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EDITORIAL

Hepatocellular adenoma: Where are we now?

Xi Wang, Xuchen Zhang

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Abstract

Hepatocellular adenoma (HCA) is a benign hepatocellular neoplasm, commonly occurs in young women with a history of oral contraceptive use. Complications including hemorrhage and malignant transformation necessitate the need for a thorough understanding of the underlying molecular signatures in this entity. Recent molecular studies have significantly expanded our knowledge of HCAs. The well-developed phenotype-genotype classification system improves clinical management through identifying "high risk" subtype of HCAs. In this article, we attempt to provide updated information on clinical, pathologic and molecular features of each subtype of HCAs.

Key Words: Hepatocellular adenoma; Subtype; Pathology; Classification; Hepatocellular carcinoma

Core Tip: Hepatocellular adenoma (HCA) has been well recognized as a benign liver neoplasm with risks of hemorrhage and malignant transformation. Studies revealed that different HCA subtypes with specific genetic mutation and pathologic findings are associated with different clinical features. Currently HCAs are classified into at least 5 major subtypes, involving 4 different pathways driving HCA pathogenesis: Hepatocyte nuclear factor 1A, interleukin-6/the Janus kinase/signal transducer and activator of transcription, β-catenin, and Sonic hedgehog pathway.

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INTRODUCTION

Hepatocellular adenoma (HCA) is an uncommon benign liver neoplasm with two major complications: Hemorrhage and malignant transformation. Epidemiological data from the United States and European countries have revealed HCAs occur mainly in young to middle-aged women (median ages: 36-38 years, female/male ratio of 8:1), often with a history of long-term use of oral contraceptives (OCPs)[1,2]. Besides the well-known risk factor of exogenous estrogen exposure, other risk factors, such as androgen use, obesity, fatty liver disease, glycogen storage disease (GSD), especially GSD type 1, hepatic vascular disorders and other genetic disorders are also associated with the occurrence of HCA[2-6]. However, epidemiological data from Asia, where the use of OCPs and the incidence of obesity are lower, are unclear. Limited studies from Taiwan, China and Japan showed a male predominance in patients with HCA[7-11]. Further exploration of these epidemiological differences is needed to better understand the pathogenesis of HCA.

Historically, HCA was thought to be a single group of tumor. Recent advances in HCA clinicopathologic features and molecular biology have not only enhanced our understanding of the disease pathogenesis, but also significantly transitioned into the daily practice of pathology-morpho-molecular correlation. It is known now that HCA is a heterogenous group of liver tumors with heterogenous etiology, clinical presentation, risk of malignant transformation or hemorrhage, radiologic findings, histopathologic features, clinical management strategies and underlying molecular changes. In the current review, we will provide an overview of the current knowledge of how HCA histomorphology correlates to its underlying molecular changes, as well as discuss the controversies in some HCA variants.

HCA: MORPHO-MOLECULAR CLASSIFICATION

Currently, HCAs are classified into hepatocyte nuclear factor 1A *(HNF-1A)* inactivated HCA (H-HCA), inflammatory HCA (I-HCA), β-catenin activated HCA (b-HCA), as well as unclassified HCA (U-HCA) based on underlying molecular changes in 3 different pathways driving benign hepatocytic proliferation: HNF-1A, interleukin-6/the Janus kinase/signal transducer and activator of transcription (IL-6/JAK/STAT), and β-catenin signaling. A new subtype of Sonic hedgehog HCA (shHCA) has been recently described[2], which still needs further characterization. The different mutations in HCA identified to date are summarized in Table 1.

H-HCA

As the first identified subtype, *HNF-1A*-inactivated HCA was proposed by a French group in their pioneer work published in 2002. In an attempt to search for tumor suppressor gene in HCA, Bluteau *et al*[12] genotyped DNA from HCAs and confirmed the bi-allelic inactivation of *HNF-1A* gene in a subgroup of tumors. HNF-1A is an important transcription factor regulating hepatocytes differentiation. It is mainly expressed in pancreatic beta cells, intestine, and liver, that plays an important role in the regulation of glycolipid metabolism[13,14]. Specifically, HNF-1A positively regulates *FABP1* gene, which encodes liver fatty acid binding protein (L-FABP). As a result of *HNF-1A* inactivated mutation, expression of L-FABP is downregulated, along with diffuse steatosis due to dysregulated lipogenesis.

