6 Esophagus

The esophagus is composed of a nonkeratinized squamous epithelium overlying a lamina propria and thin muscularis mucosa. The submucosa contains lymphatics and mucous glands with cuboidal-lined ducts running up to the luminal surface. Under the submucosa is muscularis propria (skeletal muscle proximally, smooth muscle distally), surrounded by the adventitia, which is continuous with mediastinum.

Most esophageal biopsies are performed on patients with symptoms of reflux or dysphagia and often the goal is to rule out Barrett's esophagus, a glandular metaplasia that puts the patient at increased risk for adenocarcinoma. Other common findings include reflux changes in the squamous epithelium, ulcers, or infection. Squamous dysplasia is actually uncommon.

Approach to the Slide

On low power, survey the epithelium. A normal biopsy specimen (Figure 6.1) will have a bland pink squamous epithelium and scant submucosa; muscularis propria should not be present. Occasional lymphocytes in the epithelium are typical (so-called squiggle cells because of their stretched-out appearance). The epithelium should not be interrupted or undermined by gastric-type glands, although salivary-like mucous glands are okay.

Within the squamous epithelium, look for the following:

- Basal cell hyperplasia (an increase over the normal three-cell layer) (Basal cells are the deepest layer of squamous cells and are the regenerative cell layer. They are defined by their closely packed nuclei: if you cannot squeeze a new nucleus between two existing nuclei, they are basal cells.)
- Elongated vascular papillae (over two thirds of the thickness of the epithelium)
- Balloon cell change of epithelium (an accumulation of glycogen in the cytoplasm)
- Intraepithelial neutrophils or eosinophils
- Erosions, fibrinopurulent exudate, granulation tissue
- Columnar cell mucosa or glands

Reflux Changes

A very common finding on biopsy is reflux esophagitis, which consists of the first four features in the preceding list (Figure 6.2). Not all features need be present in every case and typically are not. Severe cases may progress to erosions and ulcerations. The inflammation in reflux is mainly lymphocytic, but eosinophils may be seen; a very high number of eosinophils (or clustering of three or more) may indicate eosinophilic esophagitis. Stylistically, we often use the phrase "reactive epithelial changes" to describe changes that have some, but not all, of the features of full-blown reflux esophagitis.

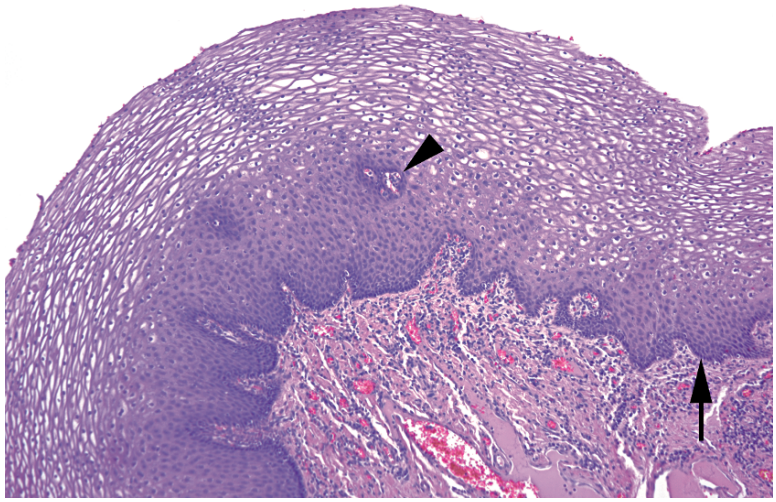

Figure 6.1. Normal esophageal mucosa. The basal layer (arrow) is seen as a crowded and blue layer at the base. The cells mature into flat nonkeratinizing squamous cells with small nuclei; the clear cytoplasm seen here is glycogen. Vascular pegs penetrate into the epithelium (arrowhead). The vascular lamina propria is visible below the basal layer.

