25 Salivary Gland

Background

With the exception of the pleomorphic adenoma, salivary gland neoplasms are rare, so you will not see many during residency training. To make matters worse, there is a great deal of morphologic overlap in some of the tumors, and immunostains are not usually helpful in distinguishing them. Your goal, early in your training, should be to recognize the more classic forms of the major tumors and also to be able to create a short differential diagnosis for any given tumor. In this organ, with all the mimics and variants, it is extremely important to approach a specimen with the question, "What *else* could this be?"

Biopsies of the salivary gland are occasionally performed in search of Sjögren's syndrome; this is a complex diagnosis with specific criteria that must be met (see your favorite pathology textbook for that). Inflammatory lesions can also create a mass, such as chronic sialadenitis or a lymphoepithelial cyst.

Anatomy

There are three major and innumerable minor pairs of salivary glands. The largest, on the cheek, is the parotid, where most neoplasms arise. The smaller major glands are the sublingual and submandibular, under the tongue and jaw. In general, the smaller the gland, the higher the proportion of its neoplasms that are malignant. Salivary neoplasms can arise in virtually any part of the sinonasopharyngeal system.

Normal Histology

The first major cell type is the *secretory cell*. The salivary glands are composed of serous and mucinous secretory units and ducts (Figure 25.1). *Serous* cells are wedge shaped (like pie slices) and arranged in acini around ducts. They are full of blue to purple granules. *Mucinous* cells have basal nuclei and apical mucin, like goblet cells; these are also arranged in acinar formations. The parotid is primarily serous, the submandibular is mixed, and the sublingual is primarily mucinous.

The second major cell type is the *duct cell*. The duct system has three types of ducts: the terminal, or intercalated ducts; the intermediate-sized striated ducts; and the interlobular large ducts. Each has a different epithelium and is theoretically associated with different tumor types. The *intercalated ducts* are small profiles with low cuboidal epithelium, similar to a bile ductule (Figure 25.2). *Striated ducts* are more proximal and are larger, with pink columnar

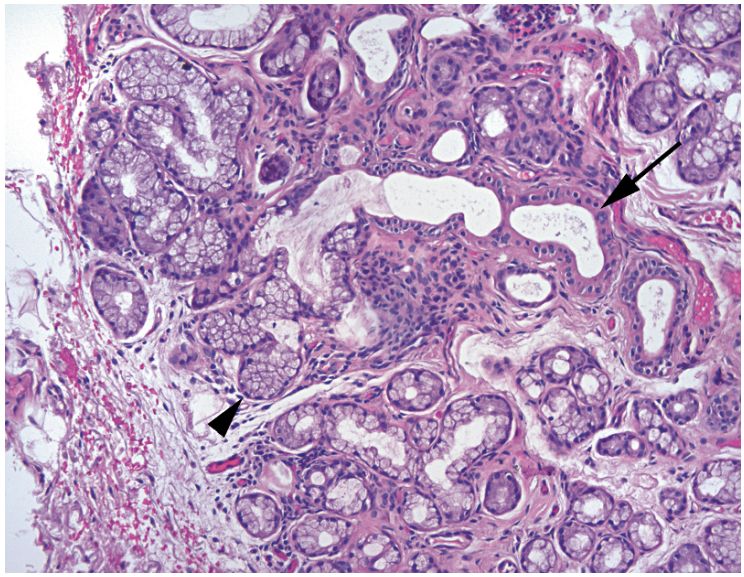

FIGURE 25.1. Normal salivary gland. In this example of mucinous salivary gland, the columnar secretory cells (arrowhead) form acini arranged around salivary ducts (arrow). Myoepithelial cells are not particularly visible on H&E stain.