As expected, *HNF-1A*-inactivated HCA histomorphologically shows diffuse marked steatosis (Figure 1A). Immunohistochemical stain for L-FABP is negative (Figure 1B), indicating the functional loss of *HNF-1A* gene. Of note, some H-HCAs may not show steatosis and some other subtype HCAs such as I-HCAs can be seen with marked steatosis. Therefore, steatosis alone should not be used as a sole feature to diagnose H-HCAs. This subtype of HCA approximately composes of 30%-35% of overall HCAs and is mainly due to somatic mutation. Typical H-HCA can also be detected in magnetic resonance imaging (MRI), with diffuse and homogenous signal dropout on T1-weighted images, due to massive fat component[15]. In the clinical aspect, cases of familial liver adenomatosis (greater than 10 adenomas in the liver) have been consistently linked to the germline mutation of *HNF-1A*[16], which is also the genotype in "Maturity onset diabetes of the young, type 3 (MODY3)". Thus, detection of liver adenomatosis with H-HCA is suggested to start family screen for familial adenomatosis, MODY3 diabetes, and the *HNF-1A* germline mutation[17]. Although H-HCA is not usually associated with malignant transformation, hepatocellular carcinoma (HCC) has been reported to arise in the settings of sporadic HCAs[18] as well as those in patients with hepatic vascular disorders or MODY3[19], especially in female patients with multiple lesions without significant steatosis and presence of myxoid change, peliosis and sinusoidal dilatation[3].

I-HCA

Accumulating evidence suggests a critical role of inflammatory response in tumorigenesis, including STAT signaling pathway in the development of breast and lung cancer[20]. Similarly, a subtype of inflammatory epithelial tumors has been described in the family of HCA, involving the IL-6/JAK/STAT3 signaling pathway[21]. IL-6 belongs to the IL-6 cytokine family, which binds to the ligand-

Table 1 Morpho-molecular features of the subtypes of hepatocellular adenoma

	Key pathogenesis	Histology	Immunohistochemical stains	Clinical features
H-HCA	*HNF1A* inactivating mutation: Negative regulation of glycolipid metabolism and L-FABP	Marked steatosis	L-FABP: Negative	Associated with maturity onset diabetes of the young (MODY3) and familial hepatic adenomatosis
I-HCA	IL-6/JAK/STAT3 pathway mutations: (1) Constitutive activation of inflammatory pathway; and (2) Upregulation of acute reactants and hepatocellular proliferation	(1) Inflammatory infiltration; (2) Pseudoportal tracts; (3) Ductular reaction; and (4) Sinusoidal dilatation/peliosis	SSA and CRP: Diffuse positive	Obesity, metabolic syndrome, glycogen storage disease, high alcohol consumption, inflammatory syndrome
b-HCA	(1) *CTNNB1* gene mutation: Activation of signaling pathway and upregulation of targeted genes including GS; and (2) Level of activation depends on mutation loci (Exon 3 Non-S45: Strong activation; S45: Weak activation, and T41: Moderate activation; Exon 7/8: Weak activation)	More atypical features: Pseudoacini and mild cytologic atypia	(1) β-catenin: Aberrant nuclear expression; and (2) GS: Positive	More in men, anabolic steroids use, glycogen storage disease, high risk of malignant transformation, and high risk of bleeding (exon 7/8)
b-IHCA	Share the features of both b-HCA and I-HCA			
shHCA	*INHBE-GLI1* gene fusion: Constitutive activation of Sonic hedgehog pathway	Hemorrhage	PTGSD and ASS1	High risk of bleeding and obesity
Unclassified	Not other specified			
Uncommon subtypes	Myxoid HCA, pigmented HCA, atypical HCA, I-ICA in cirrhotic liver			