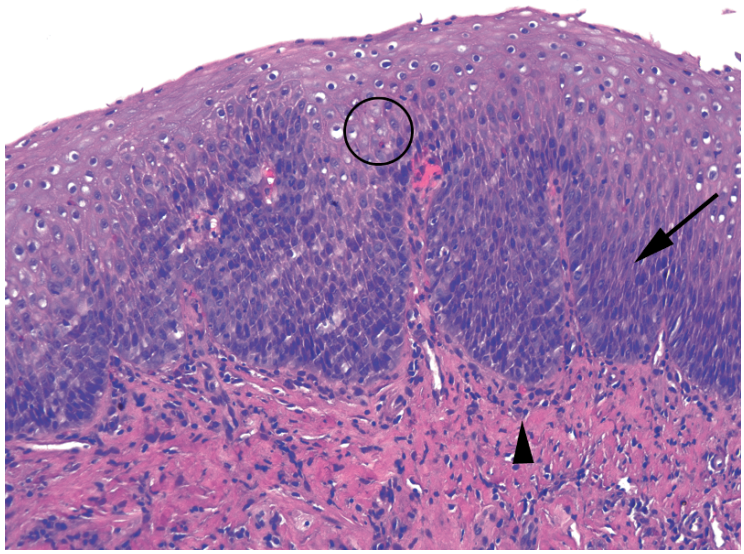

Figure 6.2. Reflux esophagitis. Compare this inflamed epithelium to the normal mucosa in Figure 6.1. The basal layer is increased in thickness (arrow), creating a more dense and blue look to the epithelium. There are inflammatory cells scattered throughout, including eosinophils (circle) and lymphocytes (arrowhead).

Neutrophils

A prominent neutrophilic infiltrate points more to an infection or acute injury rather than reflux. Look at the periodic-acid Schiff (PAS) stain to find *Candida* organisms (pseudohyphae and yeast forms in the epithelium or exudate; Figure 6.3). They may be very numerous or extremely scanty. Luminal squamous debris is another hint to look closely for *Candida*. Candidal infection is typically associated with a superficial neutrophilic infiltrate and parakeratosis (surface squames that are too red and have retained nuclei); however, some cases have almost *no* inflammation and little epithelial changes.

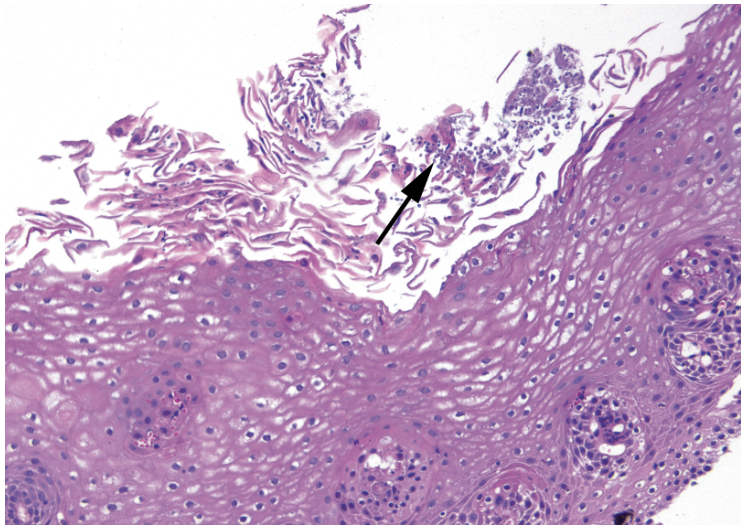

Figure 6.3. *Candida*. Tiny purple yeasts and pseudohyphae (arrow) are seen among the squamous debris at the surface of the epithelium. This is a hematoxylin and eosin stain; the yeasts are magenta on periodic-acid Schiff stain. Note that sometimes there is not a significant neutrophilic response.

Ulcers

Ulcers can be caused by severe reflux or chemical injury (especially pill esophagitis; polarize to look for pill fragments), radiation (should be accompanied by necrosis and bizarre atypia), or infection, or they can be idiopathic (particularly in acquired immunodeficiency syndrome). Viral esophagitis is rare but more common in the immunosuppressed. Herpes simplex virus and cytomegalovirus cause inflamed, punched-out ulcers.

- Herpes simplex virus infects epithelial cells. This is best seen on intact squamous mucosa adjacent to the ulcer, typically causing multinucleation with nuclear molding and glassy chromatin.
- Cytomegalovirus infects mesenchymal cells (fibroblasts, endothelial, etc.) at the ulcer base. Cytomegalovirus infection usually manifests with intranuclear and cytoplasmic red/purple inclusions that render the cells gigantic (cyto-*megalo*-virus), and thus 10× is a good objective to scan with.

