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Hepatocellular adenoma: Classification, variants and clinical relevance

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ABSTRACT

Hepatocellular adenomas are benign tumors with two major complications, bleeding and malignant transformation. The overall narrative of hepatocellular adenoma has evolved over time. Solitary or multiple hepatocellular developing in the normal liver of women of child bearing age exposed to oral contraceptives still represents the most frequent clinical context, however, new associations are being recognized. Hepatocellular adenoma is discovered on a background of liver diseases such as non-alcoholic steatohepatitis, vascular diseases, and alcoholic cirrhosis. Hepatocellular adenoma is also reported in men, young or older adults, and even in infants. On the morpho-molecular side, the great leap forward was the discovery that hepatocellular adenoma was not a single entity and that at least 3 different subtypes exist, with specific underlying gene mutations. These mutations affect the *HNF1A* gene, several genes leading to JAK/STAT3 pathway activation and the *CTNNB1* gene. All of them are associated with more or less specific histopathological characteristics and can be recognized using immunohistochemistry either with specific antibodies or with surrogate markers. Liver pathologists and radiologists are the key actors in the identification of the different subtypes of hepatocellular adenoma by the recognition of their specific morphological features. The major impact of the classification of hepatocellular adenoma is to identify subjects who are at higher risk of malignant transformation. With the development of new molecular technologies, there is hope for a better understanding of the natural history of the different subtypes, and, particularly for their mechanisms of malignant transformation.

The diagnosis of hepatocellular adenoma (HCA) relies first on the examination of slides routinely stained by hematoxylin-eosin (H&E). At first look, it is a benign hepatocellular neoplasm and the main differential diagnosis is focal nodular hyperplasia. In some cases, HCA exhibits worrisome features, which may be difficult to differentiate from very well-differentiated hepatocellular carcinoma (HCC).

Classification of hepatocellular adenoma: genotype and phenotype

Genotype

Recurrent genetic alterations have identified three major subtypes of HCA[1,2] (Table 1).

HNF1a inactivated HCA (35%)

HNF1α inactivated HCA exhibit inactivating *HNF1A* mutations that are somatic in 90% of Case (3). Germline inherited *HNF1A* mutation in one allele is associated with maturity-onset diabetes type 3 (MODY3), a monogenic non–insulin-dependent diabetes.[3,4] HCA that develop in patients with MODY3 present a second somatic mutation that inactivates the other allele of *HNF1A* in the neoplastic hepatocytes. *HNF1A* controls hepatocyte differentiation as well as glucose and lipid metabolism.

Inflammatory HCA (4045%)

Inflammatory HCA are characterized by recurrent somatic activating mutations in genes involved in the IL6/JAK/STAT3 pathway.[5] 60% of inflammatory HCA show IL-6 signal transducer (*IL6ST*) mutations coding for gp130[6]; 10% harbor mutations of the Fyn-related kinase *(FRK)*[7]; 5% have mutations in *STAT3*[8]; 5% in the *GNAS* complex locus[9]; and 3% in the Janus kinase 1 (*JAK1*).[10]

β-catenin activated HCA and β-catenin activated inflammatory HCA (20%)

In 10% of the cases of this category of HCA, there are large deletions in *CTNNB1* exon 3 leading to in-frame deletion of the phosphorylated residues involved in b-catenin degradation[11]; in the other cases, point mutations led to amino acid substitution or small in-frame deletions/insertions. Point mutations are

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Table 1
Salient characteristics of subtypes of hepatocellular adenomas (HCA).

HCA subtype (%)	Gender/Age Etiology (1)	Number	H&E criteria	Rare H&E criteria	Immunohistochemistry	Challenges in immunohistochemical interpretation	Risk for development of HCC	Genetics	Diagnosis MRI/versus biopsy
HNF1α inactivated HCA (35%)	- Females, reproductive age - Men (rare) - MODY3 (both gender)	- Solitary - Multiple -Adenomatosis	- Steatosis macro/micro - Clear cells - Ballooned cells	absence of steatosis	LFABP absent	- Weak contrast between tumor and non-tumor - LFABP not totally absent in tumor	- Low Except in absence of steatosis - MODY3	- *HNF1A* somatic (90%) - *HNF1A* constitutional (10%)	MRI good sensitivity and specificity (if steatosis present)
Inflammatory HCA (40%)	- Females, reproductive age - Men(rare) - Obesity	- Solitary - Multiple -Adenomatosis	- Sinusoidal dilatation -Inflammation -Ductular reaction	absence of sinusoidal dilatation	CRP positive	CRP+in non-tumor	Low	several mutations each leading to STAT3 pathway activation	MRI good sensitivity (if sinusoidal dilatation present)
β-catenin activated HCA (10%), exon 3 **β-catenin activated inflammatory HCA* (7%),** exon 3	- Females - Men /Females - male hormones, familial adenomatous polyposis, Glycogen storage diseases	Solitary	Cytological abnormalities may be present		-GS diffuse homogeneous -β-catenin nuclear staining		High, particularly If TERT promoter mutation	*CTNNB1* ex 3 deletions or mutations	biopsy
β-catenin activated HCA, exon 3 hotspot S45 **β-catenin activated inflammatory HCA*,**exon 3 hotspot S45	- Females - Men /Females - male hormones, familial adenomatous polyposis, Glycogen storage diseases	Solitary	Cytological abnormalities may be present		-GS diffuse heterogeneous -β-cat nuclear staining rare	GS: weak or strong expression	Present	*CTNNB1* ex3 S45	Biopsy
β-catenin activated HCA, exons 7/8 **β-catenin activated inflammatory HCA*,** exons 7/8	Females - Men /Females - male hormones, familial adenomatous polyposis, Glycogen storage diseases	Solitary	No Specificity		-GS focal around veins+occasional areas - no β cat nuclear staining	GS: weak or strong expression	Low	*CTNNB1* ex 7/8	Biopsy
Unclassified HCA ** (10%)	- Females - Obesity	- Solitary - Multiple	Hepatocytes may be smaller and crowded		all markers negative		Low		Biopsy

*CRP+
**Recently "shHCA" due to dysregulation of prostaglandin pathway have been identified. Their identification by immunhistochemistry is not yet validated.[12]
LFABP: liver fatty acid binding protein; CRP: C Reactive Protein; HCC hepatocellular carcinoma; MRI, magnetic resonance imaging; MODY: maturity onset diabetes of the Young.
(1) All HCA subtypes occur mainly in women of reproductive age taking oral contraceptives but can be observed in men, in children, and in older individuals (after menopause in women). Some subtypes are more frequent in patients with high body mass index (Inflammatory HCA, unclassified HCA), MODY 3 (HNF1α inactivated HCA) and in patients exposed to male hormones (β-catenin exon 3 activated HCA). In patients with glycogen storage diseases, all subtypes can be seen except HNF1α inactivated HCA.