HNF1A: Hepatocyte nuclear factor 1A; L-FABP: Liver fatty acid binding protein; SSA: Serum amyloid A; CRP: C-reactive protein; CTNNB1: Catenin beta 1; GS: Glutamine synthetase; INHBE-GLI1: Inhibin beta E chain/glioma-associated oncogene 1; PTGDS: Prostaglandin D synthase; ASS1: Argininosuccinate Synthase 1; HCA: Hepatocellular adenoma; I-HCA: Inflammatory HCA; H-HCA: *HNF1A*-inactivated HCA; shHCA: Sonic hedgehog HCA; b-HCA: β-catenin mutated HCA.

specific receptor gp130 to initiate the downstream signaling. This activates downstream signaling pathways such as the Src-homology 2 domain-containing tyrosine phosphatase 2 (SHP2)-Ras-ERK, JAK1/2-STAT3, mosaic G-protein alpha-subunit (GNAS), and the phosphatidylinositol-3-kinase/Akt and the mechanistic target of rapamycin (PI3K-AKT-mTOR), and further the expression of targe genes that regulate cell survival, proliferation and angiogenesis[2,22]. Rebouissou *et al*[21] demonstrated that 60% of I-HCA harbored small in-frame deletions of *IL6ST* gene (encodes the signaling co-receptor gp130), resulting in the constitutive activation of IL-6 signaling and hepatocellular proliferation in the absence of ligand binding. The remaining I-HCAs are linked to other mutations that belong to IL-6/JAK/STAT3 family. The inflammatory response is well-observed histologically[23], characterized by inflammatory infiltration of lymphocytes, plasma cells and neutrophils, ductular reaction, and sinusoidal dilatation/peliosis (Figure 1C). Immunohistochemical stain is remarkable for diffuse overexpression of acute-phase inflammatory protein such as serum amyloid A (SAA) and C-reactive protein (CRP) (Figure 1D).

Clinically, I-HCA is frequently associated with obesity, metabolic syndrome and high alcohol consumption. Furthermore, the risk of developing HCA in patients with GSD is high. The HCAs in patients with GSD are mainly I-HCAs (52%), followed by b-HCAs (28%) and U-HCAs (20%), but never H-HCAs[5]. A few I-HCA cases had also been reported to induce systemic AA amyloidosis[24]. Typical I-HCA also has unique MRI features, with hyperintensity on T2-weighted images due to sinusoidal dilatation[15]. This subtype approximately composes of 35%-45% of overall HCAs, and about 10% also have β-catenin activation. While the mutation alone is not associated with malignant transformation, it is important to remember that I-HCA can co-exist with β-catenin mutation, the latter of which can transform into HCC[2].

b-HCA

Aberrant Wnt/β-catenin signaling has been identified underlying pathogenesis of many diseases including the well-known familial adenomatous polyposis[25]. In the liver, it also plays an essential role in regulating various cellular events including differentiation, proliferation, survival and others. Not surprisingly, β-catenin (cadherin-associated protein) beta 1 (*CTNNB1*) gene mutations have been reported in around 20%-40% of HCC cases. Chen *et al*[26] detected interstitial deletions in the *CTNNB1* gene in HCAs, indicating the dysregulation of Wnt/β-catenin as a possible preneoplastic pathway for hepatocellular proliferation. Exome sequencing study[27] further subclassified into two types: Exon 3

