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Digestive System

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Cholangioma, Liver, Rat

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Synonyms. Bile duct adenoma; biliary adenoma; bile duct cystadenoma; biliary cystadenoma.

Gross Appearance

The macroscopic appearance of cholangiomas is variable. Usually, the neoplasms are observed as raised grayish-white areas of firm consistency. However, in the more cystic forms, cholangiomas have a spongy texture and, in the presence of appreciable associated vascular proliferation, the neoplasm is dark-red in color. Multilocular cystic forms have a more irregular surface than those in which there is no significant cyst formation.
Macroscopic differentiation between hepatocellular neoplasms and those of bile duct origin can be difficult and in many cases impossible.

Microscopic Features

Simple cholangioma is a generally uniform well-circumscribed neoplasm composed of acini of uniform size. The acini are lined by a single layer of cuboidal cells having somewhat basophilic cytoplasm and a round or oval nucleus, which is occasionally vesicular and contains one or two conspicuous nucleoli. The nucleus is usually located at or toward the base of the cell. Simple cholangiomas have a sparse vascular stroma and rarely contain evidence of mitotic activity. Cholangiomas can become large enough to cause considerable distortion, but there is never invasive growth. The glandular acini may vary in size and shape and the lining epithelium, which can range from columnar to flattened, is occasionally multilayered (Figs. 50, 51).
Cystic cholangioma is characteristically composed of dilated glandular acini lined by flattened, almost atrophic, epithelium. The stroma in cystic forms is less well vascularized and contains more fibrous tissue and collagen than that in the simple cholangioma. Papillary structures are occasionally observed projecting into the lumen of cystic acini and clumps of liver cells are commonly seen between the cysts (Fig. 52).
In the hemangiomatous cholangioma, the acini are morphologically similar to those in simple cholangioma, but the stroma contains cystic, blood-filled spaces lined by endothelium (Fig. 53).

Differential Diagnosis

The morphological forms of cholangioma must be distinguished from other proliferative lesions of bile duct, hepatocellular, and endothelial origin. With the exception of some forms of hepatocellular carcinoma, the morphology of hepatocellular and endothelial neoplasms is quite distinct and rarely confounds the differential diagnosis of cholangioma.
Occasionally, acinar structures are formed within hepatocellular carcinomas and these can appear very similar in morphology to the glandular acini of cholangiomas. Importantly, the morphology of such hepatocellular carcinomas is variable. The more solid areas of carcinoma, frequently demonstrating evidence of invasion, will clarify diagnosis. This distinction is more of a problem in the differential diagnosis of cholangiocarcinoma than cholangioma.
Other proliferative lesions of bile duct origin are nonneoplastic bile duct proliferation (hyperplasia), cholangiofibrosis, and cholangiocarcinoma. Simple nonneoplastic bile duct proliferation is a variable lesion which occurs spontaneously in ageing rats and as a result of exposure to hepatotoxins including carcinogens. Cells proliferate in strands, with the progressive formation of a lumen giving the appearance of bile ducts. Proliferation extends into the liver parenchyma and may be associated with fibroblastic proliferation, which can lead to cirrhosis. Bile duct proliferation of this type is, unlike cholangioma, multifocal and usually widespread throughout the affected liver. In more advanced lesions, the fibrous proliferation is much greater than that usually observed in the stroma of bile duct neoplasms.
Cholangiofibrosis, regarded by many as a preneoplastic lesion, has the characteristic appearance of clumps of glandular structures surrounded by dense connective tissue. The glandular proliferation is from bile ducts and the lesion can be single or multiple, but usually has an initial periportal distribution. The proliferation of connective tissue may be great enough to result in atrophy of the glandular elements. There is a marked production of mucus by the acini in cholangiofibrosis, which is not a characteristic of the cholangioma (see p. 52, this volume).
In contrast to cholangiomas, cholangiocarcino-

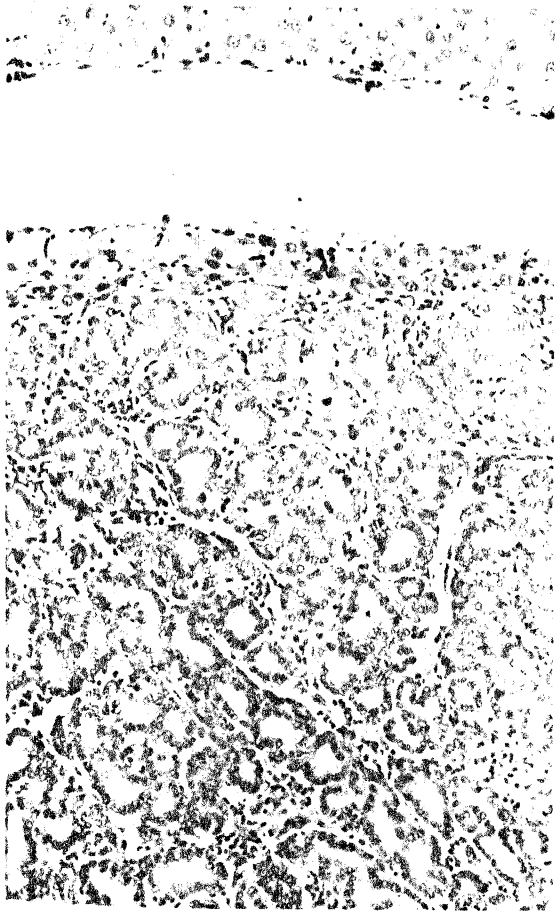

Fig. 50. Liver, rat. A well-circumscribed simple cholangioma illustrating the acinar structure of the neoplasm and the delicate connective tissue capsule. No invasive growth is evident. H and E, × 430

