change occurs in a variety of salivary gland entities; a few tumors are notable for having oncocytic variants. These variants are generally defined as having at least 50% oncocytic change and should be considered in the differential diagnosis of oncocytic tumors.

- The oncocytic variant of epithelial-myoepithelial carcinoma (EMCA) shows the classic biphasic pattern of outer myoepithelial cells and inner ductal cells. When both ductal and myoepithelial cells are oncocytic, immunohistochemical stains may be necessary to appreciate the biphasic pattern.
  - Seethala et al. noted that oncocytic EMCA has a tendency toward papillary growth and frequently demonstrates sebaceous differentiation.
  - The immunoprofile is similar to that of the usual type of EMCA: p63 and muscle markers will highlight the myoepithelial layer, and various keratins will stain the ductal component.
  - In oncocytomas, p63 only stains cells at the periphery of the tumor nodules.
- The oncocytic variant of mucoepidermoid carcinoma (oncMEC) is a rare tumor with only a few cases described in the literature.
  - The oncocytes are arranged in sheets and nests in a fibrotic stroma.
  - The majority of cases are low to intermediate grade.

Table 5.7 Variants of myoepithelial tumors, their features, and tumors in the differential diagnosis

Myoepithelial variant and morphology		Tumors in differential diagnosis	
Epithelioid	Nests, cords, pseudoglandular spaces polygonal cells, moderate amount of eosinophilic cytoplasm, indistinct cell borders Central nucleus Myxoid matrix	Polymorphous adenocarcinoma	EMA+, CEA+, DOG-1+ Muscle markers–
		Adenocarcinoma, NOS	EMA+, CEA+, CK7+ Muscle markers–
Clear cell PAS+ PASD–	Polygonal cells with abundant clear/pale, glycogen-rich cytoplasm Small, raisinoid nuclei Microcystic spaces	Squamous carcinoma	p63+, CK5/6+ Muscle markers–
		EMCA	EMA+, CEA+
		Renal cell carcinoma	Pax-8+, RCC antigen+ Muscle markers–
		Clear cell carcinoma	Muscle markers–, S100–
		Oncocytoma	AMA+, PTAH+ Muscle markers–, p63–
		Mucoepidermoid carcinoma	EMA+, CK7+ Muscle markers–
Spindle Cam5.2– CK–	Fascicular or storiform growth Elongated, spindled cytoplasm Short, oval, to elongated nuclei	Neural tumors	Muscle markers–
		Leiomyosarcoma	Muscle markers+ CK–, p63–
		Fibrosarcoma	CK–, muscle markers–
Plasmacytoid Muscle markers+/weak	Round, dyshesive cells with dense eosinophilic cytoplasm Eccentric, dark nucleus Hyalinized or mucoid stroma	Plasmacytoma	EMA+, CD138+, kappa+, lambda+ CK–, muscle markers–
		Melanoma	HMB-45+, Mart-1+ Muscle markers–, CK–
		Medullary thyroid carcinoma	TTF1+, Pax-8+ Muscle markers–
		Rhabdomyosarcoma	CK–, p63– Desmin+, MyoD1+, myoglobin+
Mucinous CK7+ E-cadherin+ Mucicarmine+	Signet ring cells with intracellular mucin, eosinophilic cytoplasm Eccentric nucleus	Secretory carcinoma (MASC)	Mammaglobin+, EMA+ Muscle markers–/wk+
		Metastatic adenocarcinoma	Site of origin markers+: TTF-1, GATA-3, Pax-8 Muscle markers–

NOS not otherwise specified, *RCC* renal cell carcinoma, *wk* weak, *TTF* thyroid transcription factor, muscle markers, SMA, MSA, calponin, caldesmon

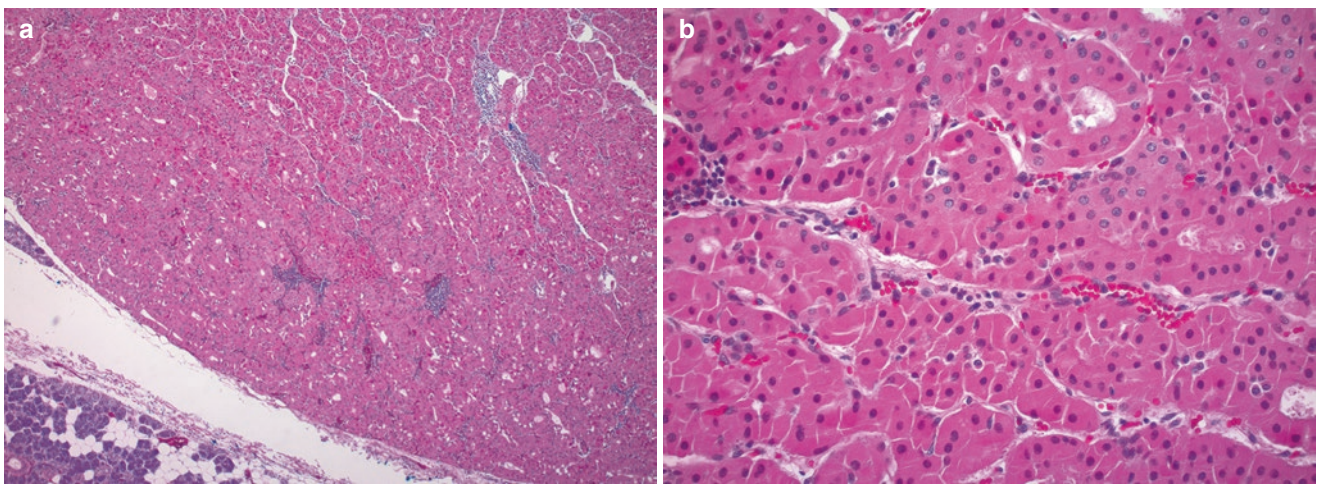

Fig. 5.17 Oncocytoma. (**a**) A well-circumscribed, solid tumor. (**b**) Cells with abundant, granular, eosinophilic cytoplasm are arranged in trabeculae with scattered duct lumens

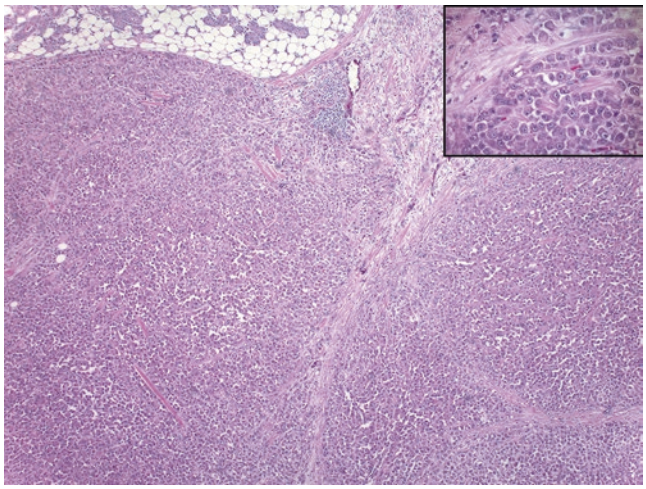

Fig. 5.18 Oncocytic carcinoma. Sheets of atypical tumor cells with a high N-C ratio, granular pink cytoplasm, and nuclear pleomorphism

Table 5.8 Pathologic features of oncocytic salivary gland lesions

	Oncocytoma	Oncocytic carcinoma	Oncocytosis
Site	Parotid (85%)	Parotid	Parotid
Well-circumscribed	Yes	No, infiltrative	Yes
Encapsulated	Yes, at least partial	No	No
Atypia	No	Yes, may be focal	No
Nodular	Single nodule	Single nodule	Multiple nodules
Multifocal	No	No	Yes
Necrosis/ Mitoses	No/No	Some/Yes	No/No

  - The tumors are mostly solid; conventional areas of MEC may be scarce, and mucous cells may be difficult to find without special stains.
  - The Warthin tumor-like variant of MEC typically shows disorganized, multilayered, oncocytic epithelium lining cysts and papillae with a dense lymphoid stroma and occasional mucus cells.
  - Awareness of both of these variants is essential in avoiding an incorrect diagnosis but conveys no prognostic value. Both variants stain strongly and diffusely with p63 and harbor MAML2 gene rearrangements.

References: [69, 81–90]

14. *What is the differential diagnosis of clear cell tumors of the salivary gland?*

Clear cell carcinoma is a rare, low-grade tumor of primarily minor salivary gland, with 80% occurring in intraoral sites (tongue and palate). Immunohistochemical stains and electron microscopy support a squamous origin.

- CCC is characterized by small nests, cords, and single files of clear cells separated by a dense, eosinophilic, hyaline stroma. The cells are small with a high nuclear to cytoplasmic ratio, bland nuclei, and clear to pale pink cytoplasm. Necrosis and mitoses are rare (Fig. 5.19).
- CCC rarely shows a predominance of optically clear cells.
- A myxoid, fibrocellular stroma may be present in lieu of the hyalinized stroma.
- CCC harbors the EWSR1-AFT1 rearrangement in 80–90% of cases. The same alteration is seen in clear cell odontogenic carcinomas, a postulated, intraosseous relative of CCC.
- Perineural invasion is frequent (40–50%).
- Increased mitotic activity or necrosis should raise concern for high-grade transformation.
- Metastatic rates to regional lymph nodes are estimated at 25%. However, CCC are considered low-risk tumors with metastases to distant sites and subsequent deaths at less than 4%.

Areas of clear cell change can be seen in a wide variety of benign and malignant salivary gland tumors. A few SG tumors such as epithelial-myoepithelial carcinoma (Fig. 5.20) and mucoepidermoid carcinoma (Fig. 5.21) are notable for their clear cell variants. The list in Table 5.9 is not comprehensive, and metastatic lesions, like squamous cell carcinoma and renal cell carcinoma, should also be considered.

References: [73, 91–98]

15. *What are the different ductal carcinomas and how are they distinguished?*

Salivary duct carcinoma (SDC) is a high-grade tumor of salivary duct origin. It is a disease of the elderly with a marked male predominance. As many as 60% occur in the parotid gland, though submandibular and minor salivary glands can also be involved. Up to 10% of cases arise in a carcinoma ex pleomorphic adenoma.

- SDC resembles high-grade ductal carcinoma in situ of the breast. It comprises large ducts/cysts lined by pleomorphic cells with coarse chromatin, prominent nucleoli, and moderate to abundant eosinophilic cytoplasm. The cells are arranged in a cribriform pattern with Roman-bridge architecture and comedo necrosis. Apical snouting, typical of apocrine differentiation, is characteristic (Fig. 5.22).
- Distinction from squamous cell carcinoma and high-grade transformation of other salivary gland carcinomas is critical, as the latter are more aggressive. Immunohistochemical stains and careful sampling to exclude a preexisting low-grade component are useful in arriving at the correct diagnosis.

