Ductular and Cholangiocellular Lesions of the Liver

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INTRODUCTION

Primary liver cancer may derive from hepatocytes or bile duct cells. Recently it has been suggested the progenitor cell compartment is also a target cell population for carcinogenesis (1). Hepatic progenitor cells (HPC) are located in the most peripheral branches of the biliary tree, i.e., the ductules and canals of Hering. Biliary epithelium is normally CK7 and CK19 positive. HPC are also immunoreactive to CK7, CK19, oval cell markers OV6 and OV1, neural cell adhesion molecules (NCAM), chromogranin-A, etc. Bile ductules, irrespective of being derived from HPC or from metaplasia of the hepatocytes, express cytokeratins of biliary pattern including CK7, CK8, CK18, and CK19, whereas mature hepatocytes express CK8, CK18, Hep-1 and albumin (2,3).

The term “ductular reaction” was first coined by Popper et al. in 1957 (4) and is now the preferred term to describe “a reaction of ductular phenomenon, possibly but not necessarily of ductular origin” by the consensus opinions from a group of expert liver pathologists (5). In normal liver, ductules are barely visible. Ductular reaction is characterized by increased ductules in and around the periphery of the portal tracts with accompanying inflammatory cells and stromal changes, which can be seen in various liver diseases, including biliary obstruction, chronic cholestasis, submassive liver necrosis with regeneration, focal nodular hyperplasia, etc. Ductular reaction is an important phenomenon that careful consideration is needed to arrive at a diagnosis (6).

BENIGN TUMORS OR TUMOR-LIKE LESIONS

Benign cysts exist in the liver, including solitary bile duct cysts, ciliated hepatic foregut cysts, and multiple intrahepatic cysts as in polycystic disease. Bile duct cysts are unilocular and lined by a single layer of columnar or cuboidal epithelium that are immunoreactive to CK8, CK18, CK7, and CK19, reflecting their cell lineages (7). Ciliated foregut cysts are usually unilocular and in part lined by ciliated pseudostratified columnar epithelium, although in part may be lined by cuboidal or even squamous epithelium. Bundles of smooth muscle are usually present, surrounding the cysts. They are thought to derive from the embryonic foregut and to differentiate towards bronchial structures in the liver. The multiple cysts in polycystic disease are lined by cuboidal, columnar, or flat epithelium. Most solitary bile duct cysts and ciliated foregut cysts are small and asymptomatic, whereas polycystic liver are most likely symptomatic (2,8).

Bile duct hamartoma (aka. von Meyenburg complex or biliary microhamartoma) is usually small (up to several mm in diameter), multiple, and located adjacent to a portal region (9). It arises as a result of developmental anomaly and is often associated with polycystic liver or kidney disease. Histologically it is composed of a variable number of
ductal structures embedded in a hyalinized stroma (2). The ductal structures are variably dilated and may have microcystic dilatation with bile in the ductal lumens. The ductal lumens are lined by a flattened or cuboidal epithelium. Bile duct hamartoma has been associated with neoplastic transformation in reported cases (10). Peribiliary gland hamartoma (bile duct adenoma) is a different entity but it can be at times challenging to discern peribiliary gland hamartoma from bile duct hamartoma. Peribiliary glands are small accessory glands of the major bile ducts in the liver. Grossly peribiliary gland hamartoma is round or ovoid, well-demarcated, but not encapsulated. The lesion is usually single, in contrast to the multiplicity of bile duct hamartoma. Histologically, peribiliary gland hamartoma is composed of tubules and acini, which are lined by a single layer of cuboidal to columnar cells. They do not show cystic changes or contain bile, but intracytoplasmic mucin may be highlighted by special stains such as the Alcian blue stain. The lining epithelial cells of both bile duct hamartoma and adenoma are immunoreactive to CK7, CK8, CK18, and CK19 (11).

Hepatobiliary cystadenoma is a solitary and multilocular cystic neoplasm that predominantly arises within the liver but may arise in the extrahepatic biliary tree including the gallbladder (8). It has striking similarities to mucinous cystic neoplasm of the pancreas and both are almost exclusively a tumor of women. Microscopically it is almost always mucinous and the locules are lined by a columnar epithelium that focally may become cuboidal, flattened or even papillary. The epithelial cells resemble biliary epithelium with cytoplasmic mucin which can be highlighted by alcian blue or mucicarmine. Intestinal metaplasia with goblet cells can be present. The typical densely cellular “ovarian-like” stroma is a feature that hepatobiliary cystadenoma shares with its counterpart in the pancreas (12,13). The ovarian-like stroma is exclusively present in women and has been shown to be immunoreactive to estrogen and progesterone receptors and inhibin (14). The epithelial cells of hepatobiliary cystadenoma and cystadenocarcinoma are immunoreactive to CK8, CK18, CK7, and CK19, a profile consistent with their respective cell lineages (7). Varying degrees of dysplasia in the epithelium may be seen in that it can develop into invasive cystadenocarcinoma (12).

Biliary papillomatosis, or the so called intraductal papillary neoplasms of the biliary tract are rare lesions that may be solitary or may spread extensively along the biliary tree within or outside of the liver including the gallbladder. Similar to intraductal papillary mucinous neoplasm of the pancreas, the involved bile ducts are dilated, containing papillary growth of columnar epithelial cells overlying fibrovascular stalks. The neoplastic epithelial cells may mimic biliary epithelium or show gastric or intestinal metaplasia. Mucin production may be present. The epithelial cells may show varying degrees of dysplasia and may progress to invasive carcinoma (8).

