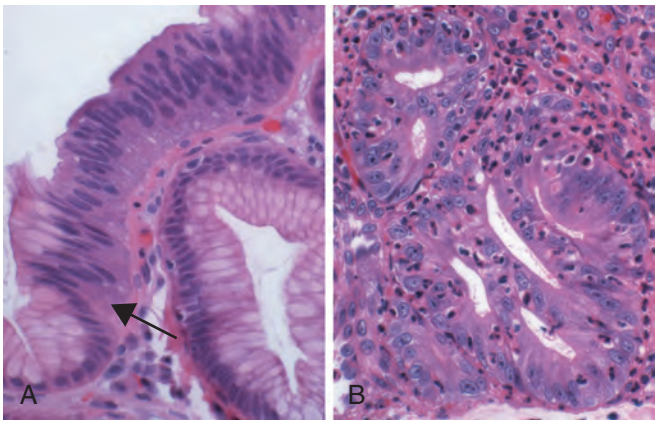

Figure 17-8 Dysplasia in Barrett esophagus. **A,** Abrupt transition from Barrett metaplasia to low-grade dysplasia *(arrow)*. Note the nuclear stratification and hyperchromasia. **B,** Architectural irregularities, including gland-within-gland, or cribriform, profiles in high-grade dysplasia.

Intramucosal or invasive carcinoma requires therapeutic intervention. Treatment options include surgical resection, or esophagectomy, as well as newer modalities such as photodynamic therapy, laser ablation, and endoscopic mucosectomy. Multifocal high-grade dysplasia, which carries a significant risk of progression to intramucosal or invasive carcinoma, is treated as intramucosal carcinoma. Many physicians follow low-grade dysplasia or a single focus of high-grade dysplasia with endoscopy and biopsy at frequent intervals. However, management of esophageal dysplasia is evolving, and it is hoped that improved molecular understanding of neoplastic progression may allow development of chemopreventive approaches that reduce the incidence of esophageal adenocarcinoma.

Esophageal Tumors

The vast majority of esophageal cancers fall into one of two types, adenocarcinoma and squamous cell carcinoma. Squamous cell carcinoma is more common worldwide, but adenocarcinoma is on the rise in the United States and other Western countries. Other malignancies of the esophagus are far less common and include unusual forms of adenocarcinoma, undifferentiated carcinoma, carcinoid tumor, melanoma, lymphoma, and sarcoma; these are not discussed here. Benign tumors of the esophagus are generally mesenchymal, and arise within the esophageal wall, with leiomyomas being most common. Fibromas, lipomas, hemangiomas, neurofibromas, and lymphangiomas also occur.

Adenocarcinoma

Most esophageal adenocarcinomas arise from Barrett esophagus. Thus, increased rates of esophageal adenocarcinoma may be partly due to the increased incidence of obesity-related gastroesophageal reflux and Barrett esophagus. Additional risk factors include tobacco use and exposure to radiation. Conversely, risk is reduced by diets rich in fresh fruits and vegetables. Some serotypes of *Helicobacter pylori* are associated with decreased risk of esophageal adenocarcinoma, because they cause gastric atrophy, which in turn leads to reduced acid secretion and reflux, and reduced incidence of Barrett esophagus. Thus, reduced rates of *Helicobacter pylori* infection may also be a factor in the increasing incidence of esophageal adenocarcinoma.

Esophageal adenocarcinoma occurs most frequently in Caucasians and shows a strong gender bias, being sevenfold more common in men. However, the incidence varies widely worldwide, with rates being highest in countries that include the United States, the United Kingdom, Canada, Australia, the Netherlands, and Brazil, and lowest in Korea, Thailand, Japan, and Ecuador. In countries where esophageal adenocarcinoma is more common, the incidence has increased markedly since 1970, more rapidly than almost any other cancer. For unknown reasons, these increases have been restricted to white and Hispanic men and white women in the United States. As a result, esophageal adenocarcinoma, which represented less than 5% of esophageal cancers before 1970, now accounts for more than half of all esophageal cancers in the United States.

Pathogenesis. **Molecular studies suggest that the progression of Barrett esophagus to adenocarcinoma occurs over an extended period through the stepwise acquisition of genetic and epigenetic changes.** This model is supported by the observation that epithelial clones identified in nondysplastic Barrett metaplasia persist and accumulate mutations during progression to dysplasia and invasive carcinoma. Chromosomal abnormalities, mutation of *TP53*, and downregulation of the cyclin-dependent kinase inhibitor *CDKN2A,* also known as *p16/INK4a,* are detected at early stages. In the case of *CDKN2A,* both allelic loss and hypermethylation-induced epigenetic silencing have been described. Later during progression there is amplification of *EGFR, ERBB2, MET, cyclin D1*, and *cyclin E* genes.

MORPHOLOGY

Esophageal adenocarcinoma usually occurs in the distal third of the esophagus and may invade the adjacent gastric cardia (Fig. 17-9*A*). Initially appearing as flat or raised patches in otherwise intact mucosa, large masses of 5 cm or more in diameter may develop. Alternatively, tumors may infiltrate diffusely or ulcerate and invade deeply. Microscopically, Barrett esophagus is frequently present adjacent to the tumor. Tumors most commonly produce mucin and form glands (Fig. 17-10*A*), often with intestinal-type morphology; less frequently tumors are composed of diffusely infiltrative signet-ring cells (similar to those seen in diffuse gastric cancers) or, in rare cases, small poorly differentiated cells (similar to small-cell carcinoma of the lung).

Clinical Features. Although esophageal adenocarcinomas are occasionally discovered in evaluation of GERD or surveillance of Barrett esophagus, they more commonly present with pain or difficulty in swallowing, progressive weight loss, hematemesis, chest pain, or vomiting. By the time symptoms appear, the tumor has usually spread to submucosal lymphatic vessels. As a result of the advanced stage at diagnosis, overall 5-year survival is less than 25%. In contrast, 5-year survival approximates 80% in the few patients with adenocarcinoma limited to the mucosa or submucosa.