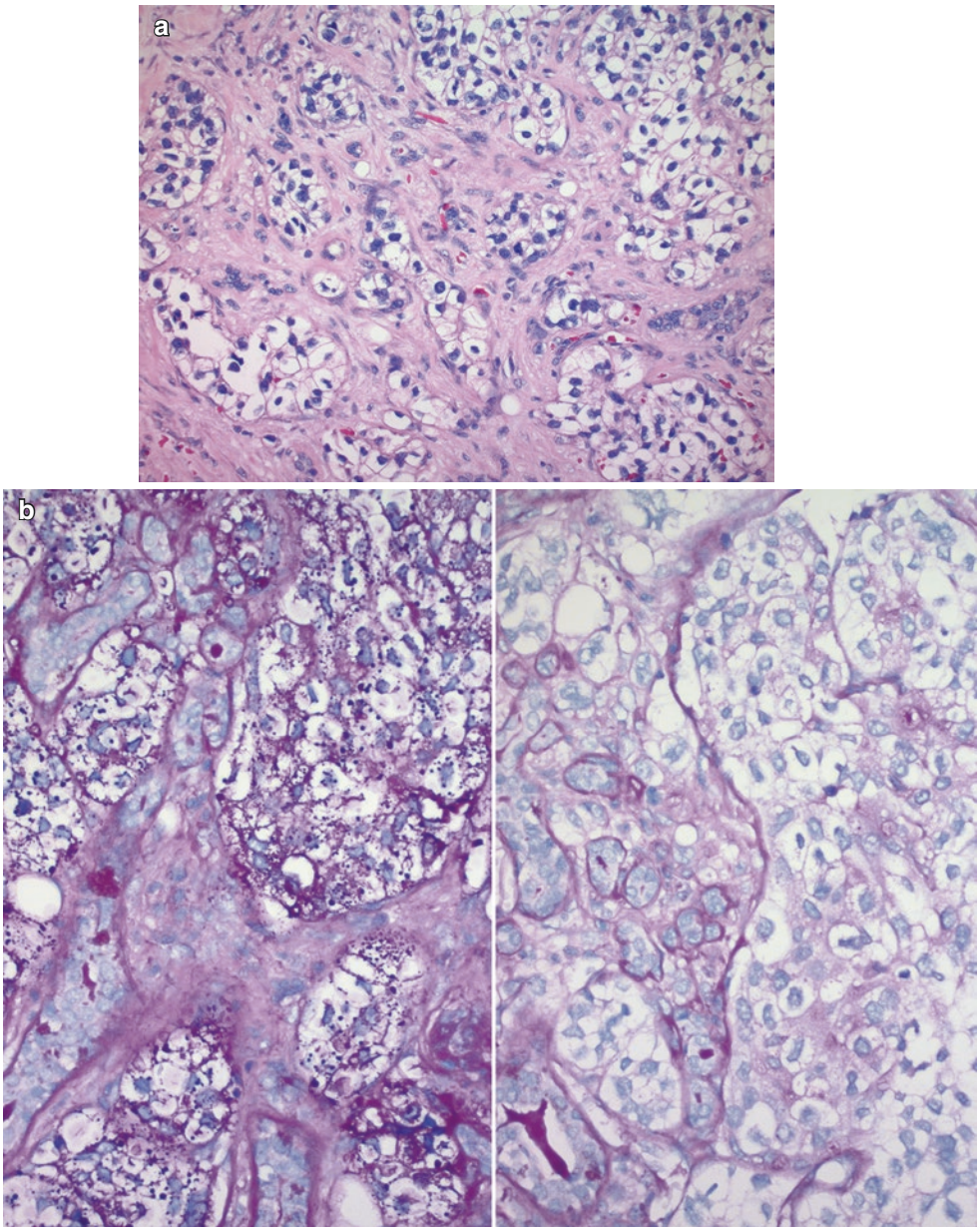

Fig. 5.19 Clear cell carcinoma. (**a**) Infiltrative nests of polygonal cells with clear cytoplasm, distinct cell borders, and atypical nuclei in a fibrous stroma. (**b**) Intracytoplasmic glycogen is (left) PAS-positive and (right) diastase sensitive

- Regardless of gender, SDC expresses androgen receptors (AR), a marker of apocrine change. Williams et al. contend that AR-negative SDC is sufficiently rare enough to question the diagnosis.
- SDC has a poor prognosis with high rates of lymph node metastasis (50–70%), distant metastases (50%), and local recurrences (40–50%). Five-year survival ranges from 23% to 64%.

Intraductal carcinoma (IDC) is an in situ, ductal proliferation that resembles atypical ductal hyperplasia or low-grade ductal carcinoma in situ of the breast. IDC is rare, shows a slight female predominance, and overwhelmingly occurs in the parotid gland.

- IDC is predominantly cystic with round smooth contours and a micropapillary, solid, or cribriform architecture. The cribriform lesions can show irregular or slit-like spaces with larger cells at the periphery and small, dark cells crowded toward the lumen center.
- The cells have a moderate to abundant amount of eosinophilic cytoplasm that may have vacuoles, apical snouts, or PASD-positive globules. The nuclei are bland with a finely dispersed chromatin and variable nucleolar prominence.
- The sine qua non of the diagnosis is the demonstration of a myoepithelial layer surrounding the cysts and ducts.

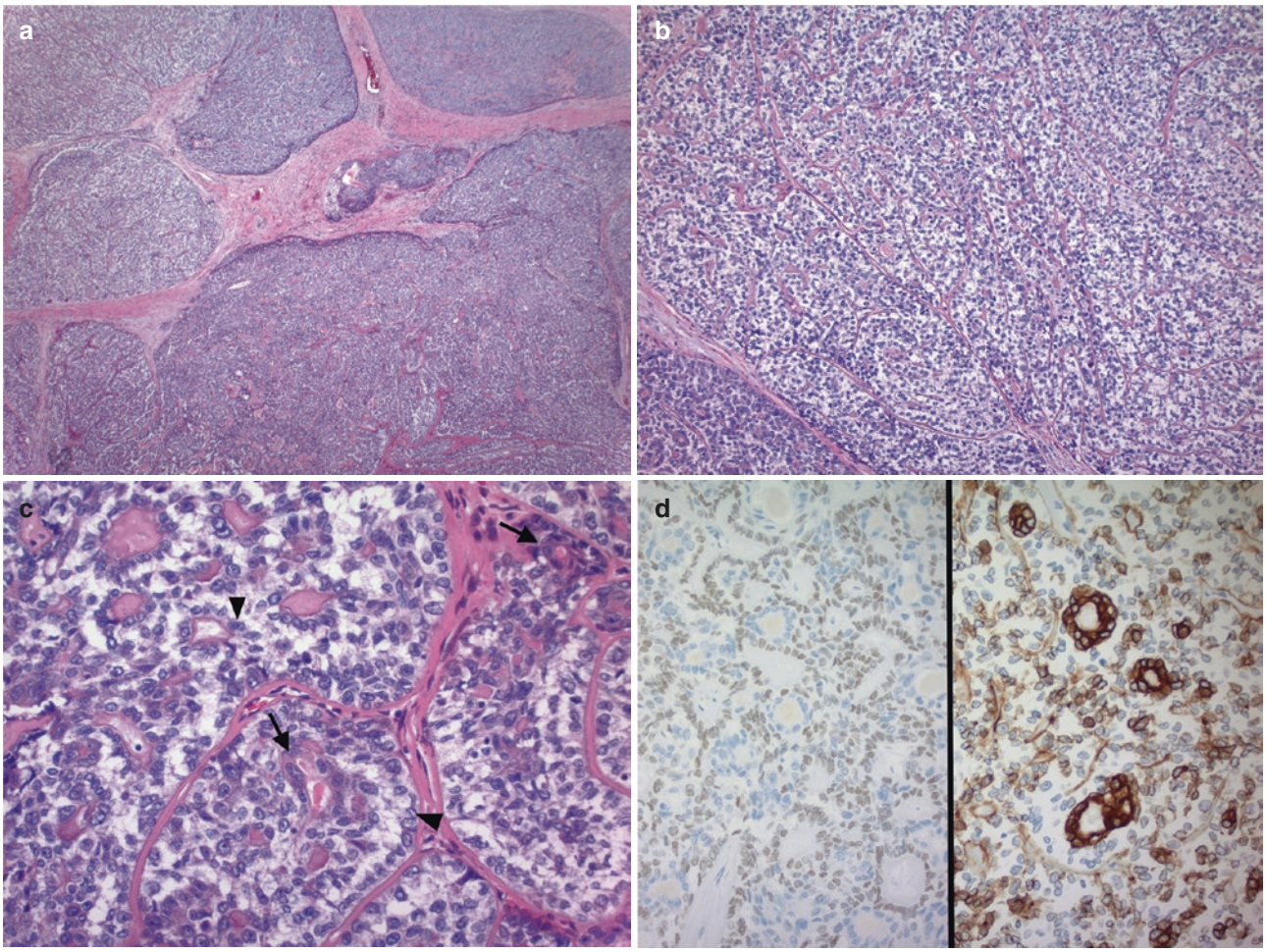

Fig. 5.20 Epithelial-myoepithelial carcinoma. (**a**) Large, irregular tumor lobules in a fibrous stroma. (**b**) Areas of clear cell change separated by thin, fibrous bands. (**c**) Higher magnification shows a distinct two cell population of cuboidal, pink luminal cells (arrows) and clear, abluminal myoepithelial cells (arrowhead). (**d**) Immunohistochemistry for (left) p63 highlights myoepithelium and (right) pan-cytokeratin strongly stains ductal cells

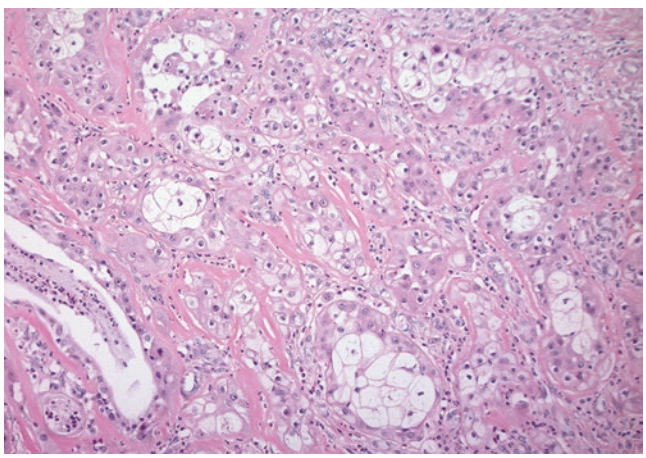

Fig. 5.21 Mucoepidermoid carcinoma. Clear cells can be seen but are usually not the predominant or only cell type

- Intermediate- and high-grade cytology occurs in 13–17% of cases. Tumors show increased mitotic activity and pleomorphism; rare foci of necrosis may be present.
- Foci of limited stromal invasion can be seen in 20–23% of cases. Even with this finding, IDC has an excellent prognosis.
  - Cases with limited invasion should be diagnosed as "IDC with focal invasion."
  - Thorough sampling should be done to assess the amount or presence of invasion.
- Rare local recurrences are attributed to incomplete excision, and no reports of distant metastases or death due to disease have been described. Table 5.10 compares SDC to low- and high-grade IDC.

