Hepatocellular Adenomas
WHO Classification and Immunohistochemical Workup

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KEYWORDS

• Hepatocellular adenoma • HCA • WHO classification • Hepatocellular carcinoma

ABSTRACT

This review discusses the various subtypes of hepatocellular adenomas (HCAs), their diagnosis, and management. HCAs are benign tumors, mostly seen in young women in a normal background liver. Recent advances in understanding HCA pathogenesis and molecular alterations led to recognition of different subtypes, now included in the WHO classification. Complications include hemorrhage and rarely malignant transformation into hepatocellular carcinoma. Diagnosis and differentiation are challenging, requiring careful attention to clinical setting, histology, and immuostaining profile. Risk of complications varies depending on the HCA; hence, subtyping has clinical significance and is performed based on morphology and use of selected immunohistochemical markers.

Key Features

- Hepatocellular carcinoma is a rare, benign liver tumor strongly associated with oral contraceptive pill use in women and androgen steroid therapy in men.
- Most HCAs develop in a noncirrhotic liver, often without any obvious liver pathology.
- The 3 main subtypes of HCA include the following:
  - Steatotic (30%–40%)
  - Telangiectatic/inflammatory
  - β-catenin activated (10%)
- Subtyping of HCA has clinical significance and can be performed based on morphology and use of selected immunohistochemical markers.

INTRODUCTION

Hepatocellular adenomas (HCAs) are benign hepatocellular tumors, mostly seen in young women usually in a normal background liver. Potential complications include hemorrhage and rarely malignant transformation into hepatocellular carcinoma (HCC). Their diagnosis and differentiation from other benign hepatocellular lesions and well-differentiated HCC remains challenging, especially on needle biopsies.

In the past decade, there have been significant advances in the pathogenesis and molecular alterations in HCA, leading to a comprehensive classification with different subtypes. Accordingly, new guidelines, in terms of diagnosis, prognosis, and therapy, have been proposed. Diagnostic criteria based on magnetic resonance imaging (MRI), for identification of the main HCA subtypes have also been developed. This has also led to a more refined approach to a biopsy diagnosis of benign hepatocellular tumors.

EPIDEMIOLOGIC AND CLINICAL DATA

HCA is a rare, benign liver tumor strongly associated with oral contraceptive pill (OCP) use in

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women and androgen steroid therapy in men.[1–3] Indeed, its incidence increases from 0.1 per year per 100,000 in non-OCP users to 3 to 4 per 100,000 in long-term OCP users. The other recognized risk factors include hereditary metabolic diseases, such as glycogenosis (type 1 or 3), galactosemia, hepatic iron overload related to beta-thalassemia, and maturity-onset diabetes of the young type 3 (MODY3).[4–6] More recently, metabolic syndrome (MS), especially obesity, has been identified as a new risk factor that is associated with specific HCA subtypes.[7–9]

Clinically, compared with focal nodular hyperplasia (FNH), HCA is more often associated with symptoms and/or liver function test abnormalities. These include abdominal pain and intraperitoneal hemorrhage associated with tumor rupture. Alfafetoprotein (AFP) is commonly in the normal range and its elevation may be suggestive of an underlying HCC. HCA may be single or multiple, and in cases of more than 10 HCAs, the diagnosis of liver adenomatosis is arbitrarily accepted.[10] Patients with multiple HCAs are predominantly women, and have similar imaging features and risk of complications; however, the use of OCPs appears to be less prevalent. Except for the number of lesions, no difference is observed between imaging features of adenomatosis and solitary HCA, and risk of complications is similar to that in patients with solitary HCA, and is not influenced by the number of tumors.

FROM PATHOLOGY TO MOLECULAR FINDINGS: THE PATHOMOLECULAR CLASSIFICATION OF HCA

Macroscopically, HCAs are usually

- Well-defined tumors of varying sizes, that range from microscopic to 30 cm
- Can be pedunculated
- May have large subcapsular vessels on their surface

On cut sections, the tumor may be homogeneous with a fleshy appearance ranging in color from white to brown, or yellow. Some are heterogeneous, especially the large ones, largely due to areas of necrosis and/or hemorrhage. Importantly, most HCAs develop in a noncirrhotic liver, often without any obvious liver pathology.

Histologically, HCA is characterized by

- Proliferation of benign hepatocytes arranged in regular plates of 1 or 2 cells thick.
- No presence of residual portal tracts, but small thin and unpaired vessels are observed throughout the tumor.
- Rare ductules can be seen, especially with cytokeratin 7 or 19.
- Tumoral hepatocytes may appear normal, clear (increased glycogen), steatotic (fat storing), or pigmented.
- A certain degree of nuclear irregularity and slightly increased nucleo-cytoplasm, especially in patients who have taken steroids for many years; however, presence of obvious dysplasia should raise a serious concern for HCC. In that context, differentiation from HCC requires careful examination of the architectural pattern and additional immunohistochemical markers.

Based on genotype-phenotype correlations, a pathomolecular classification of HCA has been elaborated, defining several distinct subtypes.[11] Given the high concordance among morphology, immunophenotype, and genotype, HCA subtyping can be done in routine clinical practice with selected immunohistochemical stains.[12]

Steatotic HCA

Steatotic HCAs represent a homogeneous group of tumors composed of steatotic hepatocytes without significant inflammation or cellular atypia. This subtype accounts for approximately 40% of HCAs, is the most common phenotype observed in liver adenomatosis, and is usually less prone to severe complications, especially malignant transformation to HCC.[13] Genetically, these HCAs display biallelic mutations of hepatocyte nuclear factor 1α (HNF1α).[14] HNF1α mutations are somatic in 90% of cases. Patients with inherited mutation in one allele of HNF1α may develop MODY3 and are predisposed to develop HCA, when the second allele is inactivated in hepatocytes by somatic mutation or chromosomal deletion.[13] As Liver Fatty Acid Binding Protein (LFABP) is positively regulated by HNF1α, its tissue expression may serve as a relevant surrogate marker of HNF1α inactivation. Thus, HNF1α-mutated HCAs are characterized by the absence of LFABP expression in tumoral cells, contrasting with a constitutive positive expression in nontumoral hepatocytes (**Fig. 1**).[12] Although identification of steatotic LFABP-negative HCA is theoretically easy, either on imaging or histology, in practice problems arise as some tumors have less steatosis. Indeed, in the seminal series, only 36% of LFAPB-negative HCAs displayed extensive steatosis (defined as greater than 60%), whereas 37% of lesions contained less than 30% steatosis.[12] Therefore, immunohistochemistry demonstrating the absence of LFABP expression in the tumor cells could be valuable.