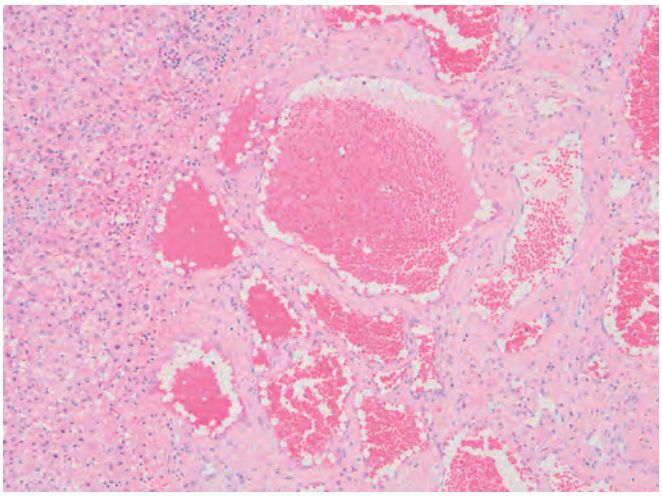

Figure 18-52 Hemangioma. Blood-filled vascular channels separated by a dense fibrous stroma.

with a different relative risk of malignant transformation. Both oral contraceptives and anabolic steroids are associated with the development of these adenomas. In fact before the advent of oral contraceptives, hepatocellular adenomas were virtually unknown. The risk of developing these tumors is increased 30-40 fold in users of oral contraceptives. The highest risk is from prolonged use of estrogen rich oral contraceptives. If surgery is not possible or is ill-advised, cessation of exposure to sex hormones often can lead to full regression.

Pathogenesis. Three large subtypes have been defined on the basis of molecular analysis and associated clinical and pathologic findings, each with a different relative risk of malignant transformation.

HNF1-α Inactivated hepatocellular adenomas. Ninety percent of these tumors have inactivating mutations of HNF1-α that are somatic, while 10% have germline mutations. HNF1-α encodes a transcription factor. Heterozygous germline mutations are responsible for autosomal dominant MODY-3 (maturity onset diabetes of the young, type 3). Patients with MODY-3 who develop hepatocellular adenomas have acquired a second somatic mutation. These lesions are most commonly found in women. Oral contraceptive pills are implicated in some.

β-Catenin Activated Hepatocellular Adenomas. Activating mutations of β-catenin are associated with neoplasia and malignancy in many organs. In the liver they may give rise to hepatocellular adenomas that are considered at very high risk for malignant transformation and should be resected even when asymptomatic. They are associated with oral contraceptive and anabolic steroid use. They are found in men and women.

Inflammatory hepatocellular adenomas. These lesions are found in both men and women and are associated with non-alcoholic fatty liver disease; thus, their incidence seems to be increasing. They have a small but definite risk of malignant transformation and should probably be resected even when asymptomatic. They are characterized by activating mutations in gp130, a co-receptor for IL-6, that lead to constitutive JAK-STAT signaling and overexpression of acute phase reactants, which you will recall are normally upregulated in systemic inflammatory states. As will be discussed later, IL-6 mediated JAK-STAT signaling has also been linked to the pathogenesis of hepatocellular carcinoma, and undoubtedly explains the inflammatory background that characterizes this subtype of hepatocellular adenoma. Ten percent of inflammatory hepatocellular adenomas also have concomitant β-catenin activating mutations and these tumors have a higher risk of malignant transformation.

MORPHOLOGY

The tumors resulting from **HNF1-α mutations** are often fatty and devoid of cellular or architectural atypia. They have almost no risk of malignant transformation. Liver fatty acid binding protein (LFABP), a downstream regulated protein of HNF1-α, is constitutively expressed in all normal hepatocytes, but is

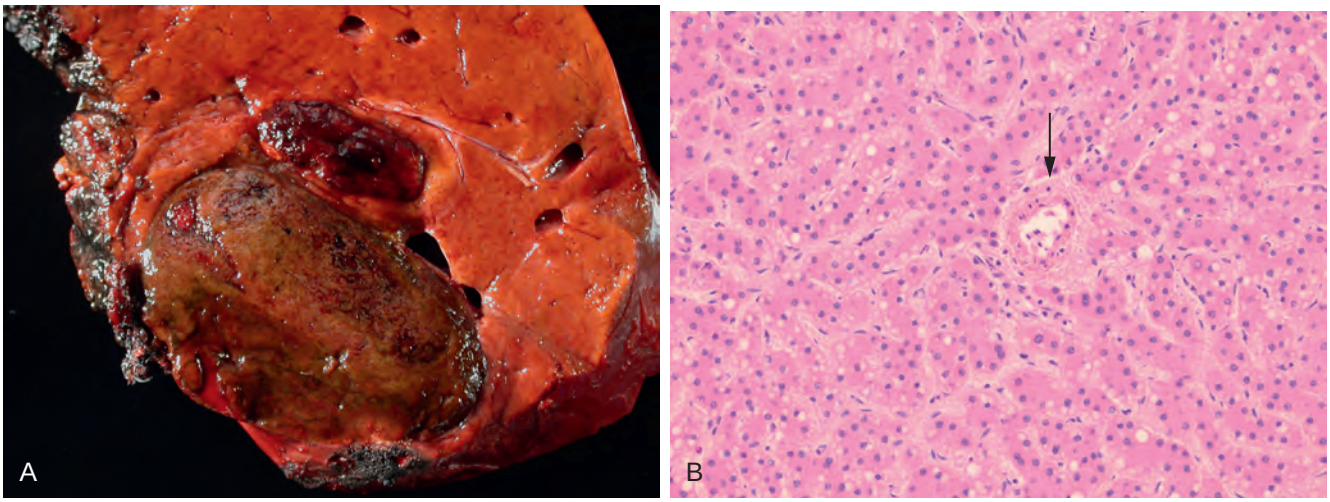

Figure 18-53 Liver cell adenoma. **A,** Resected specimen presenting as a pendulous mass arising from the liver. **B,** Microscopic view showing cords of hepatocytes, with an arterial vascular supply *(arrow)* and no portal tracts.