References: [3, 99–108]

Table 5.9 Characteristics of clear cell carcinomas of salivary gland

	Clear cell carcinoma	Epithelial-myoepithelial carcinoma	Myoepithelial carcinoma	Oncocytic carcinoma	Mucoepidermoid carcinoma
Location	80% intraoral <10% in parotid	60% parotid Sinonasal > palate	80% parotid	70–80% parotid Rare in minor SG	Major and minor salivary gland
Ducts	None ±Entrapped ducts	Prominent	None	None, microcysts	Large ducts, cysts
Myoepithelium	None	Present	Present	None	None
Papillae	None	Present	None	None	Papillary infoldings
Morphology	Infiltrative Small nests, thin cords Polygonal cells Slightly irregular, eccentric nuclei	Circumscribed, encapsulated Large, solid nests	Multinodular, infiltrative Sheets of clear cells Raisinoid nuclei	Foci of classic oncocytes with granular, pink cytoplasm	Three cell types: squamous, intermediate, and mucous cells
Stroma	Hyaline, collagenous	Hyaline, not prominent	Hyaline, myxoid	Not prominent	Extravasated mucin
PNI	Frequent	Occasional	Occasional	Frequent	Rare
Necrosis	Rare	Not typical	Present	Occasional	Rare
Mitoses	Rare	Present, low	Present	Present	Rare
Positive stains	p63, CK7, 34βE12, CK14, PAS	M: p63, S100, calponin, SMA, PAS D: Cam5.2, AE1/3	p63, S100, calponin, vimentin, GFAP, PAS	PTAH, AMA, CK7, PAS±	p63 diffuse, strong CK7, PAS
Negative stains	S100, calponin, SMA, vimentin, GFAP, PASD	PASD	CK7, PASD	S100, calponin, SMA, PASD	PASD

SG salivary gland, *PNI* perineural invasion, *M* myoepithelium, *D* ducts, *PTAH* phosphotungstic acid hematoxylin

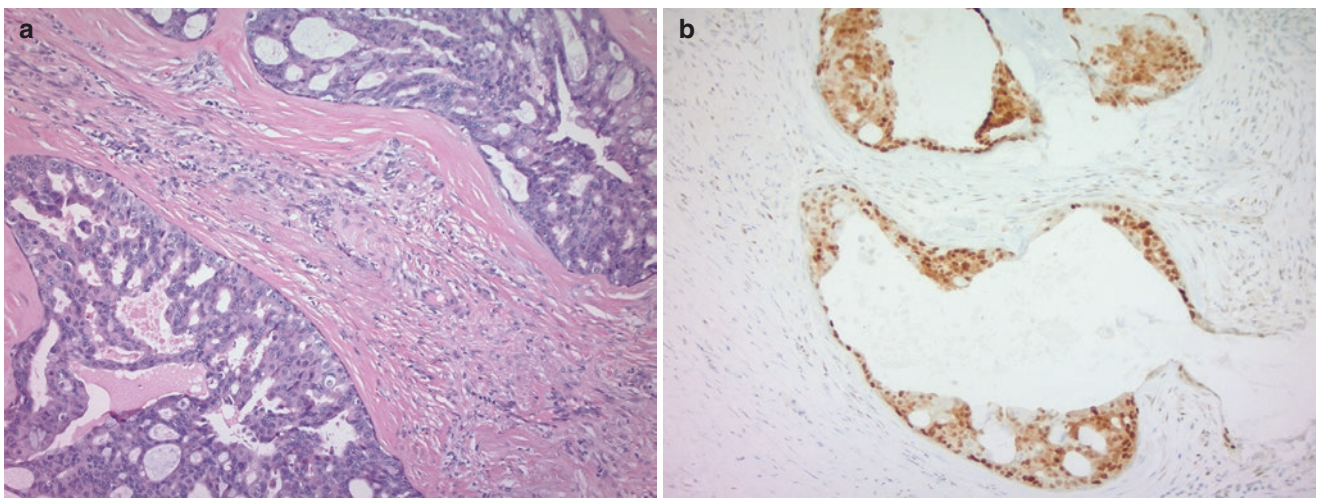

Fig. 5.22 Salivary duct carcinoma. (**a**) Cribriform, large ducts are (**b**) positive for androgen receptors

16. *Are there specific histologic features for the diagnosis of adenocarcinoma, not otherwise specified?*

By definition, adenocarcinoma, not otherwise specified (ACA, NOS) is a glandular carcinoma that does not meet histologic criteria for any other SG carcinoma; it is a diagnosis of exclusion. All cases show an infiltrative glandular or ductal proliferation; more specific histologic features are not established. Table 5.11 summarizes the clinicopathologic features of ACA, NOS.

- Tumors comprise cuboidal or columnar cells of different subtypes, including mucinous and oncocytic. The 2017 WHO classification includes mucinous and intestinal types of adenocarcinoma in the ACA, NOS category (see question 2).
- The growth patterns are numerous, including cribriform and solid architectures, papillae, nest, cords, and tubules.
- ACA, NOS are generally aggressive tumors, though low-grade tumors have a better prognosis.

Table 5.10 Histologic features of ductal carcinomas of salivary gland

	IDC, low-grade	IDC, high-grade	SDC
Myoepithelial layer	Present	Present	Absent
Invasion	None/focal	None/focal	Y, extensive
Micropapillary	Yes	Yes	Very rare
Cystic	Yes	Yes	Yes
Cytoplasmic lipofuscin	Present	Present	Absent
Necrosis	No	Focal	Yes, extensive
Cytology	Low-grade	High-grade	High-grade
Luminal spaces	Slit-like to round	Slit-like to round	Round, rigid
Mitotic activity	Rare	Scattered	Frequent
Androgen receptor IHC	Negative	Positive	Positive
S100 IHC	Positive, diffuse	Positive/focal positive	Negative
Her2/neu IHC	Variable	Variable/ negative	Positive

IDC intraductal carcinoma, *SDC* salivary duct carcinoma

Table 5.11 Clinicopathologic features of adenocarcinoma, NOS

Mean age, gender	60 years, M > F
Incidence of SG carcinoma	10–15%
Major SG	40–60% (submandibular gland <10%)
Minor SG	30–40% (palate, buccal)
5-year, 10-year overall survival	60%, 40%
High-grade: Low-grade	2–3:1

- High-grade tumors show frequent mitoses, pleomorphism, and necrosis.

References: [109–111]

17. *What is high-grade transformation, how is it different from dedifferentiation, and which salivary gland tumors can undergo such changes?*

Dedifferentiation of any tumor is characterized by the sharp demarcation of a well-differentiated tumor from a high-grade component that shows none of the histomorphologic features of the original. When salivary gland carcinomas undergo "dedifferentiation," the high-grade component is typically a poorly differentiated adenocarcinoma or an undifferentiated carcinoma. Because the high-grade component is recognized as being similar to the lower-grade component and there may be a transition from the low-grade area, the term dedifferentiation is not wholly accurate. In such a setting, high-grade transformation (i.e., from a low-grade adenocarcinoma to a higher-grade carcinoma) is the preferred term.

- Tumors with high-grade transformation (HGT) characteristically show:
  - Marked nuclear pleomorphism
  - High mitotic activity
  - Necrosis
- The percentage of tumor that is needed for the HGT designation has not been defined for any of the tumor types. Despite the lack of standardization, all reported cases, regardless of tumor type, are associated with clinical progression.
- Table 5.12 summarizes the features and diagnostic considerations of transformed SG carcinomas. HGT

Table 5.12 Features and staining of tumors with high-grade transformation

	HGT features	Comments	Stains
Acinic cell carcinoma	Solid nests Pleomorphic, vesicular nuclei Abundant cytoplasm Comedo necrosis	May resemble SDC Metastases will have LG and HG components LVI, PNI	(m)β-catenin+ AR–, Her2/neu–, p53–
Adenoid cystic carcinoma (AdCC)	Solid, irregular, confluent nests and large sheets Pleomorphic cells, large vesicular nuclei, prominent nucleoli Comedo necrosis, micropapillae Variable loss of myoepithelial differentiation Abrupt transition from LG component	In contrast, solid AdCC: admixed with tubular and cribriform types Slightly enlarged cells with angulated, dark nuclei Gradual transition from solid to tubular areas Metastases have HG component only	p53+ (50% of cells), Her2/neu+, CD117+ (LG, HG), MYB-NIFB+
Epithelial-myoepithelial carcinoma	Loss of biphasic pattern Gradual transition to myoepithelial anaplasia or abrupt transition to HGT Clear, spindle, and squamoid features	Abrupt and gradual HGT have same prognosis LN metastases, DM, death	Loss of myoepithelial markers
Polymorphous adenocarcinoma	Solid growth, pleomorphism, necrosis Loss of myoepithelial markers	Association with XRT History of multiple recurrences over long periods Disease progression, no reported DM or deaths	S100+ AR± Muscle markers–
Secretory carcinoma	Solid growth, pleomorphism, necrosis	LN metastases, DM, death	p53+ ETV6 rearrangements+

SDC salivary duct carcinoma, *LG* low-grade, *HG* high-grade, *LVI* lymphovascular invasion, *PNI* perineural invasion, *m* membranous, *AR* androgen receptors, *AdCC* adenoid cystic carcinoma, *LN* lymph node, *DM* distant metastases, *XRT* radiation therapy

is very rare, and most of the information is based on only a handful of reported cases for each tumor.

References: [54, 112–119]

18. *What are the principal papillary tumors of the salivary gland and their differential diagnosis?*

There are four main entities in the group of papillary tumors of the salivary gland: inverted ductal papillomas (InvDP), intraductal papillomas (IDP), sialadenoma papilliferum (SAP), and papillary cystadenoma lymphomatosum (Warthin tumor).

The ductal papillomas occur within the salivary duct system, at the intersection of the excretory duct and surface epithelium. So, their primary location is in the minor salivary glands. The lip, usually upper, is the most common site, followed by the buccal mucosa, palate, floor of mouth, and tongue. The ductal papillomas include inverted ductal papillomas (InvDP)and intraductal papillomas (IDP). Both are rare entities described in small series and case reports. Table 5.13 summarizes the different papillary lesions and the most common entities in the differential diagnosis.

- Inverted ductal papillomas (IDP) are well-circumscribed tumors with endophytic growth and pushing borders.
  - The junction of the tumor and the surface epithelium may show a dilated, pore-like orifice.
  - The papillae are broad and lined by basaloid cells that show epidermoid differentiation with squamous, transitional or mucous-type, columnar epithelium.
  - Mitoses are infrequent, and cellular atypia is minimal.
- Intraductal papillomas show an exophytic growth of complex, branching papillae that protrude into a well-circumscribed, unicystic cavity.
- Sialadenoma papilliferum extends from the mucosal surface and presents as a slow-growing, papillary, verrucoid mass:
  - Unencapsulated, biphasic tumor composed of complex papillae.
  - The base shows an endophytic proliferation of ducts with varying amounts of ectasia.
- Cystadenomas are a diagnostic consideration for IDP. Cystadenomas are typically well-circumscribed, multicystic tumors of major and minor salivary gland.
  - Thin, fibrous bands separate the cysts which are lined by an oncocytic, cuboidal to columnar epithelium; mucous and squamous cells may also be present.
  - Papillary growth may be focal or predominate.
- Warthin tumor (WT) is the second most common tumor of salivary gland, after pleomorphic adenoma. It occurs exclusively in the parotid gland and rarely in the peri-parotid lymph nodes. WT have a slight male predominance and may be multifocal and bilateral.
  - The tumor comprises papillae with fibrovascular cores containing a dense lymphoid stroma (Fig. 5.23).

Table 5.13 Differential diagnosis of papillary tumors of salivary gland

	Inverted ductal papilloma	Intraductal papilloma	Sialoadenoma papilliferum	Warthin tumor	Mucoepidermoid carcinoma	Cystadenoma
Site	Minor SG	Minor SG	Minor SG	Parotid ±multifocal, bilateral	Major and minor SG	Major and minor SG
Growth pattern	Endophytic	Exophytic	Exophytic, verrucoid	Exophytic	Multicystic, multinodular	Multiloculated cysts
Surface involvement	No, pore-like opening	No	Yes	No	No	No
Encapsulated	Yes	Yes	No	No, well-circumscribed	No, infiltrative	Yes
Papillae	Yes, broad, bulbous	Yes, delicate, complex	Yes, delicate	Yes, lymphoid stroma	No	Yes, focal or predominant
Cystic	Yes	Yes, unilocular	Yes, single cyst	Yes	Yes, multiple	Yes, multiloculated cyst
Cells	Basaloid cells with squamous, transitional or mucous differentiation	Cuboidal/ columnar ductal cells, ±Mucus cells	Stratified squamous-lined papillae Underlying ductal proliferation ±Associated chronic inflammation	Bi-layered oncocytes	Squamous, mucus, epidermoid	Oncocytic cuboidal/ columnar ±Squamous and mucous cells

  - A characteristic bilayer of inner columnar and outer cuboidal oncocytes lines the papillae which protrude into cystic spaces. The cells are cytologically bland and may show squamous, sebaceous, or mucous cell metaplasia.

