Cholangiocarcinoma (CCA)

Cholangiocarcinoma (CCA), the second most common primary malignant tumor of the liver after HCC, is a malignancy of the biliary tree, arising from bile ducts within and outside of the liver. It accounts for 7.6% of cancer deaths worldwide and 3% of cancer deaths in the United States. However, in some regions of Southeast Asia such as northeastern Thailand, Laos, and Cambodia where infestation with liver flukes is endemic, cholangiocarcinoma is more common than hepatocellular carcinoma.

All risk factors for cholangiocarcinomas cause chronic inflammation and cholestasis, which presumably promote occurrence of somatic mutations or epigenetic alterations in cholangiocytes. The risk factors include infestation by liver flukes (particularly Opisthorchis and Clonorchis species), chronic inflammatory disease of the large bile ducts, such as primary sclerosing cholangitis, hepatolithiasis, and fibropolycystic liver disease. It should be noted that patients with hepatitis B and C, and non alcoholic fatty liver disease, not only have a higher risk of developing HCC, but also of cholangiocarcinoma. Globally, cholangiocarcinomas are most often sporadic and not associated with any preexisting condition.

Cholangiocarcinoma may be either intrahepatic or extrahepatic. The extrahepatic forms include perihilar tumors known as *Klatskin tumors*, which are located at the junction of the right and left hepatic ducts. Fifty percent to 60% of all cholangiocarcinomas are perihilar (Klatskin) tumors, 20% to 30% are distal tumors, arising in the common bile duct where it lies posterior to the duodenum. The remaining 10% are intrahepatic. Regardless of site, the prognosis is dismal, with survival rates of about 15% at 2 years after diagnosis for extrahepatic tumors. The median time from diagnosis to death for intrahepatic CCAs is 6 months, even after surgery because intrahepatic CCAs are not usually detected until late in their course. They come to the attention because of obstruction of bile flow or as a symptomatic liver mass. In contrast, hilar and distal tumors present with symptoms of biliary obstruction, cholangitis, and right upper quadrant pain.

Premalignant lesions for cholangiocarcinoma are also known, the most important of which are biliary intraepithelial neoplasias (low to high grade, BilIN-1, -2, or -3). BilIN-3, the highest grade lesion, incurs the highest risk of malignant transformation. More rare are *mucinous cystic neoplasms* and intraductal *papillary biliary neoplasia* (Table 18-12).

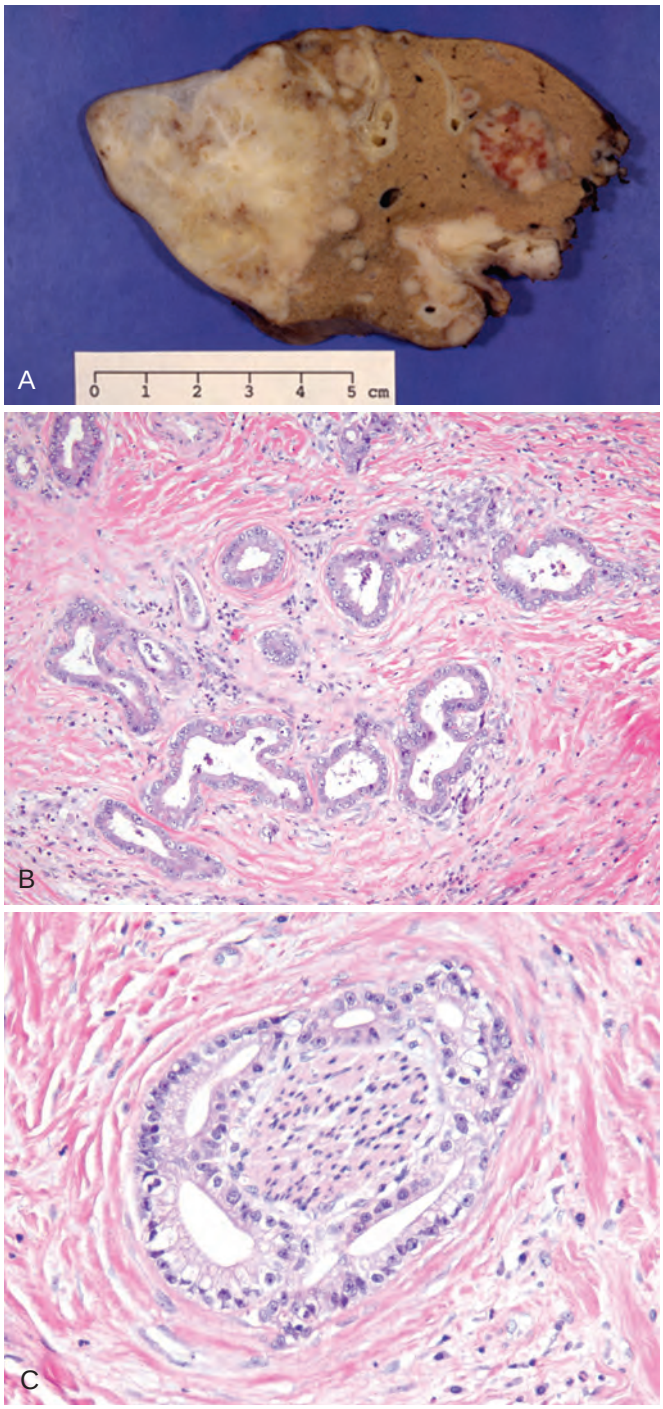

Figure 18-60 Cholangiocarcinoma. **A,** Multifocal cholangiocarcinoma in a liver from a patient with infestation by the liver fluke *Clonorchis sinensis*. **B,** Invasive malignant glands in a reactive, sclerotic stroma. **C,** Perineural invasion by malignant glands, forming a wreathlike pattern around the central, trapped nerve. (**A,** Courtesy Dr. Wilson M.S. Tsui, Caritas Medical Centre, Hong Kong.)

MORPHOLOGY

Extrahepatic cholangiocarcinomas are generally small lesions at the time of diagnosis as they rapidly cause obstructive features. Most tumors appear as firm, gray nodules within the bile duct wall; some may be diffusely infiltrative lesions; others are papillary, polypoid lesions. Intrahepatic cholangiocarcinomas occur in the noncirrhotic liver (Fig. 18-60) and may track along the intrahepatic portal tract system creating a branching tumor within a portion of the liver. Alternatively, a massive tumor nodule may develop.

Regardless of site, cholangiocarcinomas are typical adenocarcinomas. They often produce mucin. Most are well- to moderately differentiated with clearly defined glandular/tubular structures lined by malignant epithelial cells (Fig. 18-60*B*). They typically incite marked desmoplasia. Lymphovascular invasion and perineural invasion (Fig. 18-60*C*) are both common, each a path to extensive intrahepatic and extrahepatic metastases.