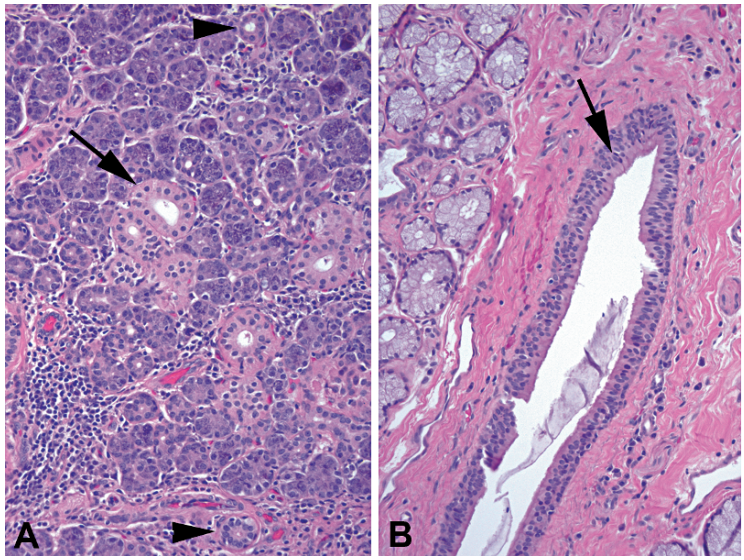

FIGURE 25.2. Types of ducts. **(A)** In the parotid, which has mainly serous glands, the terminal or intercalated ducts are visible as small tubules lined by cuboidal epithelium (arrowheads). The medium-sized striated ducts are more oncocytic in appearance, with abundant pink cytoplasm (arrow). **(B)** The large interlobular ducts have pseudostratified columnar epithelium (arrow), with occasional goblet cells, and become squamous at their junction with the gingival mucosa.

cells full of mitochondria and striated basal borders (hard to see). *Interlobular* or *excretory ducts* have pseudostratified columnar epithelium with or without goblet and squamous metaplasia. Different tumors have some morphologic similarity to these different ducts, which may help you keep all of the neoplasms straight.

The third cell major cell type is the *myoepithelial cell*. These cells, as in breast, surround acini and ducts. They are normally pale stellate cells with small nuclei and are very hard to identify in normal salivary gland. However, many neoplasms arise from the epithelial -myoepithelial

Table 25.1. Basic categories of the nine most common neoplasms.

	Probable cells of origin
Benign adenomas	
Pleomorphic adenoma (mixed tumor) and its end-of-the-spectrum variant, myoepithelioma	Epithelial–myoepithelial
Basal cell adenoma	Epithelial–myoepithelial
Warthin's tumor and oncocytoma	Striated duct cells
Low-grade malignant	
Mucoepidermoid carcinoma (low grade)	Interlobular duct cells
Polymorphous low-grade adenocarcinoma	Epithelial–myoepithelial
Acinic cell carcinoma	Serous acinar cells
Intermediate- to high-grade malignant	
Mucoepidermoid carcinoma (intermediate to high grade)	Interlobular duct cells
Adenoid cystic carcinoma	Epithelial–myoepithelial
Adenocarcinoma not otherwise specified (wastebasket of those adenocarcinomas that do not show specific differentiation)	Ducts

cell line or, more specifically, from cells that can differentiate into either line. This creates a diagnostic nightmare, because the myoepithelial cells alone can take four different forms: *spindled, plasmacytoid, epithelioid*, or *clear*. Therefore, you must recognize any of these variants as myoepithelial (their immunologic profiles change with their form, unfortunately) and lump some very different-looking tumors into the same basket. Table 25.1 lists the most common neoplasms.

Note that, in general, benign lesions are encapsulated, whereas malignant tumors are infiltrative, either as pushing fronts or as tendrils of cells (although mucoepidermoid carcinoma and acinic cell carcinoma can be deceptively well circumscribed). The first thing you should do when evaluating a salivary neoplasm is to study the periphery or capsule.

Neoplasms

This section describes the common neoplasms in order of how likely you are to see them, beginning with the most common.

Pleomorphic Adenoma (Benign Mixed Tumor)

Pleomorphic adenoma is a biphasic tumor with epithelial and myoepithelial (mesenchymal-like) components. It can occur anywhere but is very common in the parotid. The two key features to recognizing this lesion are a circumscribed, usually encapsulated tumor, and a mesenchymal-like component in the background (Figure 25.3). The mesenchymal-like stroma is often myxoid but may be chondroid or even osseous. The epithelial component can range from obviously epithelial to myoepithelial, so you may see well-defined ductular structures or pink to clear myoepithelial cells (in any of their four morphologies)—hence the designation *pleomorphic*. The individual cells, however, are notably *not* pleomorphic and in fact should be very bland (small, oval, pale nuclei).

The lesion not to miss is the polymorphous low-grade adenocarcinoma, which can look very similar but has an infiltrative periphery (see later). You should also examine the tumor for cytologically malignant cells, which may represent a *carcinoma ex-pleomorphic adenoma* (a pleomorphic adenoma gone bad).