References: [120–126]

19. *Does primary squamous cell carcinoma of salivary gland exist and how is it diagnosed?*

Primary squamous cell carcinoma (SCC) of the salivary gland is exceedingly rare and occurs in the parotid gland. Case reports involving the submandibular gland have been difficult to confirm. Many historical cases likely represent salivary duct carcinomas or metastatic squamous cell carcinomas from the skin. Most reports do not give detailed information about the clinicopathologic features, raising questions about the rigor of the diagnosis. It is essentially a diagnosis of exclusion; adherence to strict criteria is essential.

- Primary SCC of the parotid is thought to arise from squamous metaplasia involving Stensen's duct.
- One should suspect a primary SCC of the salivary gland in the following settings:
  - No history of previous skin carcinoma.
  - SCC is not solely confined to intraparotid lymph nodes.
  - Keratinization is present.
  - Other head and neck primary sites have been excluded.
  - History of radiation to the parotid.
  - Duct obstruction or elongated mass (i.e., growing along/in the main duct)
  - The presence of squamous dysplasia or arising from a large duct origin

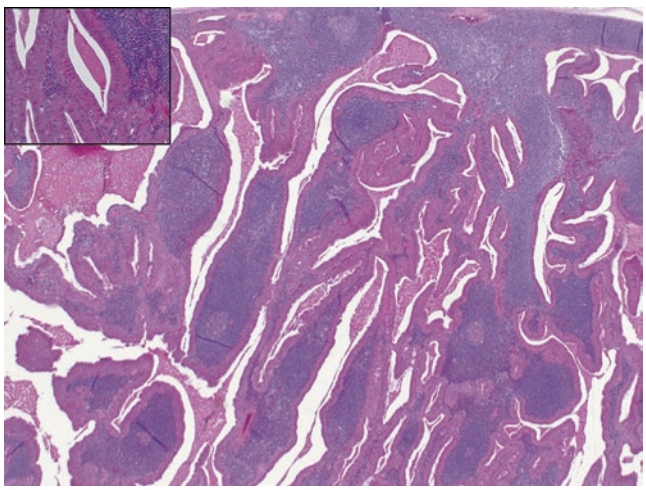

Fig. 5.23 Warthin tumor. A papillary and cystic neoplasm with a lymphoid stroma and eosinophilic cyst debris composed of (inset) a bilayer of oncocytic cells

- The handful of cases that are most plausible have a few features in common:
  - Patients are predominantly male, between 50 and 70 years old.
  - Variable smoking history.
  - Facial nerve paralysis and regional lymph node involvement at presentation.
- Other salivary gland carcinomas with squamous differentiation or metaplasia, especially those that may undergo high-grade transformation, must be excluded.
  - High-grade mucoepidermoid carcinoma (MEC) is a common mimic of SCC.
  - MEC should not show keratinization, and mucicarmine staining helps to identify mucous cells.

References: [127–130]

20. *What are the common metastases to salivary gland?*

Nonlymphoid metastases to the salivary glands account for about 15% of all malignant SG tumors. The majority of metastases to salivary gland are from the head and neck sites (80–90%), most commonly involve the parotid gland (90–95%), and are squamous cell carcinomas (40–60%).

- The most common metastases are listed in order of frequency:
  - Head and neck cutaneous squamous cell carcinoma (30–65%)

Table 5.14 Metastatic tumors to salivary gland and their differential diagnosis

Primary site	Secondary tumor	Primary SG tumor in differential diagnosis
Regional: Head and neck	Cutaneous SCC	HG mucoepidermoid carcinoma Salivary duct carcinoma Primary SCC
	Cutaneous melanoma	Myoepithelial carcinoma Undifferentiated carcinoma
	Mucosal SCC (larynx, pharynx)	Lymphoepithelial carcinoma Large cell undifferentiated carcinoma
	Merkel cell carcinoma	Primary neuroendocrine carcinoma
Distant: Infraclavicular	Lung	Adenocarcinoma, NOS Large cell undifferentiated carcinoma Primary neuroendocrine carcinoma
	Breast	Salivary duct carcinoma Secretory carcinoma Adenocarcinoma, NOS
	Kidney	Clear cell carcinoma Oncocytoma/oncocytic carcinoma

  - Head and neck cutaneous melanomas (20–30%)
  - Infraclavicular sites (10–15%)
- Metastases to intra- and peri-parotid lymph nodes occur via lymphatic spread.
- Metastases to submandibular gland are typically intraparenchymal and spread hematogenously.
- The most common distant sites are the lung, breast, and kidney, accounting for over 90% of distant secondary tumors.
  - Melanomas and tumors from distant sites are more likely to present as occult primaries.
  - Latency periods of up to several years may exist between initial diagnosis and the SG metastases.
- Primary SG tumors must be excluded with a thorough clinical history and examination. Ancillary studies can aid in this distinction, but there is some overlap in the immunoprofile and histomorphology of primary and secondary tumors (Table 5.14).

References: [131–138]

21. *Which primary tumors of salivary gland are identical to their counterparts at other sites?*

Some rare primary salivary gland carcinomas exist which are best known as primary tumors at other anatomic sites (e.g., small cell lung carcinoma). Due to their rarity in SG, all of these tumors should be distinguished from metastases, and this is best done by relying on clinical history. Primary SG lymphoepithelial carcinoma, squamous cell carcinoma, and sebaceous carcinoma are histomorphologically indistinguishable from their counterparts in other locations (Table 5.15).

- SG is the second most common site (after larynx) for neuroendocrine tumors of the head and neck.
- Under the current 4th edition of the WHO, poorly differentiated NEC and undifferentiated carcinomas all fall under the moniker of poorly differentiated carcinoma, *regardless* of NE marker expression:
  - Poorly differentiated NEC is divided into small cell and large cell types:
- The most common subtype in the SG is the small cell type.
- Behavior does not appear to differ much between the small and large cell NEC, though the number of cases are limited.
- PD NEC of salivary gland may stain for CK20, and this helps to distinguish it from primary lung tumors.
  - Undifferentiated carcinomas are composed of large cells that show no light microscopic evidence of glandular or squamous differentiation:
- Some are known to have ultrastructural evidence of neuroendocrine differentiation but don't usually demonstrate such features by immunohistochemistry.

References: [139–143]

Table 5.15 Primary carcinomas of salivary gland with identical counterparts from other locations

	Primary salivary gland tumor		Differential diagnosis	
Poorly differentiated carcinoma (WHO 4th ed.)	Small cell NEC	CK20±, CK7∓, TTF1∓	Small cell carcinoma of lung	TTF-1+ CK7∓ CK20–
	Large cell NEC	CK20±, CK7∓, TTF1∓	Merkel cell carcinoma	CK20+ CK7–
			Large cell NEC of lung	TTF-1+ CK20–
	Undifferentiated carcinoma		Sinonasal undifferentiated carcinoma Nasopharyngeal carcinoma	
Others	Lymphoepithelial carcinoma		Sinonasal undifferentiated carcinoma Nasopharyngeal carcinoma	
	Squamous cell carcinoma		Lung, mucosal HN, and skin SCC	
	Sebaceous carcinoma		Sebaceous carcinoma, skin	

NEC neuroendocrine carcinoma, *HN* head and neck, *SmCC* small cell carcinoma

22. *Which clinicopathologic features predict behavior in salivary gland carcinomas and how does tumor type relate to behavior?*

Factors effecting clinical behavior and prognosis in SG carcinomas are similar to other carcinomas. Table 5.16 lists the clinical and pathologic factors that predict survival in SG carcinomas.

  - As discussed earlier, tumor grade correlates with survival. But only a handful of SG carcinomas are routinely graded and include:
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Adenocarcinoma, NOS
  - For the remainder of SG carcinomas, specific tumor types have an implied histologic grade. But unlike grade, tumor type inconsistently correlates with survival.
  - The relationship between grade, histologic type, and behavior among the more common SG carcinomas is summarized in Table 5.17.
- Broadly, low- to intermediate-risk and high-risk tumors have a 5-year survival of ≥80% and ≤50%, respectively.
- The aggressive local behavior of adenoid cystic carcinoma, regardless of grade, is considered high risk.

References: [38, 144–149]

Table 5.16 Factors impacting survival in salivary gland carcinomas

Clinical	Pathologic
Stage Nodal status Symptoms of nerve involvement Age	Grade Perineural invasion Margin status

Table 5.17 Clinical behavior of salivary gland carcinomas by histologic type

Low/intermediate-risk	High-risk
Low-grade mucoepidermoid carcinoma Low-grade adenocarcinoma, NOS Carcinoma ex pleomorphic adenoma[a] Low-grade salivary duct (intraductal) carcinoma Acinic cell carcinoma Epithelial-myoepithelial carcinoma Myoepithelial carcinoma Basal cell adenocarcinoma Secretory carcinoma Cystadenocarcinoma Clear cell carcinoma Polymorphous (low-grade) adenocarcinoma	High-grade mucoepidermoid carcinoma High-grade adenocarcinoma, NOS Carcinoma ex pleomorphic adenoma[a] Salivary duct carcinoma Adenoid cystic carcinoma Small cell carcinoma Squamous cell carcinoma Sebaceous carcinoma

[a]Depends on amount of capsular invasion

23. *What is the distribution of salivary gland tumors in the minor salivary glands?*

Diagnosing minor SG tumors is a particular challenge because the readily accessible location encourages acquisition of small biopsies which create diagnostic difficulties. Knowing the frequency of tumors by site (Table 5.18) and other clinicopathologic features can be helpful.

- The common biphasic tumors of minor SG were discussed earlier (see Table 5.5).
- The squamoid lesions of minor SG are compared in Table 5.19.
- Common among most minor SG tumors:
  - Unencapsulated.
  - Mucosal involvement does not equate with malignancy.
- A few clinical correlates are worth noting:
  - There is at least a slight female predominance for minor SG tumors in the United States, regardless of type or site.
  - Cystadenomas are the most common benign lower lip tumor.
  - The most common site for canalicular adenomas is the upper lip.
  - There is a higher risk of malignancy for any tumor occurring in minor SG when compared to major SG.
  - The percentage of benign versus malignant tumors in minor SG varies among authors.
- In the largest series, benign tumors are slightly more common in minor SG (51–61%).

Table 5.18 Most common findings in minor salivary gland tumors

	Most common	Second most common
Overall site (frequency)	Palate (55%)	Buccal (15%)
Site of benign tumors	Palate	Buccal
Site of malignant tumors	Palate	Buccal
Tumor (all)	Pleomorphic adenoma	Mucoepidermoid carcinoma
Benign tumor	Pleomorphic adenoma	Cystadenoma
Malignant tumor	Mucoepidermoid carcinoma	Polymorphous adenocarcinoma = adenoid cystic carcinoma

Table 5.19 Differential diagnosis of squamoid lesions of minor salivary gland

Lesion	Clinical	Morphology
Mucoepidermoid carcinoma	Painless, submucosal mass	Usually cystic in minor SG location Multiple layers of cells line cysts, plaque-like solid aggregates of intermediate, or squamous cells also line cystic spaces None/very rare keratinization Bland, minimal cytologic atypia
Mucocele	Trauma history, ±pain	Paucicellular, no epithelial lining Lower lip, not palate like other tumors Mixed inflammatory reaction "denuded" cyst, no epithelial lining Pushing borders
Squamous cell carcinoma	Mucosal lesion	In situ carcinoma or dysplasia Keratinizing, atypical cells Irregular infiltrative growth
Necrotizing sialometaplasia	Painful, short clinical course	Apparent infiltrative growth but organized, follows normal ductal-lobular distribution "Infiltrative nests" appear rounded, not irregular Ulcerative or necrotic salivary tissue

- On average, benign and malignant tumors represent approximately 55% and 45% of minor SG tumors, respectively.