Focal nodular hyperplasia (FNH) is a tumor-like lesion characterized by hyperplastic nodules of hepatocytes, surrounded by fibrous septa radiating from a central stellate scar. Thick-walled arteries are present in the scar and septa, and bile ductules occur at the interface of parenchyma and septa. Hepatocytes near the fibrous septa commonly show chronic cholestasis with pseudoxanthomatous change (cholate stasis), which can be readily demonstrated by a copper stain. FNH is most common in adult women, although
MALIGNANT TUMORS

Although its incidence is far less common than hepatocellular carcinoma (intrahepatic cholangiocarcinoma accounts 10-20% of all primary liver malignancies), cholangiocarcinoma (CC) is gaining increasing recognition especially as the incidence and mortality rates of intrahepatic cholangiocarcinoma (ICC) have been increasing in several regions around the world. In the United States, the age-adjusted incidence rates of ICC increased by 165% from 0.32 per 100,000 in 1975 to 1979 to 0.85 per 100,000 in 1995 to 1999. At the same time, there has been very little improvement in long-term survival, which remains dismal (17). There are few well known risk factors for CC, including primary sclerosing cholangitis, hepatolithiasis, liver fluke infections, Thorotrast exposure, and choledochal cysts. None of these risk factors can explain the recent increasing trends of ICC in the United States. Some data, including population-based study, however, point to a potential role for chronic liver disease, liver cirrhosis, hepatitis C, and probably hepatitis B infections in the development of ICC (18,19). These observations suggest that chronic inflammation may be the common pathogenic pathway for CC. The clinical presentation of CC may vary depending on the site of the tumor. Generally speaking, peripheral ICC may reach to a large mass before detection, whereas CC occurring near the hilum is usually small but may cause obstructive jaundice that causes clinical attention (8). The tumors are generally firm, white to tan. Microscopically they may mimic adenocarcinoma of any sites. The typical structures of the neoplastic cells are glandular, although solid nests, cords or papillary structures can also be seen. The neoplastic cells are those of columnar to cuboidal epithelial cells. A desmoplastic stroma surrounding the carcinoma cells is common. While not always present, the presence of mucin can help distinguish CC from HCC. CC is immunoreactive for CK7 and CK19, reflecting its biliary phenotype, although it is worth mentioning that the expression of CK7 and CK19 in HCC is not uncommon from several series (20,21,22). The positive CA 19-9 is helpful in separating CC from HCC but not from metastatic carcinoma.

Combined hepatocellular-cholangiocarcinoma (HCC-CC) is a rare but intriguing entity in that it has both HCC and CC components. In fact a diagnosis of combined HCC-CC requires unequivocal features of HCC such as trabecular growth, bile production, or bile canaliculi, and unequivocal elements of CC including glandular structures with biliary epithelial cells, mucin production, or in a desmoplastic stroma (8). Cautions should be exercised not to mistake the “pseudoglands” in HCC as the glandular structures in CC. Being able to identify mucin in the lumens or bile in the canaliculi may be helpful in distinguishing one or the other. Some studies show they behave similarly to HCC (2), while other authors suggest these tumors in fact are more comparable to CC in some aspects (23,24,25). Whether combined HCC-CC is biologically closer to HCC or CC is still a debatable issue, but the readily demonstrated biphenotypic differentiation in these
tumors raises an attractive hypothesis that hepatic progenitor cells may be the cells of origin of this unique tumor (25,26). Further studies are needed to address this issue.

Most of the hepatobiliary cystadenocarcinoma arise from preexisting cystadenoma, but some may represent cholangiocarcinoma with cystic formation or rare adenocarcinoma arising in the bile duct cysts (2,8). For this reason cystadenocarcinoma in women often show ovarian-type stroma, but not in men. Features that can help to distinguish from cystadenoma include cytological atypia, mitosis, and invasion of underlying stroma.

**DIAGNOSTIC PITFALLS AND CONCLUSIONS**

The challenging issues in diagnosing cholangiocellular and ductular lesions are to distinguish them from metastatic carcinoma or hepatocellular carcinoma, and to distinguish malignant from benign lesions, especially if the diagnosis relies on a core needle biopsy or during intraoperative consultation. At times it may be difficult to distinguish between the neoplastic cholangiocellular or ductular epithelium and the benign ductular reaction or reactive epithelium in the background of inflammation. Likewise, bile duct hamartoma, peribiliary gland hamartoma, or reactive peribiliary glands may be mistaken for CC or metastatic carcinoma. Typical features of CC are the complex cribriform glands, nuclear pleomorphism, hyperchromasia, mitotic figures, desmoplastic stroma, and lymphovascular space invasion that are lacking in the benign lesions. In addition, epithelioid hemangioendothelioma can be misdiagnosed as ICC because its cytoplasmic vascular lumina may mimic gland formation or mucin. When ductular reaction with associated inflammation is present in a liver biopsy performed for a suspicious neoplasm, an adjacent unsampled mass has to be considered. Immunohistochemical analysis may be of value when diagnostic difficulty occurs. It has been shown the expression of p53, bcl-2, and Ki-67 was greater in CC or metastatic carcinoma than in peribiliary gland hamartoma, bile duct hamartoma, and nonneoplastic inflammatory lesions (11,27). Furthermore, although to some extent immunohistochemistry may help to distinguish CC from metastatic carcinoma from other sites, the immunophenotypic profiles of CC and pancreatic adenocarcinoma are virtually identical and the ultimate distinction relies on the clinical and image correlation. Finally, phenotypic variability is common in liver neoplasms, which may be explained by different histogenesis, or alternatively, by a phenotypic alteration of the mature elements during neoplastic transformation. The role of HPC as the cell of origin in some liver tumors is an interesting subject and ongoing studies may shed more light in the near future.

**REFERENCES**


