Grand Rounds

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Molecular classification of hepatocellular adenoma in clinical practice

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Summary

Hepatocellular adenomas (HCA) are rare benign liver tumors occurring in young women taking contraception. They are associated with rare complications such as bleeding or malignant transformation into hepatocellular carcinoma. A molecular classification has divided HCA in several subgroups linked with risk factors, clinical behaviour, histological features and imaging: *HNF1A* inactivated HCA, Inflammatory HCA, *CTNNB1* mutated HCA in exon 3, *CTNNB1* mutated in exon 7 and 8 HCA, sonic hedgehog HCA and unclassified HCA. CTNNB1 *mutated* HCA in exon 3 and sonic hedgehog HCA have been linked with a high risk of malignant transformation and bleeding respectively. Herein, we review how molecular classification has modified our understanding of the pathophysiology and risk factors of HCA development, analysing its impact on clinical care in the field of diagnosis and therapeutic stratification.

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Key point

Genomic alterations are the backbone of the new HCA classification according to defined molecular subclasses.

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Clinical vignette

An incidental liver lesion was detected on preoperative imaging for bariatric surgery in a 34-year-old woman (body mass index [BMI] = 42), with a 15-year history of oral contraceptive use, normal blood liver tests and high C-reactive protein (CRP) (11 mg/L, Nl <6). Magnetic resonance imaging (MRI) showed a 6 cm liver nodule in segment V close to the gallbladder. The nodule was moderately hyperintense on T1 (in-phase) and showed a marked and heterogeneous drop in signal intensity on the opposed-phase sequence, suggesting the presence of fat. On T2, the nodule was heterogeneous, hyperintense at the periphery and hypointense in most of its centre. Dynamic contrast-enhanced sequences showed a strong and heterogeneous enhancement of the nodule on arterial phase that predominates at the periphery. The lesion was heterogeneous on portal and delayed phase imaging, predominantly hypointense and hyperintense at the periphery. A slight drop in signal intensity on the opposed-phase sequence was observed in the adjacent liver, suggestive of mild steatosis (Fig. 1).

The diagnosis was likely to be hepatocellular adenoma (HCA): hypervascular liver lesion in a young woman, long oral contraceptive intake, absence of chronic liver diseases. However, this case raised several questions for this patient:

I. Did we need to perform a biopsy of the tumour?
II. Did we need to perform a molecular subtyping of the adenoma?
III. Are imaging features sufficient to subtype the adenoma?
IV. What type of treatment could we propose?

General introduction

HCA is a benign liver tumour derived from the proliferation of mature hepatocytes.[1,2] The main risk factor for HCA development is oestrogen exposure, explaining the predominance of female cases and the association with oral contraception.[3,4] It also explains the increased prevalence of HCA in the seventies, following the introduction of oral contraception in Western countries, with an incidence of HCA estimated at 3/100,000 in women exposed to high doses of oral contraceptives.[5,4] However, the current incidence of HCA in women taking low dose oral contraceptives is unknown. Moreover, HCA is exceptional in regions where oral contraception is not widely used, such as Asia. Several other risk factors have also been described: androgen intake, vascular liver disease, glycogenosis type 1A and familial ade-

nomatous polyposis.[6] Liver adenomatosis is defined by the presence of more than 10 HCA in the liver.[7]

Confronted with a potentially benign liver tumour, the first key clinical point is to perform a precise and unambiguous diagnosis.[3] Imaging is useful to rule out focal nodular hyperplasia (FNH) and hepatic hemangioma. Histological analysis remains the gold standard of HCA diagnosis and can also help to rule out differential diagnoses, such as hepatocellular carcinoma (HCC) or FNH.[8] When a diagnosis of HCA is confirmed, the next step is to evaluate the risk of complications. The two main complications of HCA are tumour bleeding and malignant transformation in HCC.[9] Symptomatic bleeding occurred in around 10 to 20% of patients at diagnosis. Tumour size has been linked with the risk of bleeding, with a cut off of 5 cm proposed in the literature.[9,10] Malignant transformation is a rare event observed in around 5% of HCA cases treated by liver resection.[11] The rate of malignant transformation in HCA that is not treated surgically is unknown, but probably lower. Male sex and a tumour size of more than 5 cm have been identified as factors associated with a higher risk of malignant transformation.[12,10]

Recently, major advances have refined our knowledge of the molecular mechanisms underlying HCA development.[1] The identification of genetic alterations and deregulated signalling pathways is the backbone of molecular classification in HCA. Several tumour subgroups are defined by specific signalling pathway deregulations and genomic defects linked with specific risk factors, including clinical presentation, risk of malignant transformation, histological and imaging features.[11,13] Herein, we aim to detail the recent knowledge surrounding molecular classification of HCA and highlight how the genotype/phenotype classification could impact clinical care in the future.