The *myoepithelioma* is one end of the pleomorphic adenoma spectrum, with very little mesenchymal component and no ductular differentiation. As with a pleomorphic adenoma, it should be encapsulated and circumscribed. Immunostains can help you here, as myoepitheliomas should be positive for S100, cytokeratin, glial fibrillary acidic protein, and actin. *Basal cell adenoma* is also analogous to a pleomorphic adenoma, with no mesenchymal component, but with a population of basaloid cells.

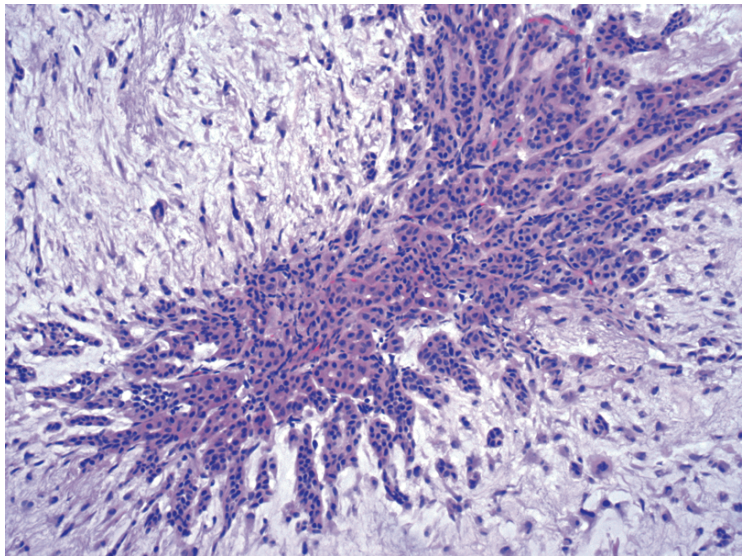

FIGURE 25.3. Pleomorphic adenoma. A cluster of cells is visible within the bluish myxoid stroma of a pleomorphic adenoma. The epithelial cells are small and cytologically benign, and they appear as small cords and tubules set within the stroma. The proportion of epithelial cells to stroma can vary widely.

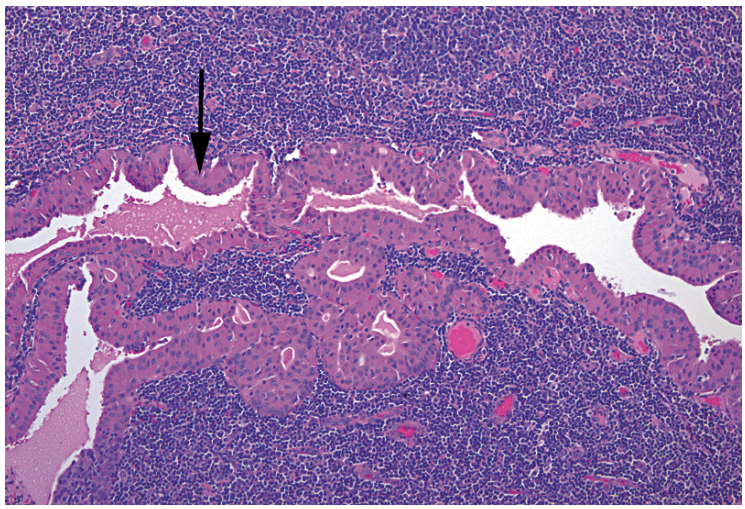

FIGURE 25.4. Warthin's tumor. This cyst is lined by a double layer of oncocytic cells (arrow) overlying a dense lymphoid infiltrate.

Rule of thumb: If it is an encapsulated solid lesion in the parotid, it probably fits into this category somehow.

Warthin's Tumor

Warthin's tumor is a papillary and cystic lesion lined by a double layer of oncocytic cells on top of a prominent lymphoid infiltrate with germinal centers (Figure 25.4). This usually occurs only in the parotid, but it can be bilateral. It is a low-power, 5-second diagnosis! This neoplasm (or reactive process?) may arise from striated ducts passing through intraparotid lymph nodes. The striated ducts are mitochondria rich, which explains the oncocytic nature of the lesion. This is to be differentiated from the *lymphoepithelial cyst*, a common lesion in

patients with the HIV that has a thin ragged epithelial lining instead of an oncocytic one. A related oncocytic lesion is the *oncocytoma*—a lesion composed of oncocytes that looks similar to a Hurthle cell nodule in thyroid or an oncocytoma in the kidney.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common malignant tumor. Mucoepidermoid carcinoma has a wide range of cellularity, from cystic to solid. It can be low grade to high grade, depending on five factors: percentage of cystic component, tumor necrosis, mitoses, anaplasia, and neural invasion. The neoplasm is a mixture of squamous cells, epithelioid cells, and clear mucinous cells. However, when one cell type dominates, it can be difficult to tell this tumor from (for example) squamous cell carcinoma or a clear cell carcinoma. In these cases, recognizing intracellular mucin is the key to the diagnosis, so a periodic acid-Schiff or mucicarmine stain may be used.