The hematoxylin and eosin (H&E) slide is the best place to find the inclusions, but immunostains may help if clinical suspicion is high and H&E is not definitive (see Chapter 3 for images of viral inclusions).

Columnar Epithelium

Collections of submucosal mucous glands resembling salivary glands or Brunner's glands of duodenum are occasionally seen in mucosal biopsy material. It is more common to see the ducts from these glands. Gastric-type epithelium (foveolar surface epithelium and underlying specialized gastric glands, usually oxyntic) in an "esophagus" biopsy specimen may represent tissue inadvertently taken from proximal stomach or hiatal hernia. The presence of cardiac mucosa should be noted but does *not* equal a diagnosis of Barrett's esophagus (see later discussion). Collections of pink-purple acinar cells beneath the epithelium, resembling normal pancreas, may in fact be normal pancreas (called *pancreatic metaplasia* or *heterotopia*).

Goblet Cells

In the tubular esophagus, the presence of goblet cells (bulbous epithelial cells that are indigo-blue on PAS/alcian blue (AB) stain, clear-to-pale-blue on H&E; Figure 6.4) in glandular mucosa, otherwise known as *intestinal metaplasia*, indicates *Barrett mucosa of the distinctive type* ("Barrett's esophagus"). There are two caveats to be considered. First, intestinal metaplasia can also occur in the true cardia of the stomach as a response to inflammation. Therefore, if the location where the biopsy tissue came from is not entirely clear, some pathologists will sign out apparent Barrett's as "consistent with Barrett's mucosa if the biopsy was taken from tubular esophagus." Second, not all that stains blue with the PAS/AB is a goblet cell. Some gastric-type foveolar cells, especially at the squamocolumnar junction, will stain blue (so-called tall blues), so, to be a genuine goblet it has to stain blue *and* have goblet cell morphology (bulbous outline of goblet cells vs. the elongated foveolar cells).

Dysplasia Within Barrett's Esophagus

Like any gastrointestinal glandular mucosa, Barrett's mucosa can progress through dysplasia, intramucosal carcinoma, and invasive adenocarcinoma. As an already abnormal cell type responding to chronic injury, it is at high risk for dysplasia and is regularly screened by biopsy.

Dysplasia in Barrett's mucosa initially begins to look like a tubular adenoma of the colon (it gets blue). The cells have the following characteristics:

- Increased nuclear hyperchromatism and pleomorphism
- High nuclear-to-cytoplasmic ratio
- Loss of mucin vacuoles
- Crowding and pseudostratification
- Loss of polarity

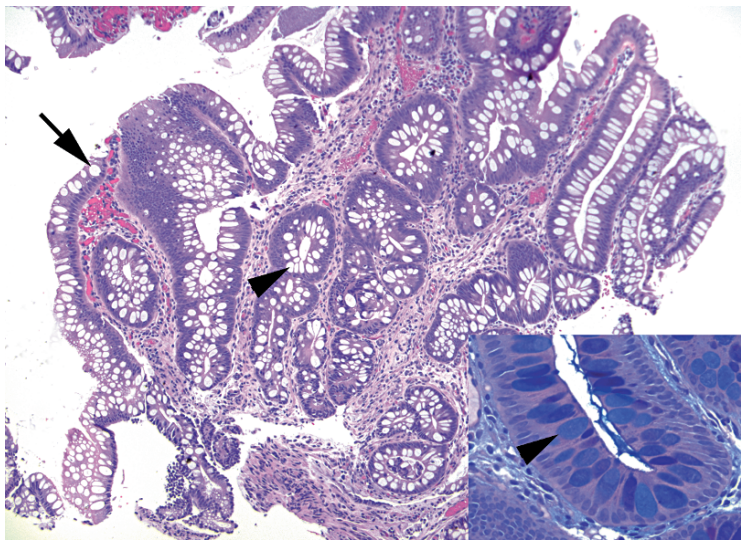

FIGURE 6.4. Goblet cells in Barrett's esophagus. The presence of columnar epithelium with goblet cells indicates Barrett's esophagus. Goblet cells are round cells that appear clear on hematoxylin and eosin stain and are typically flanked by the purplish absorptive-type cells. Back-to-back mucinous cells resembling a row of teeth are more likely to be gastric foveolar epithelium. Goblet cells may be present at the surface (arrow) or in deep glands (arrowhead). **Inset**: A periodic-acid Schiff/alcian blue stain confirms the goblet cells, which stain indigo blue (arrowhead).