The HCA molecular classification in 2017

HCAs can be classified into six major molecular subgroups associated with specific clinical features (Fig. 2).

HNF1A inactivated HCA (HHCA)

Bi-allellic inactivating mutations of hepatocyte nuclear factor 1 alpha (*HNF1A*) are present in 40 to 50% of HCA.[14] HNF1A is a key transcription factor that controls several major metabolic pathways in hepatocytes.[15] Metabolic and non-metabolic changes in hepatocytes with inactivated *HNF1A* include glycolysis activation, mechanistic target of rapamycin (mTOR) pathway activation, oestrogen metabolism and fatty acid synthesis deregulations with liver fatty acid binding protein (LFABP) down-expression leading to fatty acid accumulation and steatosis in tumour hepatocytes.[15,16]

β-catenin exon 3 mutated HCA (b^{ex3}HCA)

Mutations of *catenin β 1* (*CTNNB1*) in exon 3 (coding for β-catenin) are observed in 10 to 15% of HCA.[11] These mutations are canonical, leading to constitutive β-catenin activation, which is also observed in several other types of cancer, such as colorectal cancer and medulloblastoma.[17] Mutations in exon 3 of *CTNNB1* impair β-catenin phosphorylation, by the inhibitory complex composed of glycogen synthase kinase 3 beta (GSK3B), APC and AXIN1. Thus, preventing β-catenin degradation by the proteasome. Finally, *CTNNB1* mutations induce the translocation of β-catenin to the nucleus where it acts as a co-transcription factor with T cell factor (TCF), strongly inducing the expression of WNT/β-catenin target genes, such as *glutamate-ammonia ligase* (*GLUL*), which codes for glutamine synthase (GS), and *leucine-rich-repeat containing G protein-coupled receptor-5* (*LGR5*).[18] This subtype of HCA is associated with a higher risk of malignant transformation, making its identification key in clinical practice.[19] Interestingly, mutations in exon 3 leading to S45 residue substitution are associated with a lower activation of the WNT/β-catenin pathway, a lower overexpression of target genes (*GLUL*, *LGR5*).[20,18] On the other side, *CTNNB1* exon 3 mutations are frequent in HCC (20 to 40%), and in HCC S45 mutations are associated with a clear-cut increase in expression of *GLUL* and *LGR5*, promoted by S45 allele duplication.[20] These observations showed that a strong activation of the WNT/β-catenin pathway is required for malignant transformation in HCC.[20]

β-catenin mutated HCA exon 7/8 ($b^{ex7,8}$HCA)

A subset of HCA (5 to 10%) harboured non-canonical mutations of *CTNNB1* in two hot spots in exon 7 and 8.[21] These mutations are exclusive to mutations in *CTNNB1* in exon 3. Interestingly, mutations in *CTNNB1* exon 7 and 8 corresponded to a weak activation of the WNT/β-catenin pathway, correlated with a weak overexpression of GLUL and LGR5.[21,18] Moreover, HCA with *CTNNB1* mutations in exon 7 and 8 was not associated with a high risk of malignant transformation.[21] This observation is a paradigm of genotype/phenotype correlation with mutations in *CTNNB1* exon 3 linked with strong WNT/β-catenin activation and a high risk of malignant transformation and *CTNNB1* mutations exon 7 and 8 correlated with weak activation of the pathway and no association with malignant transformation.[13,20]

Inflammatory HCA (IHCA)

IHCA accounts for 35 to 45% of HCA cases and is defined by the constitutive activation of the IL6/JAK/STAT pathway in tumour hepatocytes, with an over-expression of acute phase inflammatory proteins like CRP and serum amyloid A (SAA).[22–24] In tumour hepatocytes JAK/STAT activation is caused

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Key point

Six major molecular subtypes of HCA have been described: *HNF1A*-inactivated HCA (HHCA), inflammatory HCA (IHCA), β-catenin exon 3 mutated HCA (b^{ex3}HCA), β-catenin exon 7/8 mutated HCA ($b^{ex7,8}$HCA), Sonic Hedgehog activated HCA (shHCA) and unclassified HCA (UHCA).