The periphery should be infiltrative, not encapsulated, although the low-grade tumors may be fairly well circumscribed. This tumor may arise from the interlobular ducts (the big excretory ducts), and you will notice that an inflamed or metaplastic duct does not look that different from a little focus of low-grade mucoepidermoid carcinoma (Figure 25.5).

A low-grade cystic mucoepidermoid carcinoma must be distinguished from a mucin-containing salivary duct cyst, usually by carefully examining the cyst wall. As mentioned earlier, an intermediate-to-high grade mucoepidermoid carcinoma may be confused with metastatic or primary squamous cell carcinoma or clear cell carcinoma.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is the prototypical cribriform tumor. It is blue, very cellular, with high nuclear to cytoplasmic ratios and fairly dense nuclei. Visually, it is reminiscent of a basal cell carcinoma of skin. It can be solid or tubular, but cribriform is the classic presentation, which makes it often instantly identifiable (Figure 25.6). Another classic feature is the balls of hyaline material found in the cribriform lumens, which are basement membrane material. It is highly infiltrative and loves nerves. Although intermediate grade at baseline, if solid growth predominates, this is a high-grade tumor.

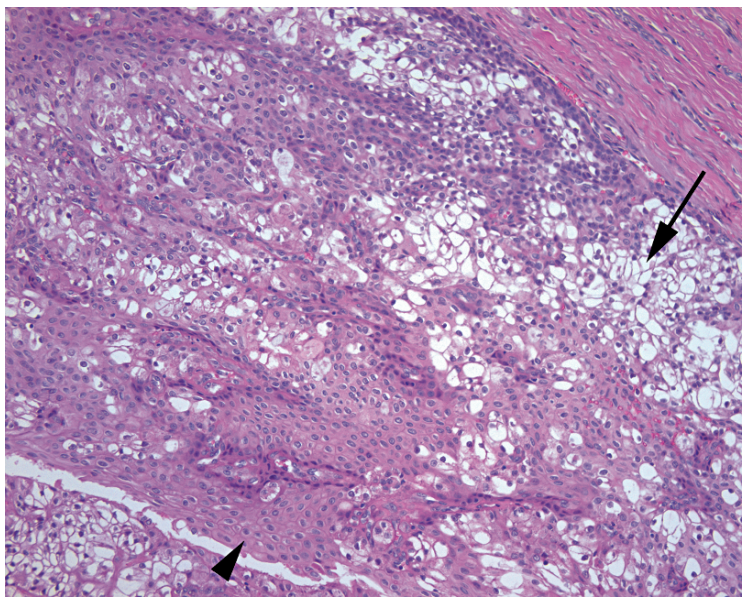

Figure 25.5. Mucoepidermoid carcinoma, low grade. This tumor resembles the metaplastic epithelium within an interlobular duct and is composed predominantly of clear goblet-like mucinous cells (arrow) and squamous cells (arrowhead).

