Pathologic Diagnosis: Pathology of Benign Nodular Lesions Mimicking HCC

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Frequently, nodular lesions that mimic hepatocellular carcinoma (HCC) have encountered, resulting from the recent remarkable advances of imaging modalities as well as incidentally during operation or autopsy. Sometimes, an approach to their diagnosis is not easy, radiologically, but also pathologically. Benign hepatic nodular lesions mimicking HCC may categorized into hyperplastic nodular lesions, neoplastic nodular lesions which are either epithelial or non-epithelial, and miscellaneous nodular lesions (Table 1). In this session, briefly the pathologic characteristics of those nodular lesions will be introduced from the point of differential diagnosis of HCC.

According to an increase of small nodular lesions in the liver, hyperplastic or dysplastic nodules we met are required to be differentiated from well-differentiated HCC. Focal nodular hyperplasia (FNH) is sometimes diagnosed as HCC and considered as one of the common lesions in the differential diagnosis of HCC. FNH has unique clinical and pathological backgrounds as already introduced. When a solitary nodular lesion which is well demarcated, but not encapsulated, close to the liver capsule, not associated with cirrhosis and has a central stellate scar is found grossly, FNH is the first approach to be differentiated. Histologically, FNH has scar tissues consisted of dense fibrous tissue with many anomalous blood vessels, ductular proliferation and sometimes lymphocytic infiltration.

The hyperplastic grades of hepatocytes in FNH are diverse from case to case, from area to area in a case, and when the hyperplastic features consisted of increased cellularity, irregularly thin trabecular or pseudoglandular patterns and increased nucleo-cytoplasmic ratio, we need to differentiate it from a well-differentiated HCC, especially with biopsied specimen without any vessels.
ductular proliferation or scar-like fibrosis. In addition, the sinusoids adjacent to arterial sources are lined by CD34 (+) endothelial cells and the perivenular hepatocytes express glutamine synthetase (GS) which is known to be one of immunomarkers for the differentiation between dysplastic nodule and well-differentiated HCC, although a broad, anastomosing "map-like" patterned immunostaining is noted in FNH. Therefore, careful histological differentiation together with clinical information should be considered for the diagnosis of FNH. Nodular regenerative hyperplasias and large regenerative nodules are previously discussed at first session.

Hepatocellular adenoma (HCA) is a well-demarcated, single or multiple, mostly not encapsulated solid mass, is usually close to the liver capsule, and is sometimes associated with hemorrhage and necrosis in non-cirrhotic liver. Histologically, proliferated benign hepatocytes of HCA arrange in a thin trabecular pattern mixed with pseudoglands, but show rare nuclear atypia or mitoses. Although CD34 (+) arterialized sinusoids may be detected in HSA, portal tracts, bile ducts or central veins are not present inside the HCA. HCA is a heterogeneous entity and recently subdivided into 4 groups (HNF1α-inactivated HCA, β-catenin-activated HCA, inflammatory HCA and unclassified HCA), according to genotype and phenotype. These 4 subtypes of HCA vary in clinical, radiological and pathological findings. Among these subtypes, β-catenin-activated HCA frequently shows nuclear atypia and pseudoglandular pattern, resulting difficulties in differentiation from well differentiated HCC. Because GLU1 encoding GS is a target substrate of β-catenin, GS is up-regulated as well, diffuse and strong expression of GS with aberrant cytoplasmic and nuclear staining of β-catenin by immunohistochemistry may favor the diagnosis of HCA. However, the molecular study for the presence of β-catenin mutation is essential for the confirmation of β-catenin-activated HCA. The bile duct adenoma (BDA) is extremely rare, mostly have been found incidentally and the BDA cells have supposed to have the phenotype of normal peribiliary glands, thus proposed as peribiliary gland hamartoma, rather than biliary epithelial neoplasm. BDA is histologically of proliferated small bile ductules within a fibrous stroma, which induce difficulties in differentiation with von Meyenburg complex, intrahepatic cholangiocarcinoma or metastatic adenocarcinoma, rather than HCC. von Meyenburg complex (biliary hamartoma) is a variable sized tumorous lesion composed of aggregated bile ducts, frequently dilated or cystic, in the fibrous stroma.

The most common benign non-epithelial tumor of liver, cavernous hemangioma is generally not hard to differentiate from HCC, clinically as well as histologically. However, sclerosed hemangioma, an atypical form of hemangioma contains variable degrees of fibrosis, thus may be confused with HCC on imaging and inflammatory pseudotumor on pathology. Angiomyolipoma (AML, PEComa) is a benign tumor composed of variable mixture of blood vessels, spindle or epithelioid smooth muscle cells and fat tissue. This hyperechoic and hypervascular tumor is frequently misdiagnosed as HCC with fatty change or sarcoma. Pathologists should distinguish the fat cell components of AML.
from the fatty change of HCC cells. Particularly, biopsy specimen may be wrongly diagnosed as well differentiated
HCC with fatty change, focal fatty change or lipoma. An important immunomarker, HMB45 is extremely valuable for
the confirmation of AML. 10

Inflammatory pseudotumor is a benign and non-neoplastic mass consisted of proliferated myofibroblasts, fibrous
tissue and remarkable infiltration of chronic inflammatory cells, predominantly plasma cells. Inflammatory
pseudotumor encompasses a wide range of localized inflammatory lesions of unknown causes. Due to the remarkably
increased vasculature in inflammatory granulation tissue, it is sometimes suspected as HCC, radiologically.11 Reactive
lymphoid hyperplasia (pseudolymphoma) has been reported as a nodular lesion which was resected with a preoperative
diagnosis of HCC in a patient with chronic hepatitis C.12

Solitary necrotic nodule of the liver (SNNL) is defined as a solitary, usually small subcapsular nodule which
composes of a core of complete coagulation necrosis and surrounding hyalinized fibrous capsule in a variable degrees
of inflammatory granulation tissue.13 SNNL is considered as the end stage of the natural history of the infections and
degenerative causes.14 Not infrequently, we can confront SNNL or likelihood nodular lesions and need to differentiate
it from spontaneous necrosis of HCC.

Finally, I'd like to introduce the first case of Korean hepatic alveolar ecchinococcosis (AE), recognized as the huge
solid mass, suspicious for malignancy on imaging.15

For the ultimate diagnosis for benign liver nodular mass resembling HCC, the establishment of a well organized
algorithm should be followed via the integration of clinical and imaging information, and histopathologic possibilities.

References

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