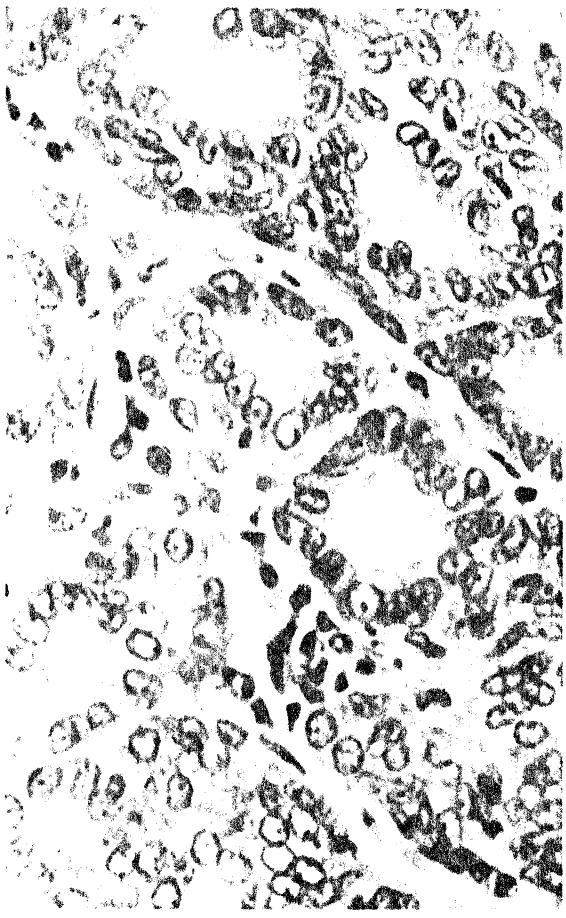

Fig. 51. Cytologic detail of the same neoplasm (Fig. 50) illustrating the single-celled cuboidal epithelial lining of the acini and sparse connective tissue stroma. H and E, × 1720

mas are made up from acini lined by atypical epithelium, the cells of which frequently contain mucus. Cholangiocarcinomas have evidence of invasive growth which is never observed in the cholangioma.

Biologic Features

An early change in the process of chemical-induced carcinogenesis in the rat liver is the proliferation of bile ducts (Farber 1963; Schaffner and Popper 1961; Bannasch and Reiss 1971). This proliferation is considered to be a reparative lesion rather than a direct cellular response to carcinogenic agents (Bannasch and Reiss 1971), and the initial bile duct proliferation does not represent preneoplasia (Schauer and Kunze 1976). However, the long-term administration of carcinogenic compounds can result in the formation of adenomatous hyperplasia, which can progress to cholangioma (Schauer and Kunze 1976).

Of greater significance in the development of cholangiomatous neoplasms is cholangiofibrosis, which is regarded as irreversible (Farber 1963) and preneoplastic (Bannasch and Reiss 1971), although cholangiomas do not always pass through cholangiofibrosis (Schauer and Kunze 1976). Bannasch and Reiss (1971) demonstrated the progression of cholangiofibrosis to cholangioma following the administration of *N*-nitrosomorpholine.

It is probable that cystic cholangiomas result from the accumulation of secretion following partial or complete obstruction of the biliary drainage: this is supported by the appearance of the flattened epithelium of the cystic acini. Such obstruction could result either from internal epithelial prolif-

Fig. 52. Cystic cholangioma with prominent connective tissue stroma. H and E, × 430

