Other Primary Hepatic Malignant Tumors

Other primary liver malignancies are rare, but noteworthy. Some tumors show *combined hepatocellular and cholangiocarcinoma*, suggesting an origin from a multipotent stem cell. *Mucinous cystic neoplasms* and *intraductal papillary biliary neoplasia* may occur as in situ lesions or as invasive cholangiocarcinoma.

Angiosarcoma of the liver resembles those occurring elsewhere and has historical associations with vinyl chloride, arsenic, or Thorotrast (Chapters 9 and 11), although with reduced exposures to these compounds in recent decades, this malignancy is becoming very rare. *Epithelioid hemangioendothelioma*, another form of endothelial malignancy, has a much more variable prognosis than the almost uniformly fatal angiosarcoma. Hepatic lymphomas are primarily diseases of middle aged men and are seen, albeit rarely, in association with hepatitis B and C, HIV, and PBC. Most are *diffuse large B-cell lymphomas*, followed by *MALT lymphomas. Hepatosplenic delta-gamma T cell lymphoma,* most common in young adult males, has a predilection for hepatic and splenic sinusoids as well as the marrow.

Metastasis

Involvement of the liver by metastatic malignancy is far more common than primary hepatic neoplasia. Although the most common primary sources are the colon, breast, lung, and pancreas, any cancer in any site of the body may spread to the liver. Typically, multiple nodular metastases are found that often cause striking hepatomegaly and replace much of the normal liver parenchyma. The liver weight can exceed several kilograms. Metastasis may also appear as a single nodule, in which case it may be resected surgically. Always surprising is the amount of metastatic involvement that may be present in the absence of clinical or laboratory evidence of hepatic functional insufficiency. Often the only telltale clinical sign is hepatomegaly. However, with massive destruction of liver substance or direct obstruction of major bile ducts, jaundice and elevations of liver enzymes may appear.

KEY CONCEPTS

Liver Tumors

- The liver is the most common site of **metastatic cancers** from primary tumors of the colon, lung, and breast.
- **Hepatocellular adenomas** are benign tumors of neoplastic hepatocytes. Most can be subclassified on the basis of molecular changes:
  - **HNF1-α inactivated adenomas,** with virtually no risk of malignant transformation, often associated with oral contraceptive pill use or in individuals with MODY-3
  - **β-Catenin activated adenoma,** with mutations in the β-catenin gene leading to marked atypia and associated with a very high risk for malignant transformation
  - **Inflammatory adenomas,** the hallmark of which is up-regulation of C-reactive protein and serum amyloid A (often derived from gp130 mutations); 10% of these have concomitant β-catenin activating mutations. Risk for malignant transformation is intermediate.
- The main **primary malignancies are HCCs and cholangiocarcinomas;** HCCs are by far the most common.
  - HCC is a common tumor in regions of Asia and Africa, and its incidence is increasing in the United States.
  - The main etiologic agents for HCC are chronic hepatitis B and C, alcoholic cirrhosis, non-alcoholic fatty liver disease, and hemochromatosis. In the Western population, about 90% of HCCs develop in cirrhotic livers; in Asia, almost 50% of cases develop in noncirrhotic livers.
  - The chronic inflammation and cellular regeneration associated with viral hepatitis or the activation of IL-6/JAK STAT pathway may be predisposing factors for the development of carcinomas.
  - HCCs may be unifocal or multifocal, tend to invade blood vessels, and recapitulate normal liver architecture to varying degrees.
- **Cholangiocarcinoma** is endemic in areas where liver flukes such as *Opisthorchis* and *Clonorchis* species are endemic. Chronic inflammatory diseases of bile ducts are also risk factors. The tumors may arise from extra hepatic or intrahepatic bile ducts. They have uniformly poor prognosis.

GALLBLADDER

As much as 1 L of bile is secreted by the liver per day. Between meals, bile is stored in the gallbladder, where it is concentrated. The adult gallbladder has a capacity of about 50 mL. The organ is not essential for biliary function, since humans do not suffer from indigestion or malabsorption of fat after cholecystectomy. **More than 95% of biliary tract disease is attributable to cholelithiasis (gallstones).** In the United States, gallstones affect 20 million people, and more than 700,000 cholecystectomies are performed annually at a cost of approximately $6 billion.

Congenital Anomalies

The gallbladder may be congenitally absent, or there may be gallbladder duplication with conjoined or independent cystic ducts. A longitudinal or transverse septum may create a bilobed gallbladder. Aberrant locations of the gallbladder occur in 5% to 10% of the population, most commonly partial or complete embedding in the liver substance. A folded fundus is the most common anomaly, creating a *phrygian cap* (Fig. 18-61). *Agenesis* of all or any portion of the hepatic or common bile ducts and hypoplastic narrowing of biliary channels (true "biliary atresia") may also occur. *Choledochal cysts*, described earlier, may be isolated findings in the gallbladder or associated with other cysts in the extrahepatic biliary tree or with fibropolycystic disease.

Cholelithiasis (Gallstones)

Gallstones afflict 10% to 20% of adult populations in developed countries. It is estimated that more than 20 million