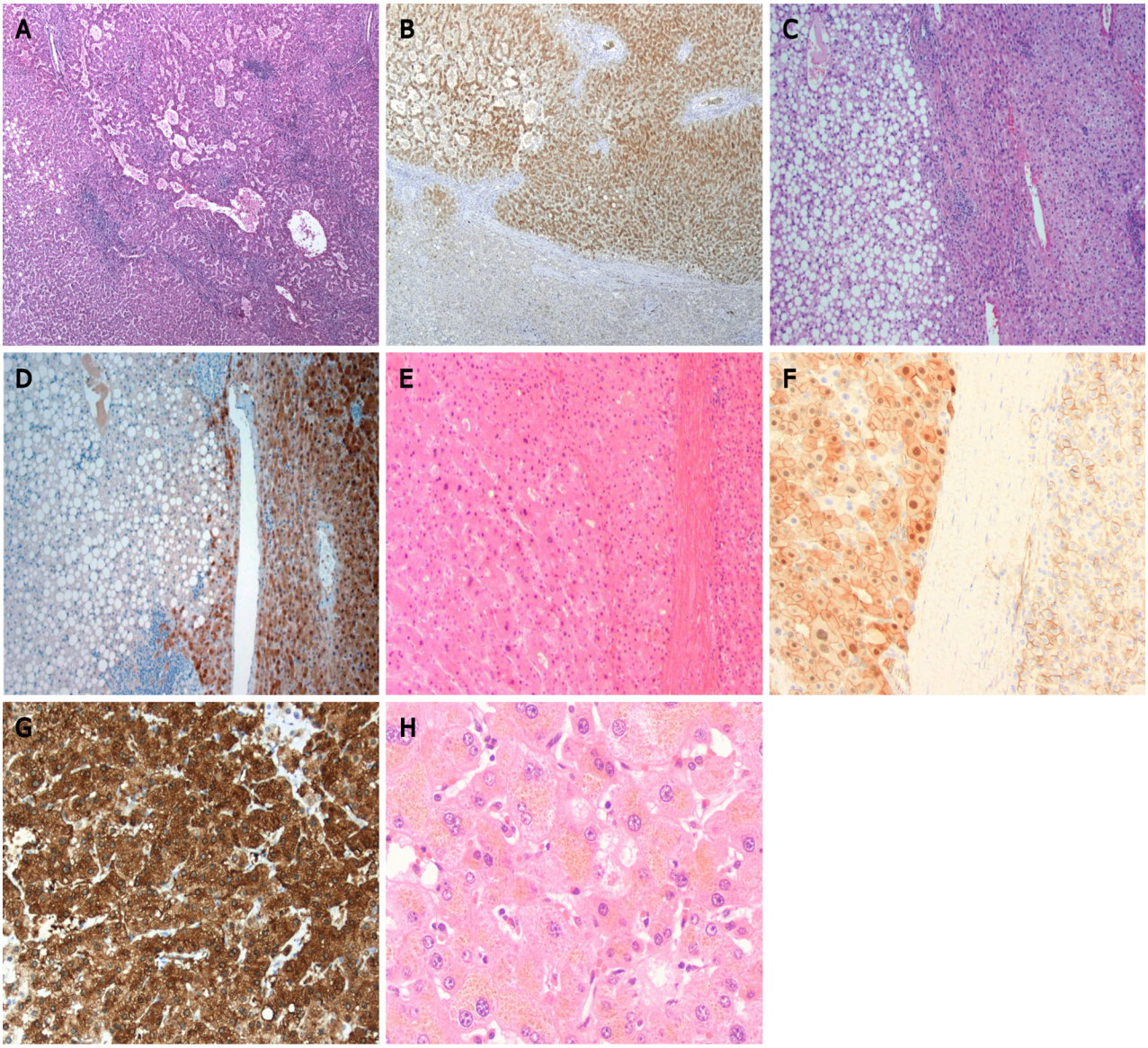

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Figure 1 Histologic features of hepatocellular adenoma. A: Hepatocyte nuclear factor 1A (HNF-1A) inactivated hepatocellular adenoma showing marked steatosis (Hematoxylin-eosin stain, original magnification 200 ×); B: HNF-1A inactivated hepatocellular adenoma showing loss expression of liver fatty acid binding protein in tumor component (Immunohistochemical stain, original magnification 200 ×); C: Inflammatory hepatocellular adenoma showing marked sinusoidal dilatation and pseudoportal tract with inflammatory infiltrate and ductular reaction (Hematoxylin-eosin stain, original magnification 200 ×); D: Inflammatory hepatocellular adenoma showing strong and diffuse expression of C-reactive protein in tumor component (Immunohistochemical stain, original magnification 200 ×); E: β-catenin activated hepatocellular adenoma showing mild cytologic atypia and pseudoacini (Hematoxylin-eosin stain, original magnification 200 ×); F: β-catenin activated hepatocellular adenoma showing nuclear expression of β-catenin in tumor component (Immunohistochemical stain, original magnification 400 ×); G: β-catenin activated hepatocellular adenoma showing strong and diffuse expression of glutamine synthetase in tumor component (Immunohistochemical stain, original magnification 200 ×); H: Pigmented hepatocellular adenoma showing marked cytoplasmic lipofuscin (Hematoxylin-eosin stain, original magnification 400 ×).