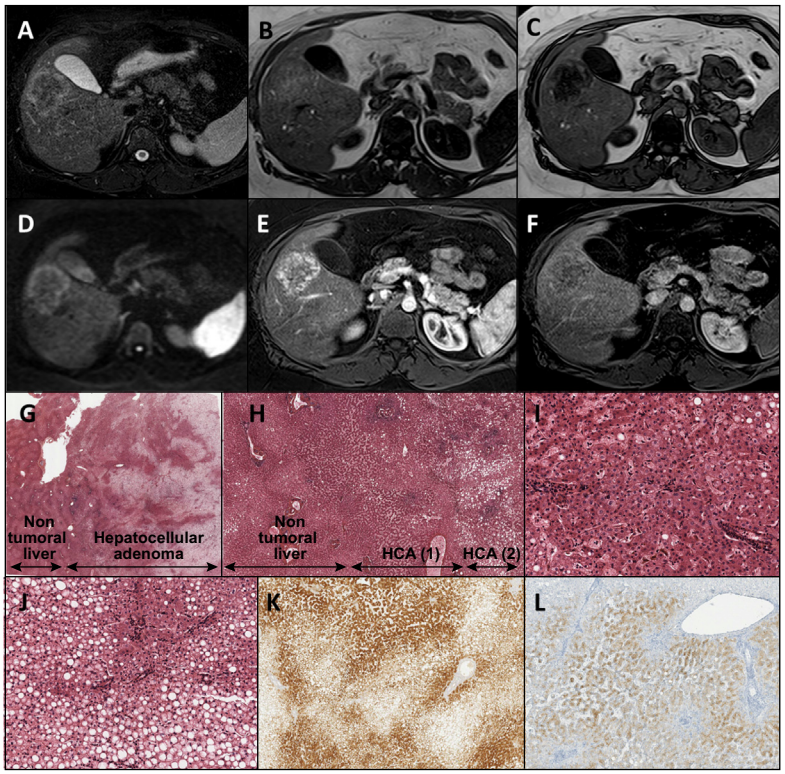

Fig. 1. Histological and imaging features of an inflammatory adenoma. A–F: Magnetic resonance imaging (MRI). A: T2-W MRI showing a heterogeneous lesion with hyperintense periphery. B and C: in- and opposed-phase T1-W MRI. Drop of signal intensity on opposed-phase indicating the presence of fat in the center of the lesion. D: diffusion-W MRI highlighting the restricted diffusion at the periphery. E and F: contrast-enhanced MRI obtained at the arterial and delayed phase. The lesion strongly enhances at the periphery and remains hyperintense while the center of the lesion becomes hypointense. G-l: Histology. G: Low magnification showing a tumour nodule poorly limited, mostly steatotic. H: the lesion displays two different tumoural parts (1) peripheral, nonsteatotic with telangiectatic features and (2) central, mostly steatotic. Higher magnification of (I) peripheral part showing trabecular hepatocellular proliferation with small unpaired arteries and slight sinusoidal dilatation and (J) central part showing the proliferation of steatotic tumoural hepatocytes. The hepatocellular adenoma is C-reactive protein (K) and serum amyloid A (L) positive.

by activating mutations of any one oncogene belonging to this pathway: *IL6ST* (coding for gp130, 77%), *STAT3* (4%), *GNAS* (3%), *FRK* (9%) and *JAK1* (1%).[22,25,21,26,13] All these oncogenes induce the translocation of the STAT3 transcription factor to the nucleus, leading to the uncontrolled activation of the inflammatory pathway, underlining the concept of "oncogene induced inflammation".[1] Inflammatory syndrome and anaemia and/or fever are sometimes observed in these patients and can be considered paraneoplastic syndromes induced by the uncontrolled production of cytokines.[27,28] Tumour resection may suppress paraneoplastic symptoms.[27] Importantly, half of b^{ex3}HCA and $b^{ex7,8}$HCA also harboured an inflammatory phenotype, leading to mixed b^{ex3}IHCA and $b^{ex7,8}$IHCA tumours that share the clinical features of each subgroup.[21] Consequently, activation of the WNT/β-catenin pathway should be assessed in IHCA.[19]

Sonic hedgehog HCA (shHCA)

Recently, we identified a constitutive activation of sonic hedgehog pathway in 5% of all HCAs.[13] These tumours were previously considered unclassified because of the lack of mutations in typical HCA genes and the absence of activation of pathways classically deregulated in HCA. The key genetic driver of the sonic hedgehog activation was the somatic fusion between *inhibin beta E subunit* (*INHBE*), a highly expressed gene in the liver, and *GLI family zinc finger 1* (*GLI1*), the key transcription factor of the sonic hedgehog pathway.[13] This fusion gene leads to the uncontrolled activation of sonic hedgehog pathway due to the overexpression of GLI1.[13] Interestingly, shHCA was associated with a higher risk of bleeding, both at the histological and clinical levels.[13] Consequently, identification of sonic hedgehog pathway in clinical practice could be useful to stratify clinical care according to the risk of tumour bleeding.