True dysplasia should extend *all the way to the surface epithelium*, as in a tubular adenoma (Figure 6.5). Features that should make you back off from dysplasia include surface maturation (base looks bad, but surface looks fine), big grey-purple nuclei with prominent nucleoli (more likely to be reactive), and pronounced inflammation (also points to reactive).

Progression to high-grade dysplasia (Figure 6.6) includes increasing atypia (loss of polarity, nuclei that begin to look like boulders: large with irregular outlines), mitotic activity (although mitoses alone are not worrisome), and architectural dysplasia (glands that are crowded and complex: budding, branching, cribriform, papillary, or villiform). High-grade dysplasia tends to be diagnosed in situations in which you are worried about invasive carcinoma but cannot prove it. Think of high-grade dysplasia as synonymous with carcinoma in situ.

The next step along the malignancy progression is invasive carcinoma (Figure 6.7). As in other organs, clues to invasion include a ragged basement membrane border, single cells infiltrating, and a desmoplastic stromal response. Note that in the esophagus, unlike in the colon, intramucosal carcinoma (invasive adenocarcinoma confined to the lamina propria) *is* thought to have metastatic potential and thus is considered a "T1" lesion (not "Tis") in the TNM (tumor, node, metastasis) staging classification. This is due to the presence of lymphatics in the lamina propria of the esophagus.

Squamous Dysplasia

Within the squamous epithelium, dysplasia, carcinoma in situ, and invasive squamous cell carcinoma are diagnosed by criteria similar to those for the cervix. Dysplastic changes include enlarged, pleomorphic nuclei, increased nuclear/cytoplasmic ratio (a general blueness at low power), mitoses above the basal layer, and loss of order and polarity. Prominent nucleoli are more consistent with reactive/reparative changes. Dysplasia begins at the base and progresses to the surface. If the changes persist all the way to the surface, it is carcinoma in situ. Invasion can be hard to identify; a deep pushing front is not necessarily invasion. Look for deep aberrant keratinization (pinking up) and single cells trailing off as a clue to invasive carcinoma.

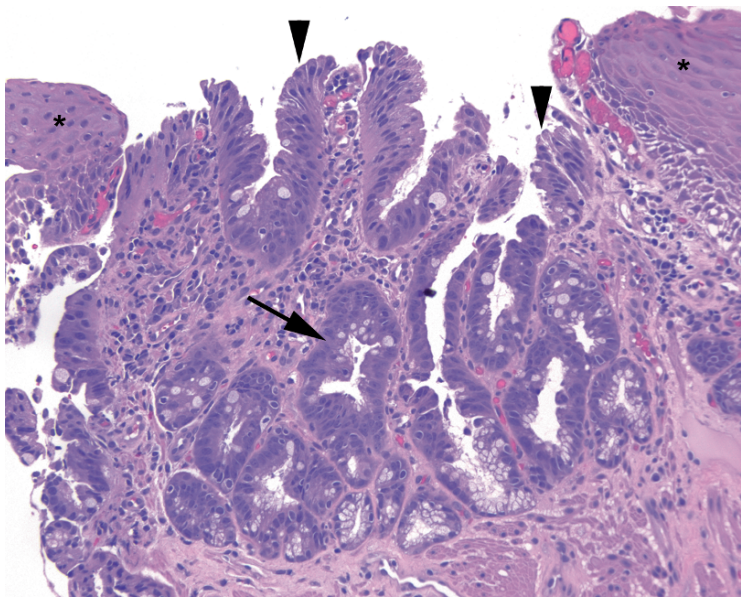

Figure 6.5. Low-grade dysplasia in Barrett's esophagus. The cells begin to lose polarity and organization, with nuclei becoming more pleomorphic and lifting up off the basement membrane (arrow). The changes must extend to the surface (arrowheads) to count. Compare with the nondysplastic epithelium shown in Figure 6.4. Adjacent squamous epithelium can be seen on either side (asterisks).