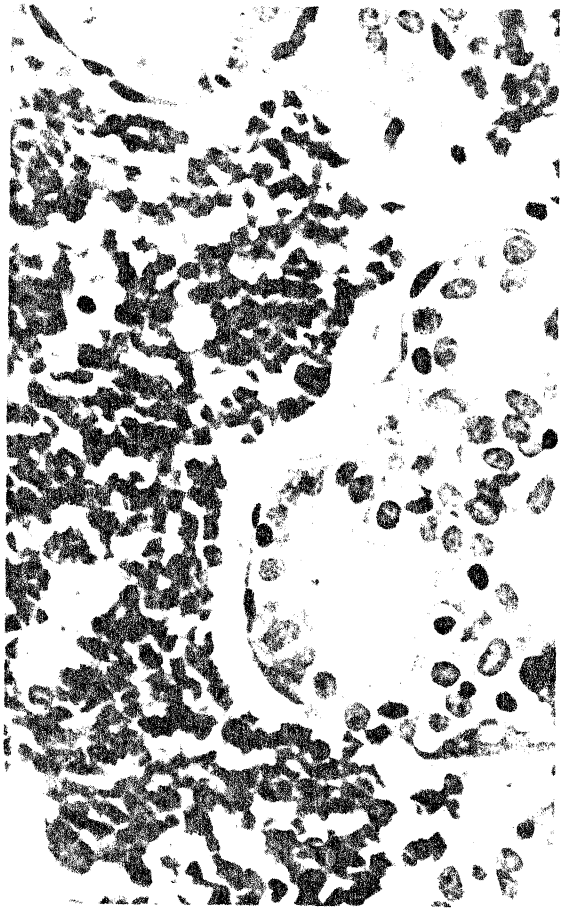

Fig. 53. Hemangiomatous cholangioma demonstrating cystic, endothelial lined spaces in the stroma. H and E, × 1720

eration or from compression resulting from the external proliferation of connective tissue (Schauer and Kunze 1976). Apart from the cystic appearance of the acini, this form of cholangioma is morphologically similar to the simple cholangioma and presumably behaves in much the same way. Cystic transformation of the simple cholangioma seems to be a likely means by which the cystic cholangioma can be formed, although the possibility that some cystic forms arise de novo cannot be excluded, and the appearance of islands of hepatocytes trapped between the cystic acini in some instances is support for a primarily proliferative origin rather than a consequence of cystic transformation of a preexisting simple cholangioma.

Where hemangiomatous areas are present within a cholangioma, there are no indications of a primary proliferation of endothelial cells. Simple endothelium-lined blood-filled spaces surround the glandular acini.

There is no evidence to suggest that, as a general rule, either the simple or cystic forms of cholangioma progress to cholangiocarcinoma.

Comparison with Other Species

Cholangiomas are observed rarely in man and are usually only encountered as an incidental finding at autopsy. In the cat and dog, simple and cystic forms of the neoplasm exist with much the same morphology as that described for the rat. In particular, multilocular cystic forms demonstrate the same pressure-related epithelial flattening, with occasional papillomatous outgrowths, and collagenous septal stroma.

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Hemangiosarcoma, Liver, Rat

James A. Popp

Synonyms. Angiosarcoma; malignant hemangioendothelioma

Gross Appearance

The gross appearance is variable. Lesions may be barely visible or up to 1 cm in diameter. They frequently bulge above the surface of the liver capsule, but are sometimes deeply embedded in the liver parenchyma and not visible on the capsular surface. The lesion usually lacks a capsule and has poorly defined borders. Perhaps the greatest variability occurs in the color, usually red, reddish-brown, or black with a mottled appearance, and in the consistency of the lesion. The more cellular and less vascular areas may be white to light tan. Hemangiosarcomas typically are soft and pliable and ooze blood or blood-tinged fluid when sectioned. Cysts are common due either to greatly dilated vascular spaces or to areas of necrosis which subsequently fill with blood. Rupture of cysts or friable vascular walls results in hemoperitoneum or hemothorax from metastatic lesions in over 75% of rats dying of hemangiosarcoma (Ward et al. 1975). Hemangiosarcomas are frequently multicentric within the liver. Metastatic sites in other tissues have a gross appearance similar to the primary lesion in the liver.

Microscopic Features

Early developing and small hemangiosarcomas consist of small areas (1 mm in diameter) in which the sinusoids are lined by numerous neoplastic endothelial cells that may be multilayered (Fig. 54). The sinusoids are frequently dilated with underlying atrophied hepatocytes. The neoplastic endothelial cells vary in both size and shape, with individual large cells occasionally observed. Mitotic figures may be relatively numerous even in the smaller lesions.

As the neoplasm enlarges, hepatocytes are no longer found within it. Large sheets of neoplastic cells with little evidence of vascular formation are seen. However, in all or nearly all lesions some vessels can be identified even though they may occupy a small percentage of the lesion. The vascular channels may be large dilated cysts or thin capillary-sized openings in the neoplastic tissue. Individual cells of the larger lesions tend to be more pleomorphic, assuming either a polyhedral or spindle shape in different areas of a single lesion (Fig. 55). Large cells with large single nuclei as well as abnormal mitotic figures and numerous mitotic cells are observed: multinucleated giant cells are rare. Necrotic areas are invariably found in large lesions (~1 cm in diameter) and frequently contain hemorrhage.

The border of all hemangiosarcomas, irrespective of size, is indistinct. Neoplastic cells may merge with adjacent normal tissue or may actively invade the sinusoids of adjacent tissue. Encapsulation is never observed although a thin fibrous zone may be found along some edges associated with compression.

Ultrastructure

Limited information is available on the ultrastructural features of hepatic hemangiosarcomas in rats. The large nuclei have an irregular outline but