Unclassified HCA (UHCA)

Finally, less than 7% of HCA harboured no genetic alterations or clear-cut deregulation of signalling pathways and are still considered as unclassified HCA.[13]

HCA risk factors: Relations with molecular subtypes

Germline HNF1A mutations and liver adenomatosis

In the 1990s, germline *HNF1A* mutations were identified as the cause of autosomal dominant maturity-onset diabetes of the young type 3 (MODY3), a genetic type 2 diabetes occurring in young patients in a familial context.[29] At the beginning of the 2000s, we described familial cases of liver adenomatosis associated with MODY3 owing to a germline mutation of *HNF1A*.[30,31] This observation fits the Knudson two hit model, with a first hit due to a germline inactivating mutation of *HNF1A*, with a second hit caused by a somatic mutation that inactivates the second allele in the tumour.[14] To the best of our knowledge, all the familial HCA cases reported worldwide are linked with *HNF1A* germline mutations and HCA frequently occurs in children.[32] However, the development of liver adenomatosis in patients with MODY3 is infrequent, suggesting the role of additional environmental and/or genetic factors.[13] Faced with a liver adenomatosis composed of HHCA, familial liver adenomatosis and *HNF1A* germline mutations should be studied, so that familial screening of adenomatosis and MODY3 can be proposed.[31]

Androgen exposure and b^{ex3}HCA

Whereas the predominance of oestrogen influence in HCA development is obvious in the literature,