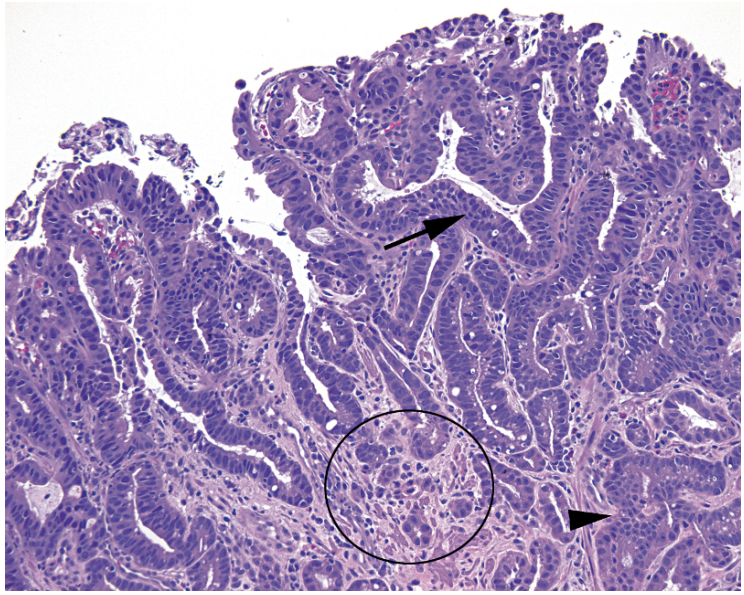

FIGURE 6.6. High-grade dysplasia. Nuclei here show marked hyperchromasia, pleomorphism, and disorganization (arrow), and the glands are beginning to show cribriform growth (arrowhead). There is a focus suspicious for invasion highlighted in the circle.

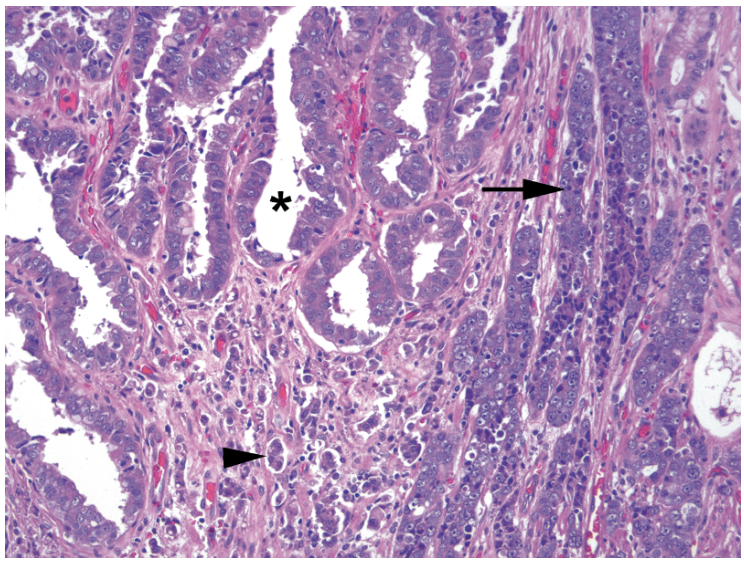

FIGURE 6.7. Invasive adenocarcinoma. The carcinoma can be seen invading the stroma as glands (asterisk), cords (arrow), and single cells (arrowhead). Notice the prominent nucleoli, which are not typically a feature of dysplasia.

Polyps

A reasonable differential for a polypoid structure in the esophagus includes the following:

- Benign
  - Inflammatory fibroid polyp: vascular, inflamed, fibrous stroma covered by benign squamous epithelium, may be ulcerated; looks like granulation tissue
  - Fibrovascular polyp: fibrovascular core covered by benign squamous epithelium, plus or minus fat

- Squamous papilloma: fibrovascular core covered by hyperplastic, but benign, squamous epithelium
- Submucosal nodules such as leiomyoma and granular cell tumor

- Malignant
  - Verrucous squamous cell carcinoma
  - Other carcinomas

Neoplasms in the Esophagus

One way to create a differential of neoplasms within an organ is to list all of the normal cell types and then think about what tumors can arise from each one. In the esophagus, the whopping majority of cancers arise from the epithelium and therefore are squamous or adenocarcinoma, but soft tissue tumors, although unusual, can occur. These include leiomyoma, granular cell tumor, hemangioma, angiosarcoma, and others.