References: [150–155]

24. *What are the most common salivary gland tumors in children?*
    - There are some unique characteristics of salivary gland tumors in children when compared to adults. Table 5.20 highlights notable findings between the two groups.
    - Several authors eliminate vasoformative tumors (hemangiomas and lymphangiomas) from their study design, as many of these lesions will not undergo surgery. But when these lesions are taken into consideration, their incidence exceeds that of pleomorphic adenoma.

    References: [156–165]
25. *What are the most common benign (nonlymphoid) mesenchymal tumors of salivary gland and their characteristics?*
    - Lymphomas of salivary gland account for almost 8% of all SG tumors and will be addressed separately in Chap. 10. Here we discuss the common nonlymphoid mesenchymal tumors of SG.
    - Hemangiomas are by far the most common benign mesenchymal tumor of SG.
      - Hemangiomas occur in children and represent the most common salivary gland tumor in children under 1 year old.
      - The tumors comprise thin-walled, nonmuscular, vascular spaces lined by bland endothelial cells. Mitoses may be frequent, but atypia is absent.
      - Most lesions undergo involution by age 10, obviating the need for surgery.
    - Lipomas represent about 20% of benign mesenchymal tumors of SG. They occur primarily in the major SG of adults (>85% parotid) with an average age of 55 years and a male predominance.
      - Lipomas of SG are histologically identical to those of soft tissue, composed of encapsulated, mature fatty tissue. They should be devoid of salivary gland structures, except for rare residual acini or ducts at the tumor periphery.
      - Variants of lipomas (e.g., spindled lipoma, angiolipoma) are seen less commonly in SG but do occur. Table 5.21 lists the morphologic features which distinguish the benign lipomatous tumors.
      - Several SG tumors may show fatty metaplasia, most especially pleomorphic adenomas and myoepitheliomas.
    - Peripheral nerve sheath tumors (Table 5.22) are ranked among the top three benign mesenchymal lesions, after vascular and fatty tumors.
      - Schwannomas are more common than neurofibromas.
      - As much as 35% of neurofibromas in SG are associated with neurofibromatosis type 1.

    References: [6, 166–170]
26. *What are the most common primary malignant mesenchymal tumors of salivary gland?*
    - Primary sarcomas of the salivary gland are rare, representing approximately 0.5% of all salivary gland tumors and 2% of malignant salivary gland tumors.

Table 5.20 Comparison of salivary gland tumors in children and adults

Most common finding	Children	Adults
Age at diagnosis	Second decade	Fifth decade
Site of all tumors	Parotid 65% Minor SG 25%	Parotid
Minor SG site	Palate	Palate
Benign tumor	Hemangioma, lymphangioma	Pleomorphic adenoma
Benign epithelial tumor	Pleomorphic adenoma	Pleomorphic adenoma
Malignant tumor	Mucoepidermoid CA	Mucoepidermoid CA
Malignancy rate among SG tumors	30% for all tumors 50–60% for epithelial tumors	15–25%
Mesenchymal tumor	Hemangioma	Lipoma
Mesenchymal malignancy	Rhabdomyosarcoma	Variable[a]
Overall 5-year survival	95%	60%

[a]See question 27

Table 5.21 Clinicopathologic features of fatty tumors of salivary gland

	Lipoma	Sialolipoma	Lipoadenoma
Clinical	Adult, male	Adult, rarely children	Adult, rarely children
Site	Parotid	Parotid > oral > submandibular	Parotid > oral > submandibular
Encapsulated	Yes	Yes	Vaguely lobular
Fat predominates	Yes, mature fat only	Yes	No
Epithelium	None	Normal salivary elements evenly distributed in fat	Predominantly epithelium with interspersed fat Amount of fat varies widely
Sebaceous metaplasia	None	Frequent, associated periductal fibrosis, and chronic inflammation	Frequent, associated periductal fibrosis, and chronic inflammation
Oncocytes	Absent	Absent/rare	Present in oncocytic variant

Table 5.22 Comparison of schwannomas and neurofibromas

	Schwannoma	Neurofibroma
Clinical	NF type 2, bilateral Carney complex	NF type 1, multiple
Encapsulated	Yes	No, infiltrative
Nuclei	Short spindled nuclei	Short, spindled, wavy hyperchromatic
Morphology	Antoni A hypercellular areas Antoni B hypocellular, edematous, myxoid areas Verocay bodies – nuclear palisading around an eosinophilic center	Haphazardly arranged cells in an edematous stroma with scattered collagen bundles
Stroma	Collagenous, myxoid, cystic	Myxoid
Thick-walled vessels	Present	Absent
Atypia	Yes, degenerative	No/rare
Immunoprofile	Strong, diffuse S100 Strong, diffuse Sox-10	Weak, variable S100 and Sox-10

NF neurofibromatosis

- Approximately 80% occur in the parotid gland. There is male predominance, and the average age is 40 years old.
- Patients present with a painless mass that may show rapid growth and eventual tenderness.
- Luna et al. outlined four criteria used to classify a sarcoma as primary to salivary gland:
  1. The patient must not have a history of a similar sarcoma at any other site.
  2. Metastatic disease to the salivary gland must be excluded.
  3. Gross and microscopic examination must establish the salivary gland, and not adjacent soft tissues, as the primary site.
  4. Carcinosarcoma must be excluded.
- Cockerill et al. reported 17 primary sarcomas of salivary gland along with a literature review of an additional 170 cases. The most common tumor types (Table 5.23) are listed in order of frequency.
- Salivary gland sarcomas, as a group, carry a poor prognosis related to tumor size, type, and histologic grade. The behavior of individual tumor types, when compared to their soft tissue counterparts, is variable.
  - SG sarcomas have high rates of recurrence (30–35%), distant metastases (25–40%), and mortality (28–40%).
  - The lung is the most frequent metastatic site.
- An accurate diagnosis is critical, given the prognostic implications. Carcinosarcoma and myoepithelial carcinoma should be excluded.

References: [169, 171–176]

Table 5.23 Frequency of sarcomas in salivary gland

Sarcoma type	Number of cases
Rhabdomyosarcoma (all types)	33
Liposarcoma (all types)	19
Hemangiopericytoma/malignant SFT	18
Malignant peripheral nerve sheath tumor (all types)	17
Malignant fibrous histiocytoma	17
Angiosarcoma (including Kaposi's sarcoma $n = 2$)	15
Leiomyosarcoma	11
Synovial sarcoma	10

SFT solitary fibrous tumor, Based on findings from reference [171]

Table 5.24 Comparison of lymphoepithelial cysts relative to HIV status

	LE cysts (HIV-negative)	HIV-related LE cyst
Age, gender	50–70 years old, male	25–50 years old, male
Site	Parotid, unilateral	Parotid, bilateral
Clinical	Usually asymptomatic, occasionally painful	Lymphadenopathy, LE cyst may precede HIV diagnosis
Cyst type	Unilocular	Multilocular
Cyst lining	Stratified squamous	Stratified squamous
Cyst wall	Dense lymphoid tissue	Dense lymphoid tissue
Lymphoid tissue	Germinal center formation	Germinal centers with follicle lysis Irregular follicles, neutrophils, plasma cells, macrophages
LE lesions	Absent	Present

27. *What is the differential diagnosis of benign cystic lesions of the salivary gland?*

Lymphoepithelial (LE) cysts are squamous-lined lesions with an associated dense, lymphoid population. They occur almost exclusively in the parotid gland with rare cases reported in the floor of mouth. The demographics vary depending on the presence of HIV (human immunodeficiency virus) infection. Table 5.24 compares LE cysts in HIV-positive and HIV-negative patients. Surgical excision is the treatment of choice.

- The differential diagnosis of LE cyst includes a cystic metastatic squamous cell carcinoma to intra- or periparotid lymph nodes.
  - The more common metastatic squamous cell carcinoma to this area is from the skin, and it is typically not cystic.
  - The epithelium of LE cysts lacks the atypia and keratinization seen in squamous cell carcinoma.

The remaining, nonneoplastic cystic lesions are all related to duct obstruction or trauma. They typically

Table 5.25 Clinicopathologic features of common salivary gland cysts

	Mucocele	Mucus retention cyst	Salivary duct cyst
Age (years)	Younger than 30, children	Peak incidence 70, all ages	Older than 30, usually 50–80
Etiology	Trauma	Obstruction	Obstruction, mucus stasis
Site	Lower lip (80%), FOM, cheek	Major and minor SG	Parotid (80%), submandibular, FOM
Cyst lining	No epithelium lining	Attenuated duct lining	Attenuated or metaplastic duct lining
Cyst contents	Mucin, macrophages, and inflammation	Mucin	Mucin and mucus plugs are generally absent
Comments	Older lesions may show only granulation tissue, muciphages, and scant mucin	May be inflamed if duct wall is disrupted	Cyst wall may be inflamed or has salivary lobules Unilocular

FOM floor of mouth

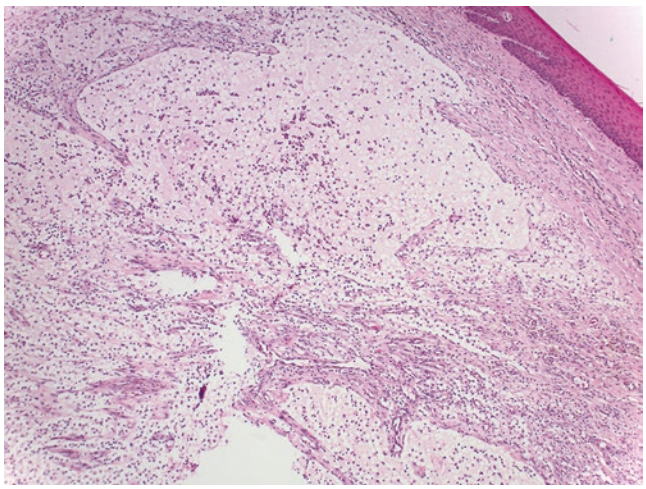

Fig. 5.24 Mucocele. The submucosa of the lower lip squamous epithelium contains a pseudocyst filled with proteinaceous fluid and inflammatory cells. A true epithelial lining is absent

present as a compressible, painless mass. Table 5.25 compares the primary nonneoplastic cysts of salivary gland.

- Mucoceles are the most common nonneoplastic lesion of the salivary gland. They lack epithelium and are, therefore, not true cysts (Fig. 5.24). They are essentially a cystic space created by extravasated mucin into the submucosa.
  - Large mucoceles of the floor of mouth are called ranulas.
- Mucus retention cysts and salivary duct cysts represent true cysts, lined by an attenuated or metaplastic epithelium.