and exon 7/8 with distinct canonical and non-canonical mutations respectively. In the canonical pathway, inactive β-catenin is attached with E-cadherin at cell membrane to maintain cell-cell adhesion. Cytoplasmic β-catenin is sequestered by a "destruction protein complex", then phosphorylated, and further recognized by E3 ubiquitin, eventually degraded in the cytoplasm by proteasomes. The overall net effect is low β-catenin levels within the cells. In the activate states or upon WNT binding, the phosphorylation activity is inhibited and the disheveled protein complex becomes disintegrated. As a result, β-catenin accumulates in the cytoplasm and translocates into the nucleus to regulate downstream target gene expression, such as a glutamate-ammonia ligase, which codes for glutamine synthase (GS) and leucine-rich-repeat containing G protein-coupled receptor-5 (LGR5). Thus, the overall net effect is abnormally high expression level of β-catenin within the nucleus and cytoplasm[28]. HCAs with β-catenin mutation are divided into two groups based on the mutation loci in the *CTNNB1* coding for β-catenin: β-catenin exon 3 mutated HCA and β-catenin exon 7/8 mutated HCA[29].

b-HCA exon 3: Approximately 10%-15% of HCAs harbored canonical mutations in *CTNNB1* gene exon 3. The level of β-catenin pathway activation further depends on the specific mutations: Large in-frame deletions, D32-S37 deletions and T41 exon 3 mutations are associated with high level, whereas S45 exon 3 mutations are associated with low level of activation[29]. Comparing with other HCA subtypes, this subtype HCA has more atypical features including mild cytologic atypia, cholestasis, and/or pseudoacinar formation (Figure 1E), which sometimes can be difficult to distinguish from well differentiated HCC. Of note, no specific histologic features can be reliably used to predict a diagnosis of b-HCA. Immunohistochemical stains for β-catenin shows aberrant nuclear and cytoplasmic expression (Figure 1F). While the interpretation of β-catenin expression can be challenging, a better surrogate marker, GS, is also widely used. A recent study has revealed that diffuse homogenous GS staining pattern was strongly associated with exon 3 non-S45 mutation (Figure 1G). Whereas, a diffuse heterogenous GS staining pattern with strong positivity at the tumor periphery indicated exon 3 S45 mutation [30].

Clinically, β-catenin exon 3 mutated HCA is more frequent in men than other subtypes and is more often associated with androgen exposure. In addition, this subtype especially with large in-frame deletions is associated with a high risk of malignant transformation. It is hypothesized that *CTNNB1* exon 3 mutation is the earliest genetic alteration, while additional mutations such as telomere reverse transcriptase (TERT) promoter mutation is involved in the final step of transition from HCA to HCC [27].

b-HCA exon 7/8: A smaller subset of HCAs (5%-10%) harbor non-canonical mutations of *CTNNB1* gene in exon 7 and 8, which is exclusive to mutations in exon 3. In comparison with exon 3 mutations, mutations in exon 7 and 8 result in a weak activation of β-catenin. A focal patchy GS staining pattern in the tumor with strong positivity at the tumor periphery by immunohistochemistry can indicate exon 7/8 mutation[30]. This subtype is associated with a low risk of malignant transformation. A recent study demonstrated that b-HCA exon 7/8 is significantly associated with tumor hemorrhage[31].

