Adult Hepatocellular Lesions: Diagnosis and Differential Diagnosis

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Hepatocellular lesions can be neoplastic or non-neoplastic. The common non-neoplasms include regenerative hyperplasia, focal accumulation of fat, focal nodular hyperplasia (FNH), macroregenerative nodules (MRN), and nodular regenerative hyperplasia (NRH). The neoplasms include hepatic adenomas, hepatocellular carcinomas (HCC) and their variants. Accurate diagnosis of these lesions can be sometimes difficult, particularly in liver biopsy specimens. I will briefly discuss the main characteristics of each of these lesions.

Non-Neoplastic Hepatocellular Lesions:

Focal Accumulation of Fat in Liver

Fat accumulation in the liver is common in the liver. However, focal or multifocal fat accumulation with unusual imaging patterns may cause diagnostic difficulty. Sometimes, these lesions are biopsied under CT guidance. Histologically, the liver tissue just exhibits steatosis and non-specific reactive changes. Radiological information is crucial for accurate diagnosis. The major differential diagnosis includes focal nodular hyperplasia, hepatic adenoma, macroregenerative nodules, hepatocellular carcinoma or metastatic tumors.

Macroregenerative Nodules

MRN is often associated with cirrhotic liver. The prevalence of these nodules is approximately 25% in cirrhotic livers. The size of these nodules is usually 0.5 cm to 1.5 cm, but they can be several centimeters. It has been proposed that MRN may be a precursor for HCC. The supporting evidence came from the fact that such nodules are common in HCC patients and dysplastic changes (i.e., dysplastic nodules) are frequently identified in MRN. When these lesions are biopsied, it may be difficult to distinguish from well differentiated HCC. A good reticulin stain, which should highlight the hepatic architecture, is helpful. The other differential diagnosis includes FNH or hepatic adenoma. Examination of the histology of surrounding liver tissue is critical for making accurate diagnosis.

Nodular Regenerative Hyperplasia

NRH is characterized by the presence of small regenerative nodules, the adjacent hepatic acinar atrophy, and occluded portal vessels. It usually occurs in non-cirrhotic livers. NRH is associated with numerous variable systemic diseases, including immunological diseases, vascular disorders, infection, drug toxicity, and cancers. The clinical manifestation of NRH is variable, ranging from asymptomatic, mild liver function abnormality to symptoms related to portal hypertension.
The nodules are usually smaller than 0.3 cm. There is no fibrosis between the nodules. The key histological features are: nodules with regenerative hepatocytes (two cells thick hepatic plates), compressing adjacent hepatic tissue (atrophy), occluded portal veins, dilated sunusoids, presence of bile ducts, and absence of fibrosis or inflammation. NRH should be considered in any liver biopsies taken from patients with non-cirrhotic portal hypertension. A reticulin stain is essential to aid histological evaluation. The key differential diagnoses are: hepatic adenoma, cirrhotic nodules, FNH, and congenital hepatic fibrosis.

NRH is believed to be caused by abnormal blood flow in the liver. The nodules are compensatory liver cell regeneration. Interestingly, Notch1 gene knockout mice show NRH-like lesions in the liver. The natural history of the disease is not clear. It is possible that this disorder is reversible.

Focal Nodular Hyperplasia

FNH is a benign non-neoplastic lesion; it occurs in both men and women; and it is most commonly seen in young women. It is thought that the lesion represents local compensatory hepatocyte regeneration in response to a vascular abnormality. It has been proposed that hormonal use is associated with the development of FNH, but the role of oral contraceptives in FNH remains controversial.

The characteristic gross pathology finding is presence of stellate scars. Microscopically, the nodule is composed of benign hepatocytes arranged in two cells thick hepatic plates. The fibrous septa contain proliferating bile ductules with inflammatory cells. Abnormal, thickened arteries are present. The key differential diagnosis is hepatic adenoma. Presence of bile duct differentiation and abnormal arteries aids FNH diagnosis. Ruling out cirrhotic nodules is critical for accurate diagnosis. Distinction between FNH and adenoma in a small biopsy tissue may not be possible in some instances. Occasionally, both FNH and adenoma are present in the same liver.

Neoplastic Hepatocellular Lesions:

Hepatic Adenoma:

Hepatic adenoma is a benign liver neoplasm. It usually occurs in a normal liver, but it can also occur in glycogen storage disease. Its development is associated with hormonal or metabolic disorders, particularly the use of oral contraceptives. Therefore, hepatic adenoma occurs frequently in young women. When there are multiple adenomas, it is referred as "hepatic adenomatosis". Genetic mutations in hepatocyte nuclear factor 1 alpha (HNF1alpha) gene has been recently identified in hepatic adenomas.

Histologically, hepatic adenoma is comprised of sheets of hepatocytes without forming normal acinar architecture. No bile duct differentiation is present. Steatosis in the neoplastic hepatocytes is common. Abnormal small arteries can be identified.
The major differential diagnosis includes well-differentiated HCC and FNH. It can be very challenging in liver biopsy specimens.

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common primary malignancy in the liver. It usually develops in the setting of chronic liver diseases, in particular, chronic viral hepatitis. The incidence of HCC is increasing. Unfortunately, many cases of HCC are diagnosed in later stages, which tend to have poor clinical outcome.

HCC can be accurately diagnosed in the majority of the liver biopsy cases, although some clinical practices are against the idea of liver biopsy to diagnose HCC for concerns about tumor spreading along the needle track. Classical HCC is not difficult to diagnose, although care must be taken to distinguish dysplastic nodules from definitive HCC. The dual differentiation potential of liver progenitor cells (presumably involved in liver carcinogenesis) may impose a diagnostic dilemma when both biliary and hepatocellular cells are present. The histological variants can be established with the assistance of immunohistochemical staining. The most important histological criterion is the architectural changes (more than three-layers of hepatic plates). Identification of bile production or bile canaliculi is very helpful for diagnosis.

Several histological variants are identified in HCC. Fibrolamellar variant appears to have better clinical outcome than classical HCC. Although there are still no uniformly accepted histological features that predict the tumor behavior, vascular invasion and nuclear features seem to be associated with patient overall survival. The well-accepted system of grading HCC is the one proposed by Edmondson and Steiner in their 1954, which grades HCC with 1-4 based on the overall architectural and cytological evaluation. Identification of HCC biomarkers is currently an active research field. It is expected that novel markers will be available in coming years.

Distinction between HCC and other metastatic cancers can be challenging in some cases. Immunostains are helpful. Most HCCs are reactive to Hep Par1 antibody. We have recently identified the liver specific antigen for this antibody. Polyclonal CEA antibody stains bile canaliculi, which is a very specific for HCC. Detection of AFP can also be helpful for differential diagnosis. Recently, glypican-3 expression has been used to differential HCC from benign hepatic tumors.

References