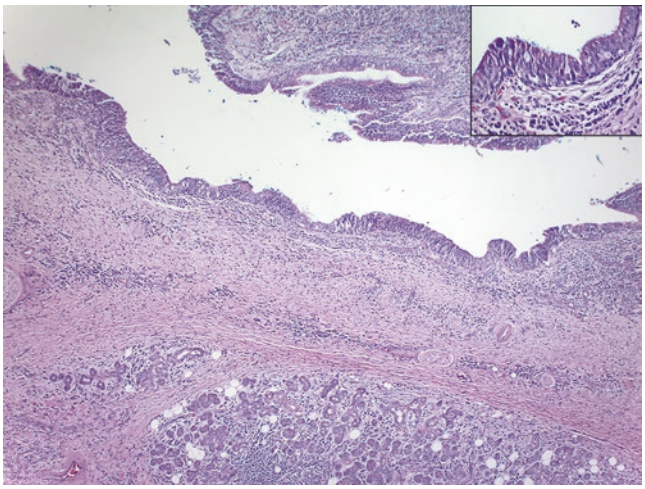

Fig. 5.25 Salivary duct cyst. Chronic sialadenitis with salivary duct cyst lined by (inset) ductal epithelium with focal goblet cell metaplasia

  - The pathogenesis is related to intermittent, partial duct obstruction or mucus stasis with subsequent dilatation.
  - Salivary duct cysts (Fig. 5.25) may show oncocytic, squamous, or mucinous metaplasia raising concern for mucoepidermoid carcinoma or cystadenoma.
    - Unlike MEC, the cyst is generally unilocular and the lining is typically attenuated or lined by a single-cell layer.
    - Cystadenomas are typically multicystic.

References: [1, 177–181]

28. *What are the major inflammatory lesions of the salivary gland?*
    - Lymphoepithelial sialadenitis (LESA) is characterized by an extensive lymphoid infiltrate primarily involving the parotid gland. Bilateral disease and isolated submandibular disease are very uncommon.
      - LESA has a strong female predilection and is associated with, but not exclusive to Sjögren syndrome.
      - A diagnosis of Sjögren syndrome requires confirmation of various clinical and laboratory findings. Focal lymphocytic sialadenitis is usually diagnosed on a labial biopsy and requires one or more aggregates of ≥50 lymphocytes with minimal plasma cells (focus score ≥1).
      - The hallmark of LESA is the lymphoepithelial lesion: proliferative, slightly spindled duct epithelium infiltrated by slightly enlarged lymphocytes.
      - Extranodal marginal zone B-cell lymphoma of SGs is typically preceded by LESA.
    - Chronic sclerosing sialadenitis (CSS, Kuttner tumor) is an inflammatory process that most commonly affects the submandibular gland.

Table 5.26 Clinicopathologic features of inflammatory lesions of salivary gland

	Chronic sclerosing sialadenitis	Obstructive chronic sialadenitis	LESA	Necrotizing sialometaplasia
Age (years), sex	50–60, M	50, M	40–50, F	40–60, M
Site Bilaterality	Submandibular 25%	Submandibular No	Parotid Yes	Palate, minor SG No
Clinical presentation	Mass, painless	Intermittent, prandial pain, swelling	Dry mouth, pain, swelling	Pain, swelling, mucosal ulceration
Follicular HP/Florid follicular HP	Yes/Yes	Yes/No	Yes/Yes	No/No
Cellular fibrosis with inflammation	Yes, storiform	No	No	No
Sheets of plasma cells	Yes	Rare	Rare	No
Other inflammation	Eosinophils	Neutrophils, granulomatous	No	Neutrophils, necrosis
Obliterative phlebitis	Yes	No	No	No
Lymphoepithelial lesions	Rare	No	Yes	No
Dilated ducts, periductal inflammation	Focal	Yes	No Duct proliferation	No Extensive squamous metaplasia
IgG4 plasma cells per hpf (percent of total IgG)	100–200 (70%)	10–20 (<5%)	1–20 (<5%)	None
Clinical associations	Other organ involvement Allergic disorders	Sialoliths	Sjögren syndrome MALT lymphoma	Trauma, ischemia Bulimia
Other findings	Elevated serum IgG4	Rule out infection in granulomatous cases	Anti-Ro/SSA, anti-La/SSB antibodies Labial biopsy with focus score ≥1	Overlying pseudoepitheliomatous hyperplasia Extensive squamous metaplasia

LESA lymphoepithelial sialadenitis, *HP* hyperplasia, *hpf* high-power field

  - Recent studies show that most cases of CSS are a manifestation of IgG4-related diseases, an inflammatory disorder resulting in tumor-like, fibroinflammatory lesions in multiple organs (e.g., pancreas, SG, orbit, kidneys, lung).
  - CSS-/IgG4-related sialadenitis must be clinically distinguished from obstructive chronic sialadenitis given the far-reaching clinical implications and its therapeutic response to corticosteroids.
- A subset of cases previously labeled as CSS is best classified as an obstructive chronic sialadenitis and is likely related to sialolithiasis. Table 5.26 highlights the salient features of the different types of sialadenitis.

References: [182–188]

29. *What are the common lymphomas of salivary gland?*

Lymphomas of salivary gland account for almost 8% of all salivary gland tumors. Here we highlight salient features of hematolymphoid lesions in the SG, but the reader is referred to Chap. 10 for a more detailed discussion.

- Salivary gland accounts for 5% of all extranodal lymphomas.
- Eighty percent of SG lymphomas occur in the parotid.
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is the most common lymphoma of salivary gland, followed by follicular lymphoma and diffuse large B-cell lymphoma.
  - Lymphoepithelial sialadenitis (LESA) is a precursor of MALT and is associated with Sjögren syndrome (see question 28).
- A subset of follicular lymphomas occur primarily in intraparotid LNs and is, therefore, not always of an extranodal origin.

References: [189–194]

30. *Which nonneoplastic lesion of salivary gland may represent a premalignant process?*

Sclerosing polycystic adenosis (SPA) is a rare fibroproliferative lesion of SG with only a handful of cases reported in the literature. It occurs predominantly in the parotid gland with a wide age range. Average age at presentation is in the fourth decade, and there is a slight female predominance. Patients usually present with a painless, slow-growing mass and occasional minor nerve pain and tingling.

- SPA is well-circumscribed with a pseudocapsule; prominent, cystically dilated ducts in a dense, scle-

rotic stroma; and variable amounts of chronic inflammation.
- Cystic spaces are lined by apocrine, clear, or oncocytic-like cells. Attenuated or denuded epithelium is replaced by foamy histiocytes. Large, serous acinar cells with abundant eosinophilic cytoplasm and PAS-D-positive granules are distinctive. The granules may coalesce to form intracytoplasmic globules.
- The intraductal proliferations in SPA may be exuberant with cribriform architecture and atypia. An associated myoepithelial layer expresses p63 but may be negative for muscle markers.
- Atypical SPA is clonal and some regard it as neoplastic with a low malignant potential.
  - High-grade atypia should be regarded as an intraductal carcinoma. The significance of mild to moderate cytologic atypia is unclear.
- Densely fibrotic areas may resemble radial scars of the breast and should not be mistaken for carcinoma. The normal lobular architecture should be maintained.
- Recurrence rates approach 20% and may occur over several years. A single report of an associated invasive carcinoma exists.

References: [195–202]

Case Presentations

Case 1

Learning Objectives

1. To become familiar with the morphologic features of a salivary gland adenocarcinoma
2. To develop a differential diagnosis for a parotid gland adenocarcinoma

Case History

A 68-year-old female presents with a firm, painless, preauricular mass.

Gross Findings

Poorly circumscribed 2.0 cm mass of the parotid gland with attached skin. The cut surface is solid, tan-white, and homogeneous. Extra-glandular extension is present into adjacent skin.

Histologic Findings (Fig. 5.26)

Large sheets and lobules of tumor are composed of back-to-back glands with foci of cribriform architecture. Tumor cells are columnar with oval nuclei, fine chromatin, and absent nucleoli. Focal single-cell necrosis is present, but geographic and comedo necroses are absent.

Differential Diagnosis

- Metastatic adenocarcinoma
- Adenocarcinoma, not otherwise specified
- Neuroendocrine carcinoma, large cell type
- Salivary duct carcinoma

IHC and Other Ancillary Studies (Not Shown)

- Positive: pan-cytokeratin, strong CK7, weak, focal CK20
- Negative: TTF-1, CDX2, synaptophysin, chromogranin, p63, CK5/6

Final Diagnosis *High-grade adenocarcinoma, not otherwise specified (NOS)*

Follow-Up 4 months later the patient had disease progression with lung and lymph node metastases while receiving chemotherapy.

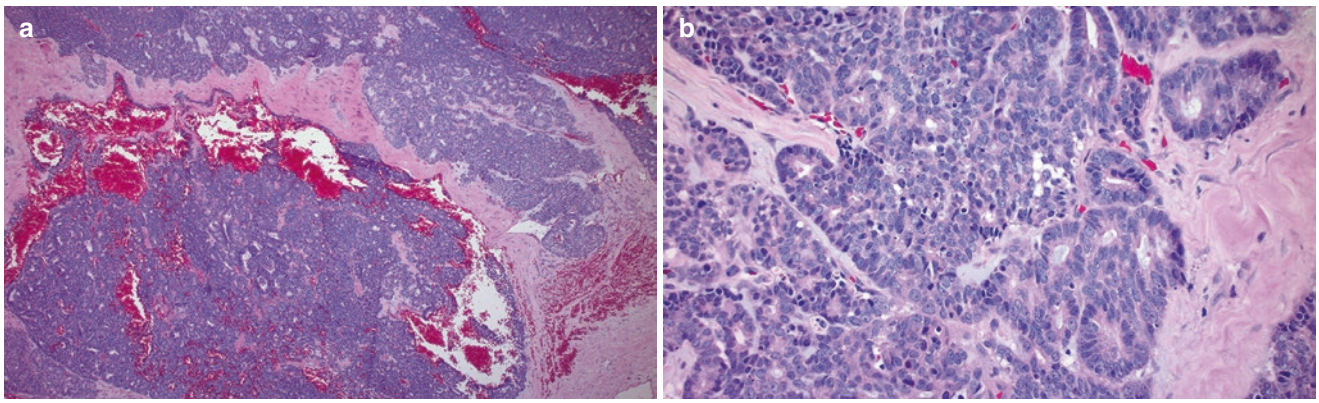

Fig. 5.26 Adenocarcinoma, NOS. (**a**) Infiltrative lobules of tumor (**b**) are composed of complex glands with cigar-shaped nuclei, luminal mucin, and single-cell necrosis

Take-Home Messages

1. Adenocarcinoma, NOS must demonstrate glandular or duct differentiation. By definition, it cannot meet criteria for the diagnosis of any named carcinoma of salivary gland. It is a diagnosis of exclusion. Metastases from other sites should be excluded clinically and by immunohistochemistry.
2. Intestinal-type of adenocarcinoma, NOS has a similar appearance to this case and may express CK20 or CDX2. A primary gastrointestinal carcinoma should be excluded clinically but is highly unlikely to present as an unknown primary with parotid metastasis and strong CK7 expression.
3. Large cell neuroendocrine carcinoma will not show such clear glandular differentiation. Salivary duct carcinoma has a high nuclear grade, more cribriform structures, and comedo necrosis.

References: [109, 110, 203]

Case 2

Learning Objectives

1. To generate a differential diagnosis of squamous malignancies of the parotid
2. To become familiar with the grading of salivary gland carcinomas

Case History

A 58-year-old female presents with a firm, painless, posterior auricular mass.

Gross Findings

A 1.8 cm solid, tan-white circumscribed, but invasive mass in the parotid gland. Areas of necrosis are identified on sectioning. Cysts are not present.