β-catenin activated I-HCA

While β-catenin mutations are nearly exclusive to *HNF-1A* mutations, they can be associated with altered JAK/STAT pathway and demonstrate inflammatory features. If the I-HCA shows beta-catenin activation, then a diagnosis of I-HCA with beta-catenin activation can be rendered [β-catenin activated I-HCA (b-IHCA)], which shares the histopathologic features of both b-HCA and I-HCA, and carries malignant transformation potential similarly. It is thus important to continue workup for β-catenin inactivation when a diagnosis of I-HCA is made.

shHCA

ShHCA is a recently recognized subtype of HCA with sonic hedgehog pathway activation[2]. This subtype represents approximately 4% of overall HCAs and was previously classified as unclassified HCA due to the lack of mutations in typical HCA genes. Genetic studies demonstrated that this type of HCA is caused by inhibin beta E subunit (*INHBE*) gene and *GLI1* gene fusion (INHBE-GLI1). The Hedgehog pathway is a complex signal transduction pathway including 4 main components: The ligand Hedgehog, the receptor Patched, the signal transducer Smoothened and the effector transcription factor, Gli[32]. It is not only crucial for embryogenesis of liver, but also plays a role in liver regeneration. Evidence has shown that the Hedgehog pathway is dormant in healthy adult liver, while significantly activated after liver injury. INHBE is a growth factor belonging to the transforming growth factor-beta family. It is highly expressed in the liver and regulates hepatocellular growth and differentiation. As a result, the INHBE-GLI1 fusion leads to uncontrolled activation of sonic hedgehog pathway due to overexpression of transcription factor GLI1.

Clinically, shHCAs are more frequently seen in women and are associated with higher body mass index and/or OCP use. While there are no specific histopathologic features in this HCA subtype, it seems that prostaglandin D synthase and argininosuccinate synthase 1 (ASS1), particularly ASS1 positivity by immunohistochemistry is a hallmark of shHCA[2,33]. Although ASS1 may be expressed in other HCA subtypes with hemorrhage and thought to be a marker of hemorrhage[34], a recent study showed ASS1 expression did not correlate with HCA hemorrhagic complications[35]. Interestingly, higher risk of hemorrhage has been consistently observed both histologically and clinically in shHCA[2, 31]. This serious complication warrants a thorough understanding of pathogenesis of shHCA for better diagnosis and clinical management.

Unclassified HCA

Even though extensive studies have been conducted to explore molecular features of HCAs, approximately 5%-10% remain unclassified. These HCAs lack distinct histopathologic features and any specific molecular abnormality[2].

UNUSUAL SUBTYPES AND CONTROVERSIES

In addition, uncommon HCA subtypes have been well documented, which do not fit well into the current classification.

Pigmented HCA

Pigmented HCAs are a heterogenous group of HCAs with different genetic mutations, which contain pigment deposition of lipofuscin (Figure 1H) as confirmed by electron microscopy[36]. Although H-HCA is the commonest subtype, other subtypes such as b-HCA, I-HCA, b-IHCA, and unclassified HCA also can be seen in pigmented HCAs[36-38]. Pigmented HCAs often show histologic atypia with higher risk malignant transformation. Besides the heavy deposition of lipofuscin in tumor cells, lipofuscin pigment deposition is commonly seen in hepatocytes of the background livers[36]. Although unclear, the underlying biology may be related to dysregulation of autophagy resulting in lipofuscin accumulation, which could contribute to carcinogenesis including the liver[39,40].

Myxoid HCA

Myxoid HCAs are characterized by the deposition of myxoid materials between the hepatic cords within the tumor[41-44]. In addition to loss of L-FABP expression and/or *HNF-1A* mutation as documented in all myxoid HCAs, a recent study identified recurrent mutations in genes within the protein kinase A (PKA) pathway or in genes that regulate the PKA pathway, such as GNAS, CDKN1B (p27) and RNF123, in myxoid HCAs[44]. Myxoid HCAs are often seen in individuals with older age and carry a high risk of malignant transformation[3,44]. It is still controversial whether this is a rare variant of H-HCA with additional mutations or a distinct subtype of HCAs.