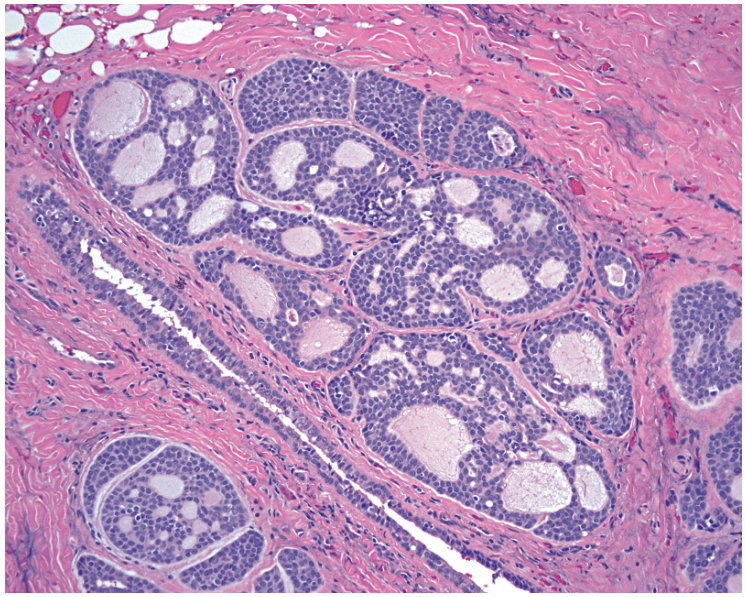

Figure 25.6. Adenoid cystic carcinoma. Although the nuclei are small, the nuclear to cytoplasmic ratio is high, making the tumor appear blue at low power. The architecture is classically cribriform, with sharply punched-out spaces full of pink secretions.

The presence of squamous areas favors a *basaloid squamous cell carcinoma*, which is in the differential diagnosis. The adenoid cystic carcinoma is very similar to the cylindroma of the skin, which can be in the differential around the ear (skin vs. tail of the parotid). Finally, if occurring in the lip or palate, rule out polymorphous low-grade adenocarcinoma, which can sometimes mimic an adenoid cystic. If you have a tumor that is cribriform and reminds you of an adenoid cystic, but is encapsulated or well-circumscribed, think instead of one of the adenomas, such as a basal cell adenoma.

Acinic Cell Carcinoma

Acinic cell carcinoma is a tumor of the serous acinar cells, and in its most differentiated form it looks quite similar to normal parotid, except without the ducts (Figure 25.7). Acinic cell is invasive, but as pushing borders rather than single cells. There are four common architectural patterns: solid, microcystic, papillary cystic, and follicular (such as thyroid). The microcystic pattern is full of little holes, but they are irregular holes that look as though the tissue has been pushed apart by expanding bubbles, very different from the rigid punched-out holes of adenoid cystic (Figure 25.8). There can be other nonserous cell types present, too, including clear cells, vacuolated cells, and ductal cells. However, finding a focus of serous differentiation (blue granular cytoplasm) pretty much seals the diagnosis.

The nonserous tumors can be quite pink and nonspecific in appearance. However, look for the microcystic pattern, the absence of cytoplasmic mucin (rules out mucoepidermoid carcinoma), and uniform well-spaced nuclei (either small and dense or medium-sized and very round with small nucleoli), similar to the follicular thyroid lesions. Note the pronunciation: it is ass-inic, not ax-inic.

Adenocarcinoma Not Otherwise Specified (NOS)

Adenocarcinoma NOS is the category for any ductal-derived carcinoma without other distinguishing features. It is the most common form of malignancy in a *carcinoma ex-pleomorphic adenoma*, which is a pleomorphic adenoma with a component of carcinoma.

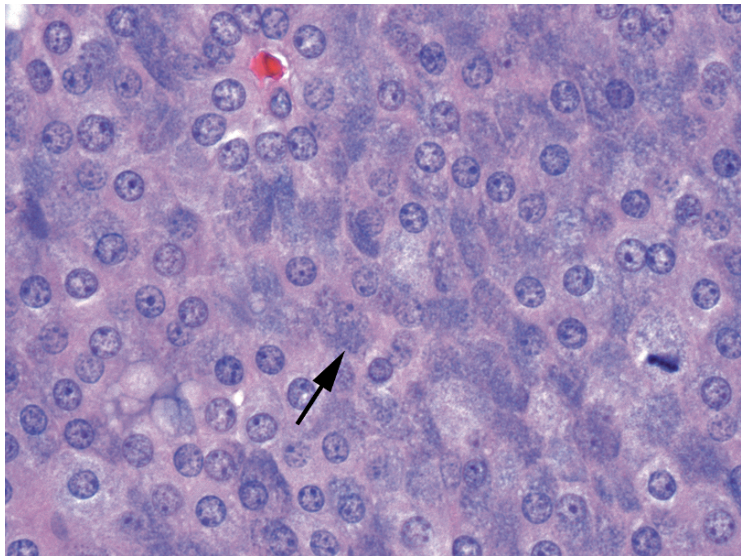

Figure 25.7. Acinic cell, solid pattern. The cells in acinic cell carcinoma replicate those of serous acini, with blue granular cytoplasm (arrow).

