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Solid Tumour Section

Mini Review

Liver tumors: an overview

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Classification

WHO histological classification of the liver and intrahepatic bile ducts.

Epithelial tumors

Benign:
- Hepatocellular adenoma
- Focal nodular hyperplasia
- Intrahepatic bile duct adenoma
- Intrahepatic bile duct cystadenoma
- Biliary papillomatosis

Malignant:
- Hepatocellular carcinoma
- Intrahepatic cholangiocarcinoma
- Bile duct cystadenocarcinoma
- Combined hepatocellular and cholangiocarcinoma
- Hepatoblastoma
- Undifferentiated carcinoma

Non-epithelial tumors

Benign:
- Angiomyolipoma
- Lymphangioma and lymphangiomatosis
- Hemangioma
- Infantile hemangioendothelioma

Malignant:
- Epithelioid hemangioendothelioma
- Angiosarcoma
- Embryonal sarcoma
- Rhabdomyosarcoma
- Others

Miscellaneous tumors
- Solitary fibrous tumor
- Teratoma
- York sac tumor
- Carcinosarcoma
- Rhabdoid tumor
- Others

Hematopoietic and lymphoid tumors

Secondary tumors

Epithelial abnormalities
- Liver cell dysplasia
- Dysplastic nodules
- Bile duct abnormalities

Miscellaneous lesions
- Mesenchymal hamartoma
- Nodular transformation
- Inflammatory pseudotumor

Clinics and pathology

Disease

Benign tumors

Hepatic hemangioma: Hemangioma is the most common benign tumor of the liver and is more frequent in women. Many cases are discovered incidentally and the reported incidence is 2-20%. Tumor size may be associated with pregnancy and estrogen levels. Hepatic hemangioma is usually asymptomatic, and rarely grows or bleeds. Surgical excision is required in some symptomatic cases. No genetic alterations heave been reported.

Focal nodular hyperplasia (FNH): FNH is the second most frequent benign tumor of the liver and occurs mainly in women (80-90%). In a hyperplastic lesion, all of the normal liver constituents are present but in an abnormally organized pattern. Underlying congenital arteriovenous malformation, oral contraceptives, and some medicines such as azathioprine are considered to be pathogenic factors. FNH has no malignant potential but a combination of various imaging techniques may be needed for correct diagnosis. FNHs exhibit few chromosomal abnormalities. Strong immunostaining of

ras oncogene p21 has been reported and epithelial cells of the ductular proliferation were bcl-2-positive.

Hepatocellular adenoma: Adenomas occur almost exclusively in younger women. Evidence is accumulating that the intake of oral contraceptives is associated with the occurrence of hepatocellular adenoma. Most are asymptomatic and found by chance at the time of a scan. Prognosis is relatively good. Occasionally, hepatocellular adenomas can be complicated by bleeding either spontaneously or following trauma. The risk of evolution to hepatocellular carcinoma is small. Hepatic adenomas exhibit few chromosomal abnormalities. In one study, nuclear accumulation of β-catenin was reported in 46% of hepatic adenomas, which indicates activation of the Wnt signaling pathway. In another report, truncated forms of β-catenin were detected. Uneven and relatively weak p21 reactions were noted in hepatic adenomas.

Angiomyolipoma: Angiomyolipoma is a relatively rare tumor and is composed of fatty cells, blood vessels, and smooth muscle cells in varying proportions. Thick-walled blood vessels are usually arranged in an island-like formation. Malignant degeneration has not been reported. In one report, of 15 hepatic angiomyolipoma samples tested, all were KIT (CD117), transmembrane growth factor receptor, positive.

Bile duct cystadenoma: Hepatic cystadenoma is a rare multilocular cystic tumor probably occurs as a result of congenital bile duct malformations. It is seen more frequently in women and usually arises from ducts near the hilum of the liver. Owing to its trend towards malignant degeneration, surgical resection may be recommended. No cytogenetic alterations have been reported.