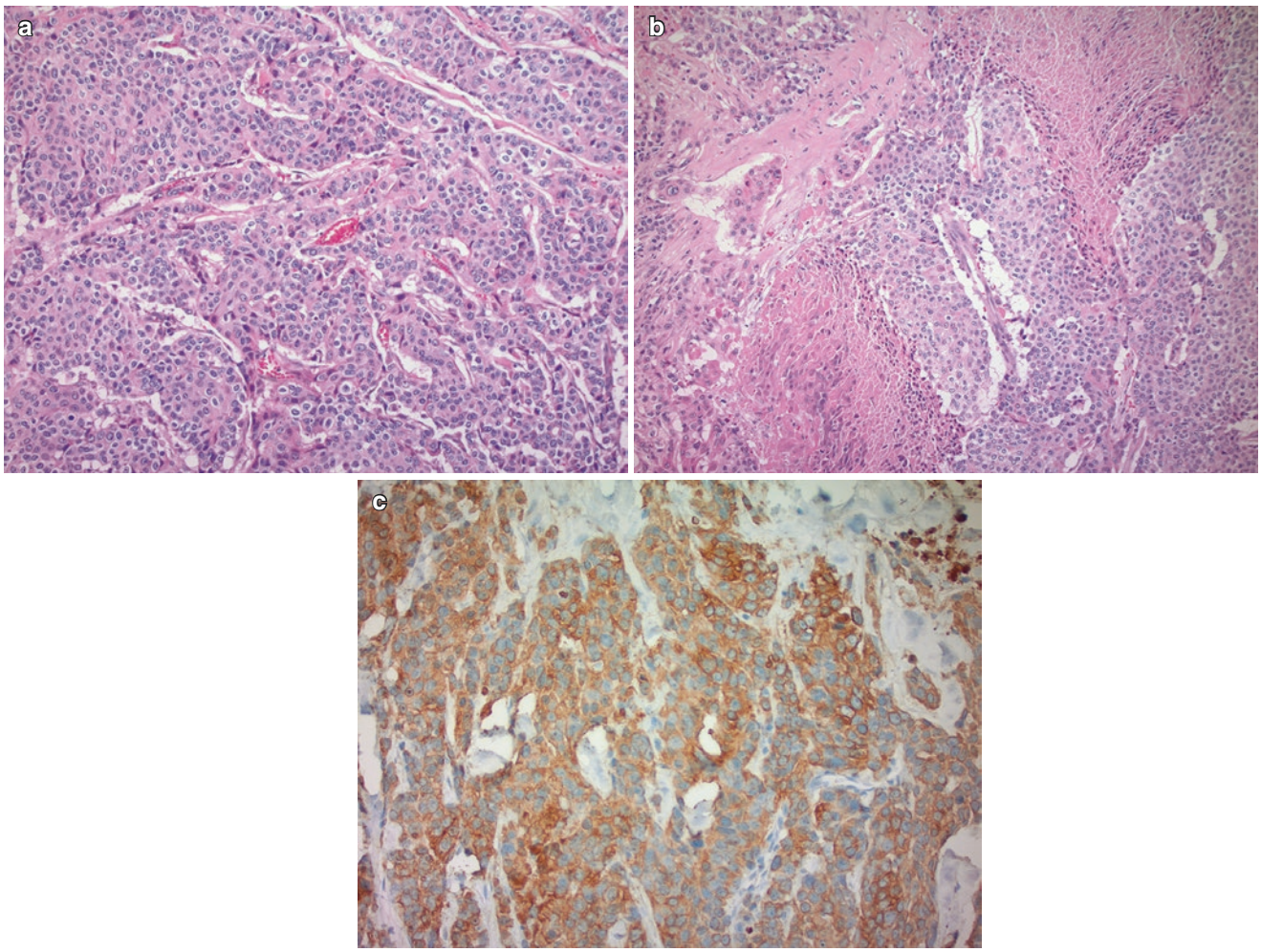

Fig. 5.27 Mucoepidermoid carcinoma, high-grade. (**a**) Solid nodules of intermediate cells with (**b**) foci of infiltrative nests, extensive necrosis, and LVI (upper left). (**c**) Tumor cells are strongly positive for CK5/6

Histologic Findings (Fig. 5.27a, b)
Nodules of tumor cells with areas of necrosis and a rounded, infiltrative border. The tumor cells are relatively monotonous with mild to moderate nuclear atypia and a moderate amount of eosinophilic cytoplasm. Mucus cells are not identified. Foci of lymphovascular invasion (LVI) are present. Rare clear cells and squamous cells are seen. Perineural invasion (PNI) and extra-glandular extension are present (not shown). Three peri-parotid lymph nodes are positive for carcinoma.

Differential Diagnosis
- Squamous cell carcinoma
- Oncocytic carcinoma
- Mucoepidermoid carcinoma

IHC and Other Ancillary Studies
- Positive: CK5/6 (Fig. 5.27c), p63 strongly positive

Final Diagnosis *High-grade mucoepidermoid carcinoma*

Take-Home Messages
1. The three principal grading systems for mucoepidermoid carcinoma (MEC) all show correlation with patient outcomes. The most important features are solid growth, pleomorphism, necrosis, mitoses, and perineural invasion. This case is difficult to grade because, despite lymphovascular invasion (LVI) and extensive necrosis, the cytologic features are relatively bland (e.g., minimal pleomorphism and mitotic activity). Application of the three main grading systems for this MEC yielded the following results:
   (a) Modified Healy: high-grade (HG) – solid growth, lymphovascular invasion, PNI, soft tissue extension. Using a "best fit" approach, this tumor would qualify as high-grade despite the absence of pleomorphism and frequent mitoses.
   (b) Brandwein: 13 pts, HG: less than 25% cystic (2 pts), necrosis (3 pts), PNI (3 pts), lymphovascular invasion (3 pts), and infiltrative border (2 pts).
   (c) AFIP, 7 pts; HG, less than 20% cystic (2 pts); necrosis (3 pts); and PNI (2 pts).
2. The tumor shows a predominance of intermediate cells with scattered clear and squamous cells. This varied population helps to exclude oncocytic carcinoma
3. The absence of keratin and a known squamous cell carcinoma of a head and neck site make this diagnosis highly unlikely.

References: [32, 37, 38, 204]

Case 3

Learning Objective
1. To generate a differential diagnosis of squamous malignancies of the parotid

Case History
An 80-year-old male complains of a firm mass in the preauricular region. Physical exam reveals marked actinic changes of the skin on his face and head. He reports having several "small cancers burned off of his face" over the years.

Gross Findings
A large 2.6 cm, circumscribed mass is present in the parotid gland with two to three similar appearing, smaller masses in other areas of the gland. The largest is tan-white and firm and associated with a caseous, white material.

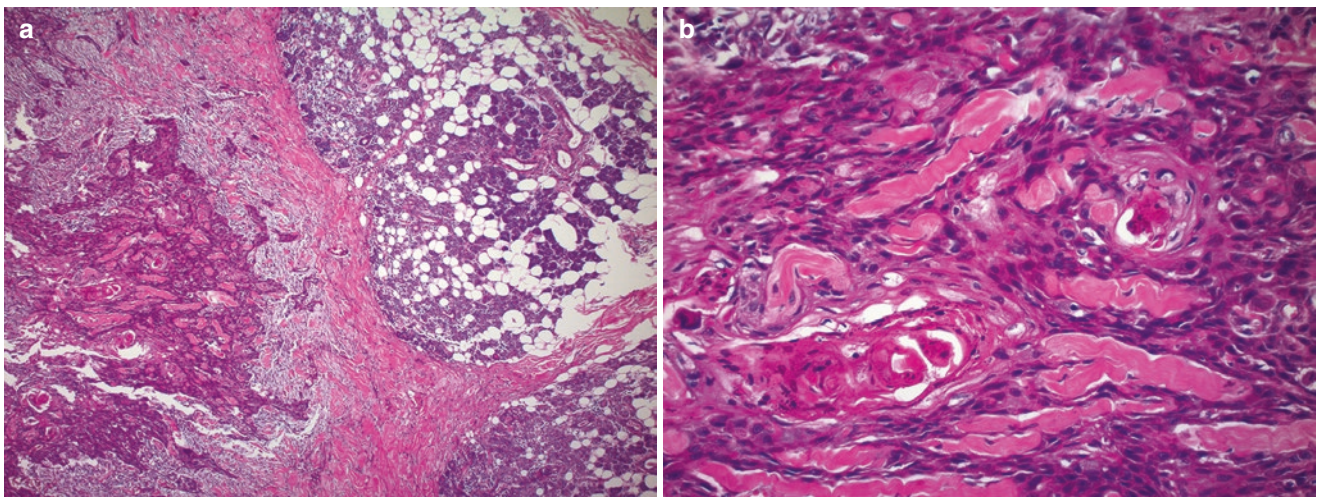

Fig. 5.28 Metastatic squamous cell carcinoma. (**a**) Infiltrative sheets of squamous cell carcinoma involving parotid gland parenchyma. (**b**) High magnification shows keratinizing tumor cells with keratin pearls

Histologic Findings (Fig. 5.28)
A circumscribed, partially encapsulated, but infiltrative mass is present. The tumor shows nests of polygonal cells with abundant eosinophilic cytoplasm, hyperchromatic nuclei with coarse chromatin, and occasional pleomorphism. Keratin pearls are easily identified. Additional intraparotid lymph nodes show similar tumor cells.

Differential Diagnosis
- Primary squamous cell carcinoma (SCC)
- Metastatic squamous cell carcinoma
- High-grade mucoepidermoid carcinoma

IHC and Other Ancillary Studies
None

Final Diagnosis *Metastatic squamous cell carcinoma of the skin*

Take-Home Messages
1. There are no markers to definitively distinguish the source of a squamous cell carcinoma, especially if it is a keratinizing carcinoma.
2. Squamous cell carcinoma of the major salivary gland should be considered a metastasis until proven otherwise. A primary SCC at this site is exceedingly rare and should adhere to specific criteria, previously discussed in question 19.
3. High-grade mucoepidermoid carcinomas are rarely keratinizing and should only be focal. This patient's history of multiple skin "cancers" and multiple intraparotid lymph node metastases supports a diagnosis of metastatic SCC from the skin. This is one of the most common metastases to the parotid gland.

References: [127, 129, 133, 205]

Case 4

Learning Objectives
1. To understand the criteria used to subclassify neuroendocrine carcinomas of the salivary gland (SG)
2. To develop a differential diagnosis for neuroendocrine carcinomas of SG

Case History
A 57-year-old male present with a mass at the angle of his mandible and cervical lymphadenopathy.

Gross Findings
A large, fleshy, necrotic tumor mass diffusely infiltrates the parotid parenchyma. Several peri-parotid lymph nodes also show tumor involvement.

Histologic Findings (Fig. 5.29a–c)
The tumor comprises large sheets of cells with extensive areas of necrosis. The cells are small to intermediate sized with scant to more appreciable, pale cytoplasm. The nuclei range from oval to slightly spindled with a fine, stippled chromatin, and an absence of nucleoli. There are frequent mitoses and single-cell necrosis. LVI and PNI are present (not shown).

Differential Diagnosis
- Metastatic small cell carcinoma
- Primary small cell carcinoma
- Large cell neuroendocrine carcinoma
- Metastatic Merkel cell carcinoma

IHC and Other Ancillary Studies (Fig. 5.29d–f)
- Positive: pan-cytokeratin (dot-like), CK5/6 (dot-like), synaptophysin, neuron-specific enolase (NSE)
- Negative: CK7, CK20, TTF-1, CD45
- Merkel cell oncoprotein serum antibody is negative

Final Diagnosis *Primary neuroendocrine carcinoma (NEC), small cell type (small cell carcinoma)*

Follow-Up A neck dissection was performed and yielded 6 positive lymph nodes out of 18 throughout levels 2 through 5.