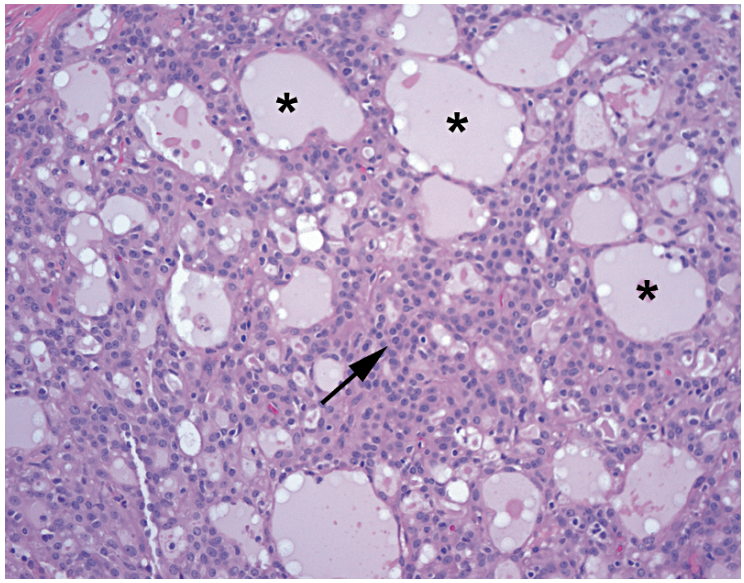

Figure 25.8. Acinic cell, microcystic pattern. In this example, the cells are nonspecifically pink (arrow) and do not have the telltale blue granules. However, the microcystic pattern, in which cells appear to be pushed apart by expanding pockets of fluid (asterisks), is typical of acinic cell. Compare these microcysts to the sharp cribriform spaces in adenoid cystic carcinoma (see Figure 25.6).

Polymorphous Low-Grade Adenocarcinoma

Importantly, polymorphous low-grade adenocarcinoma (PLGA) occurs almost exclusively in the intraoral minor salivary glands (lip and palate), so do not agonize over a funny-looking pleomorphic adenoma in the parotid! The PLGA looks very similar to a pleomorphic adenoma in terms of the epithelial component, and like a pleomorphic adenoma the cells are very bland. The key is in the margin of the tumor, which in a PLGA is infiltrative (Figure 25.9). The cells tend to spiral out of the central mass like a hurricane and may remind you of lobular carcinoma

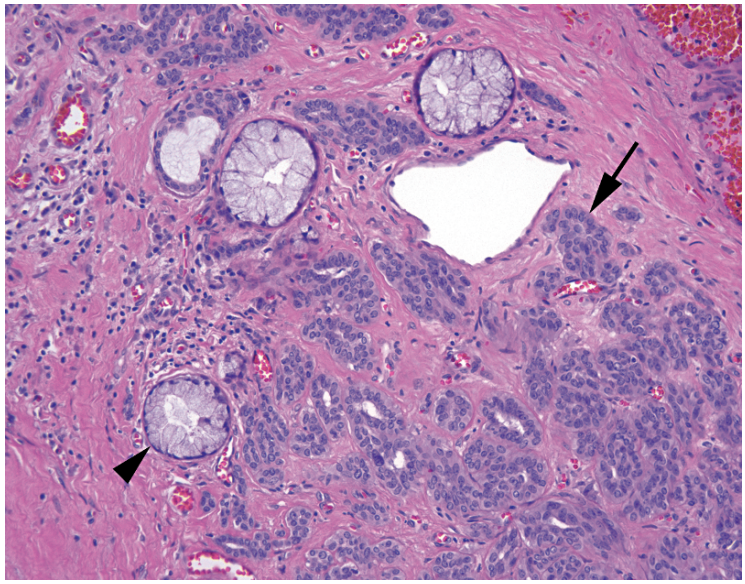

FIGURE 25.9. Polymorphous low-grade adenocarcinoma. Small tubules of bland cells (arrow) creep between benign mucinous glands (arrowhead). On high power, these infiltrative cells resemble those of the pleomorphic adenoma, but, unlike that benign tumor, the PLGA infiltrates surrounding tissues. PLGA cells may also invade as single-file lines, like lobular breast carcinoma.

(its former name, incidentally). Polymorphous low-grade adenocarcinoma can also sometimes be cribriform in appearance, mimicking an adenoid cystic.

Miscellaneous Malignant Neoplasms

Many of the benign adenomas described here have malignant counterparts, although they are rare. They include myoepithelial carcinoma, epithelial–myoepithelial carcinoma, basal cell adenocarcinoma, and oncocytic carcinoma. In general, features that favor malignancy include an infiltrative periphery, cellular pleomorphism, mitoses, or necrosis.