Malignant tumors

Hepatocellular carcinoma (HCC): HCC is the most frequently observed and clinically important primary hepatic neoplasm. It occurs more commonly in men than women and its geographical distribution varies considerably. In areas with high incidence, chronic infection with HBV or HCV is a well-known underlying cause. A frequent association with chronic liver disease/cirrhosis has also been reported. a-fetoprotein and PIVKA-II are the most commonly used tumor-associated markers. It has been reported that chromosomal aberrations on 1p, 6q, 8p/q, and 13p occur almost exclusively in HCCs. Overexpression of c-myc oncogene and a-prothymosin was also reported. An uneven and comparatively weak ras p21 immunohistochemical reaction was noted in HCC. The frequency of p53 mutations varies among different geographic areas. In recent reports, expression of nuclear Jun activation binding protein 1 (Jab1) was observed in 57% of HCCs, and MDM mutations and GAGE-1, GAGE-2 expression were also commonly observed in HCC specimens. In an immunohistochemical evaluation of HCC specimens, altered expression of bcl-2 and human Mut S homologue-2 (hMSH2) proteins was observed during hepatocarcinogenesis. c-erbB-2 oncopeptide was immunohistochemically detected in HCCs although the percentage of samples positive for c-erbB-2 was low.

Intrahepatic cholangiocarcinoma: Intrahepatic cholangiocarcinoma (CC), the second most prevalent intrahepatic primary cancer, arises from the intrahepatic bile duct epithelium. It occurs primarily in the middle-aged and elderly patients with no obvious sex differences. Its incidence varies widely between geographic regions: the highest incidence is reported in Southeast Asia. Opisthorchis viverrini-induced CCs are common in Thailand. Liver fluke infection, carcinogenic nitroso-compounds, hepatolithiasis, and primary sclerosing cholangitis are high-risk factors for intrahepatic CC. CA19-9, CEA, and CA125 are well studied as tumor-associated markers. In intrahepatic CCs, loss of heterozygosity (LOH) at chromosomal loci 3p13-p21, 5q35-qter, 8p22, 17p13, and 18q has been reported. The reported mutation rates of K-ras, which is converted to an active oncogene by point mutations, in intrahepatic CCs vary widely; for example, a mutation rate of 50-56% has been reported in Japanese patients versus 0-8% in Thai patients. Inactivation of p53 by mis-sense or non-sense mutations and by loss of chromosome 17p induces disruption of critical growth-regulating mechanisms and may have a crucial role in carcinogenesis. It has been reported that the p53 mutation and loss of chromosome 17p was present in 11-37% and 38% of intrahepatic CCs, respectively. Alterations of the tumor suppressor gene, p16INK4A, were found to be frequent in a study of intrahepatic CCs. Therefore, the p16 gene may be crucial for intrahepatic biliary carcinogenesis and progression. Amplification and overexpression of proto-oncogene c-erbB-2 are frequently seen in cancers of the biliary tract.

Combined hepatocellular and cholangiocarcinoma: Combined hepatocellular and cholangiocarcinoma (combined tumors) is a more aggressive malignancy with a poorer prognosis than ordinary HCC. Its reported frequency varies widely; but a rate of 1.0-6.5% has been observed among patients with primary liver cancer. Statistically, combined tumors occur predominantly in men, with a mean age of onset in the sixth decade. In Asian cases, a high incidence of HBV or HCV infection and frequent association of cirrhosis have been reported. LOH at 4q, 8p, 13q, 16q, and 17p is frequently seen in combined tumors similar to that in HCC. LOH at 3p and 14q are reported to be specific in CCs and combined tumors in contrast to HCCs. Mutations of the K-ras gene have been reported to be common in CC but rarely in HCC. The reported incidence of p53 mutation is 10-29% in combined tumors.

Hepatoblastoma: Hepatoblastoma, the most common hepatic tumor in children, is arises in the endodermal

liver epithelium and displays various histological patterns. The incidence is twice as high in boys than girls. Key markers include elevation or non-decreasing expression of a-fetoprotein, hepatomegaly, and weight loss. It is strongly associated with familial adenomatous polyposis probably owing to altered expression of the adenomatous polyposis coli (APC) gene. The most common genetic aberrations are extra copies of chromosomes 1q, 2q, 4q, 7q, 8, 17q, and 20, and LOH for 11p. It has been reported that p53 mutations contribute to hepatoblastoma.

Bile duct cystadenocarcinoma: Hepatic cystadenocarcinoma is a rare multilocular tumor containing mucinous fluid. However, it is uncertain whether the incidence differs between sexes. After curative resection, the prognosis is good. In an immunohistochemical study of hepatic cystadenocarcinomas, p53, c-erbB-2, and bcl-2 were focally expressed in the tumor epithelium.

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