Atypical/borderline HCA/hepatocellular neoplasm of uncertain malignant potential

HCA, as described above, has potential of malignant transformation that sometimes can be challenging to distinguish from well-differentiated HCC, especially in biopsy specimens. Various terms, such as atypical HCA, borderline HCA, atypical hepatocellular neoplasm, well-differentiated hepatocellular neoplasm with atypical or borderline features, and hepatocellular neoplasm of uncertain malignant potential (HUMP) have been used for hepatocellular neoplasms that demonstrate features atypical for HCA but insufficient for an unequivocal diagnosis of HCC. So far there are no widely accepted criteria in diagnosing this entity, however, these clinical (male, females > 50 years or < 15 years) and pathologic (focal cytological atypia, small cell change, pseudoacini, focal reticulin network loss, presence of β-catenin activation or *CTNNB1* mutations) features have been consistently used when an atypical/borderline HCA (A-HCA)/HUMP is diagnosed[45-47]. A recent study showed that greater than 60% HCAs would be re-classified as A-HCAs/HUMPs using the above suggested criteria. Furthermore, in this study A-HCA/HUMP does not seem to correlate in patients with or without synchronous or metachronous HCC[45]. The high rate of HCAs placed in the category of A-HCA/HUMP, particularly in resected tumors may cause confusion to clinicians in managing those tumors. Molecular study of *TERT* promoter mutations, a marker of HCC, may be useful to distinguish A-HCA/HUMP from well-differentiated HCC and predict the risk of malignant transformation. Studies have demonstrated that *TERT* promoter mutations have been identified in 17% of A-HCAs/HUMPs compared with 50%–60% of HCC[48]. Further study to refine the widely accepted criteria of diagnosing A-HCA/HUMP and to predict its malignant behavior by combining the clinical, pathological and molecular features is warranted.

I-HCA in cirrhotic livers

HCAs typically arise in the livers without significant fibrosis. The background liver can be histologically normal or have steatosis or steatohepatitis or other genetic and vascular disorders that have been recognized as risk factors for developing HCAs. Thus, a solid mass arising in a cirrhotic liver is generally not considered as HCA. However, rare HCAs with SAA positivity or harboring activating mutations in *IL6ST* or *STAT3* same as I-HCAs have been described in metabolic syndrome and/or alcoholic cirrhosis[49,50]. Of note, some cirrhotic nodules and HCCs can be positive for CRP and SAA, the two important I-HCA markers. Furthermore, activation of IL-6/gp130/STAT3-dependent pathway is involved in the development of liver fibrosis[51]. Therefore, classifying those SAA-positive cirrhotic nodules with *IL6ST* or *STAT3* mutations as I-HCAs is thought to be premature[52]. Additional data are warranted to confirm whether HCA can arise in a background liver with cirrhosis.

MANAGEMENT

Guidelines from both the American College of Gastroenterology[53] and the European Association for Study of the Liver[54] recommend a surgical resection when HCAs are > 5 cm, since they have a higher potential for hemorrhage and malignant transformation. The adoption of a genotype-phenotype classi-

fication is increasingly relevant to clinical decision-making given growing evidence that the risk of complications is likely dependent on HCA subtype and gender. Currently, the treatment of HCA is based on HCA subtype and gender[17,54,55]. Briefly, surgery is recommended for all men with HCAs since they carry a high risk of malignant transformation. For women, after the initial 6 mo lifestyle management including the discontinuation of OCPs and control of body weight, the management of HCAs is based on the size and HCA subtypes. For tumors persistently > 5 cm, or increasing in size after lifestyle change, irrespective of their subtypes, resection or curative treatment is indicated. For tumors < 5 cm of the H-HCA subtype, or those that are either inflammatory or β-catenin negative on biopsy, conservative management is recommended. Of note, surgical resection is recommended for b-HCAs, b-IHCAs and A-HCAs/HUMPs, irrespective of size. Of note, HCAs arising in patients with underlying liver diseases, such as GSD and hepatic vascular disorders seem to have a higher risk of malignant transformation, that should also be considered when manage these HCAs.

CONCLUSION

Recent molecular studies have significantly expanded our knowledge of HCAs. The newly developed phenotype-genotype classification system not only fulfils our curiosity academically, but more importantly, helps improving clinical management through identifying the "high risk" subtype of HCAs. However, further studies are needed, including how to incorporate the uncommon HCA subtypes into the classification system, how to effectively guide the HCA management by using the classification system and identifying the underlying molecular changes of the unclassified HCAs.

FOOTNOTES

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