Take-Home Messages
1. Primary small cell carcinomas, though well-defined, fall under the category of poorly differentiated carcinomas. This is primarily because they are all undifferentiated (e.g., no glandular or squamous differentiation) and may show variable or *no* neuroendocrine differentiation at all. The presence of two neuroendocrine markers, epithelial differentiation, and typical morphology support a diagnosis of small cell carcinoma.
2. NSE and CD56 alone are non-specific for neuroendocrine differentiation. The addition of synaptophysin or chromogranin expression is required for a diagnosis of NEC.
3. Small cell carcinomas can show a range of cell size. This patient's tumor has cells that are at the upper limit of size for small cell carcinomas (30 μ). Large cell NEC tends to have more pleomorphism; larger, polygonal cells; rosette formation with palisading; and prominent nucleoli. The distinction in head and neck sites does not appear to be clinically relevant as outcomes are equally dismal in both groups.
4. Merkel cell carcinomas are usually positive for CK20, but primary NEC of the parotid can also express CK20. Co-expression with CK7 and a negative CK20 excludes Merkel cell carcinoma. Salivary NECs may even express

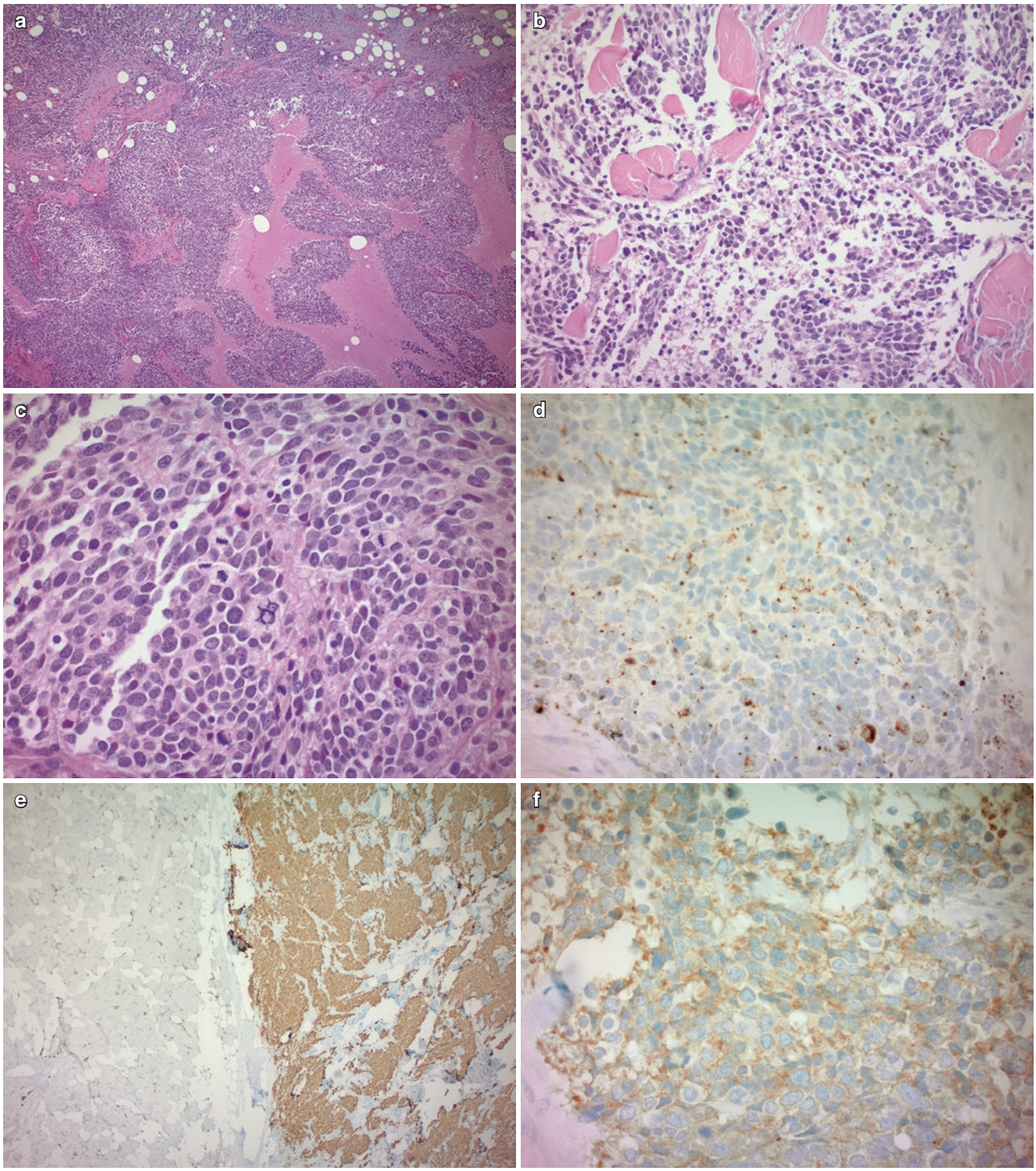

Fig. 5.29 Small cell carcinoma. (**a**) Large areas of necrosis alternate with ribbons of carcinoma. (**b**) The tumor cells show slight spindling and single-cell necrosis. (**c**) Tumor nuclei have a finely stippled chromatin and frequent mitoses. Cell size is at the upper limit for small cell carcinoma, but the absence of nucleoli and pleomorphism do not favor a large cell NEC. (**d**) Pan-cytokeratin shows a dot-like, cytoplasmic staining pattern. (**e**) CD56 is strongly positive. (**f**) Synaptophysin is diffusely positive with focal granular staining

TTF-1, so clinical history is essential in arriving at the correct diagnosis.

References: [139–143, 206–208]

Case 5

Learning Objectives

1. To understand the classification of poorly differentiated carcinomas of the salivary gland
2. To generate a differential diagnosis of poorly differentiated carcinomas

Case History

An 81-year-old female complains of a right cheek mass. CT scan shows a right cheek mass with duct dilatation and possible duct derivation versus involvement.

Gross Findings

A 1.7 cm firm, tan-gray tumor mass is present in the buccal submucosal. The tumor is infiltrative with a tan-white cut surface. The overlying mucosa shows no gross lesions. Chest and neck CT scans are negative for metastatic disease.

Histologic Findings (Fig. 5.30a, b)

The tumor is composed of sheets of small- to intermediate-sized cells with scant, pale cytoplasm. The cells are arranged in cords and trabeculae. Glands, tubules, ducts, and squamous features are not identified. The nuclei are round with prominent, central nucleoli. Mitotic activity is brisk. Perineural invasion is present. Necrosis is not identified.

Differential Diagnosis

- Primitive neuroectodermal tumor
- Undifferentiated carcinoma
- Lymphoma
- Melanoma

IHC and Other Ancillary Studies (Fig. 5.30c, d)

- Positive: pan-cytokeratin (strong), CK7, CD56 (weak, focal)

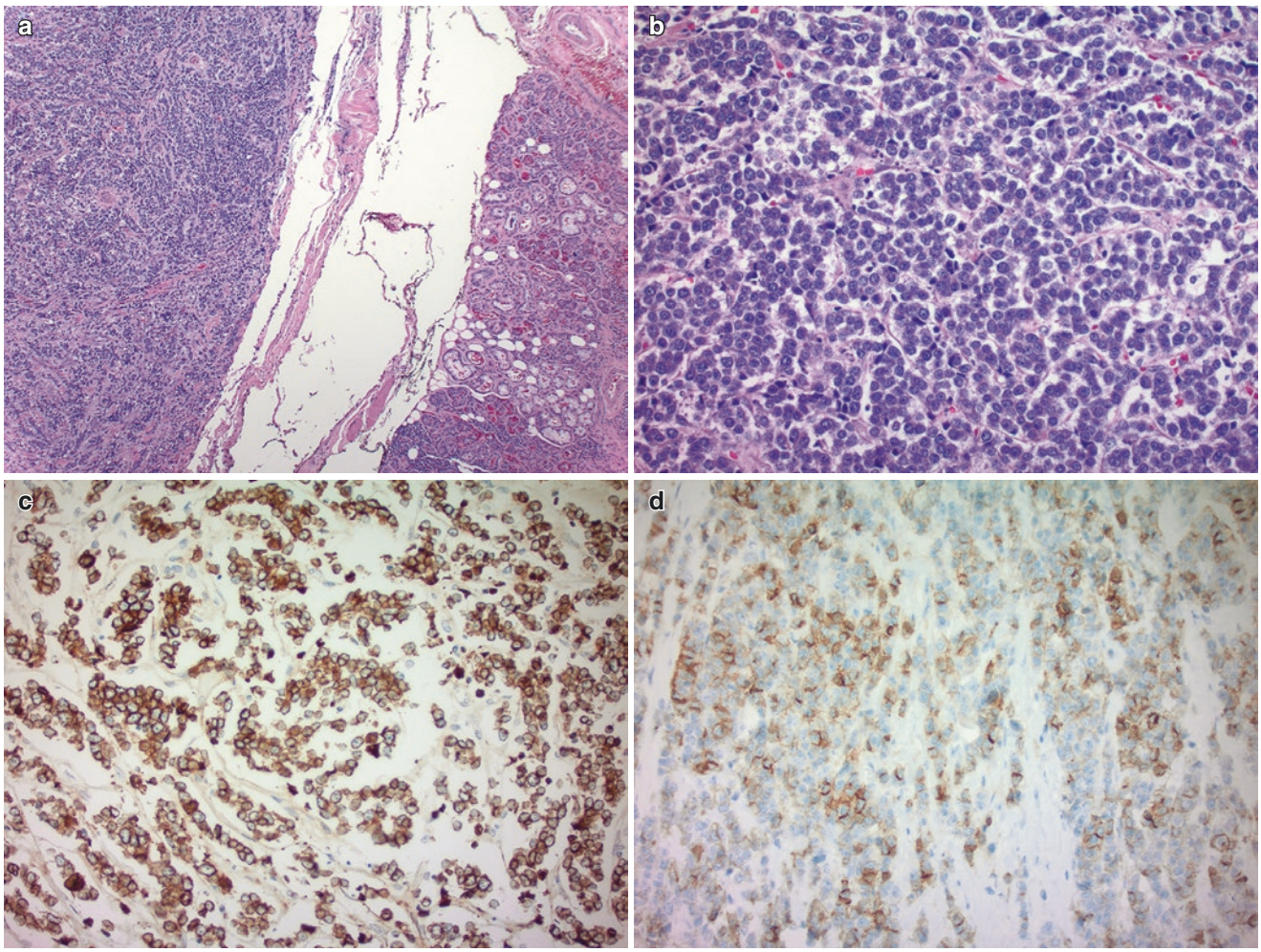

Fig. 5.30 Poorly differentiated carcinoma. (**a**) Sheets of tumor cells adjacent to minor salivary gland of the cheek. (**b**) The tumor shows a vaguely organoid pattern. The cells are small, with a high N-C ratio, scant pale to basophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Frequent mitoses and single-cell necrosis are present. (**c**) CK7 immunohistochemistry is strongly positive. (**d**) CD56 shows focal staining

- Negative: synaptophysin, chromogranin, androgen receptors

Final Diagnosis *Poorly differentiated carcinoma*

Follow-Up 5 months later, the patient presents with a new neck mass in level 2. PET (positron emission tomography) scan shows liver and bone metastases.

Take-Home Messages

1. According to the WHO classification, poorly differentiated carcinomas include undifferentiated carcinomas like this case. By definition, undifferentiated carcinomas show no evidence of squamous or glandular differentiation. They may or may not demonstrate neuroendocrine features. The CD56 expression and morphologic features of this case are not sufficient for a diagnosis of NEC.
2. Lymphoma and melanoma are easily excluded with IHC stains.
3. As with all the tumors in this category, metastatic carcinomas must be excluded.

References: [2, 209]

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