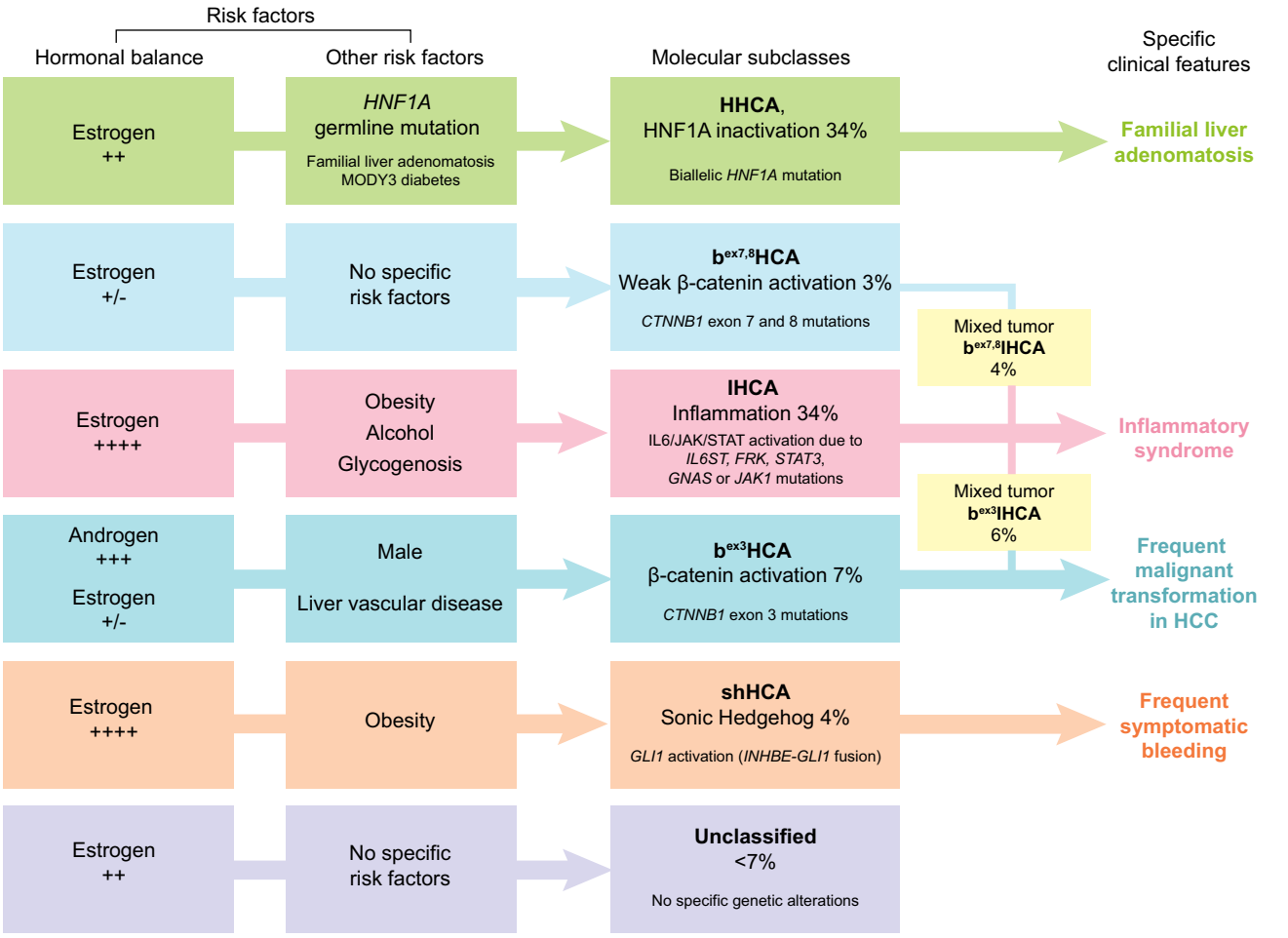

Fig. 2. The genotype/phenotype classification of hepatocellular adenomas (HCAs). The main molecular subtypes of HCA linked with specific risk factors, clinical features and risk of complications were represented. Mixed forms between inflammatory HCA (IHCA) and β-catenin exon 3 mutated HCA, and between IHCA and β-catenin mutated HCA exon 7/8 have been described.

since most patients with HCA are female, an over-representation of males is recurrently observed in the subgroup of HCA that harbour mutations in exon 3 of *CTNNB1*.[11] Overall, the occurrence of b^{ex3}-HCA is closely related to androgen exposure either endogenous (male) and/or exogenous (androgen intake for bodybuilding or for treatment of Fanconi anaemia for example).[13] Most of the cases of HCA that develop in patients taking anabolic steroids are b^{ex3}HCA.[13,33] Moreover, females that develop b^{ex3}HCA are clearly less exposed to oestrogen during their life than patients with other molecular subgroups.[13] Overall, occurrence of b^{ex3}HCA is mostly influenced by androgen exposure, without clear and strong evidence for a role of oestrogen in its pathogenesis.

Oestrogen exposure in inflammatory and sonic hedgehog HCA

Patients with IHCA and shHCA have a high cumulative intake of oral contraceptive during their lives.[13] Moreover, obesity is a risk factor for inflammatory HCA and sonic hedgehog HCA development.[13] Putting together the different determinants of oestrogen exposure, such as the number of years of oral contraceptive use, the BMI and alcohol intake, we demonstrated that IHCA and shHCA are related to a high exposure to oestrogen, whereas *CTNNB1* mutated HCAs (in exon 3 and in exon 7/8) have a low lifetime exposure to oestrogen.[13] In contrast, HHCA show an intermediate level of oestrogen exposure, suggesting a role for additional environmental and/or genetic factors that promote their development. Consequently, the balance between oestrogen and androgen, as well as the magnitude of oestrogen exposure, are important in the development of the different molecular subtypes of HCA.[13]

Underlying liver disease and HCA

HCA developed mostly on normal liver. However, this assumption should be tempered after the close examination of the non-tumour liver in patients

Key point

Specific risk factors including androgen exposure and oestrogen exposure predispose to development of specific HCA subtypes.

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with HCA, and the observation that chronic liver diseases are sometimes present.[13] Steatosis and sometimes non-alcoholic steatohepatitis are described in the non-tumour liver of patients with IHCA and shHCA owing to the association between these molecular subgroups and obesity.[13] We also identified rare cases of IHCA harbouring activating mutations in *IL6ST* or *STAT3* developed on cirrhosis, related to metabolic syndrome or chronic alcohol intake.[34,35] The same observations have also been described on cirrhosis in Japan. However, additional data are warranted to confirm that HCA can arise on cirrhotic liver. Glycogenosis type 1 is a genetic disease caused by germline mutations of glucose-6-phosphatase and responsible for severe hypoglycaemia in childhood.[36] These patients harboured frequent steatosis on their livers, together with glycogenic inclusion and liver metabolic defect. More than half of these patients will develop multiple HCA in adulthood, a critical issue in their management.[36] Interestingly, HHCA were never observed in patients with glycogenosis that could be explained by similar metabolic defects observed with *HNF1A* inactivation and glucose-6-phosphatase deficiency.[36] Finally, several vascular liver diseases, such as Budd-Chiari syndrome, portal vein agenesis, hepatoportal sclerosis or Fallot tetralogy have been associated with a large spectrum of liver nodules, from FNH to HCA or HCC.[37] We also described an enrichment of b^{ex3}HCA in patients with vascular liver diseases.[13]

Molecular classification to improve histological diagnosis of HCA

Diagnosis of HCA relies on well-defined histological features (a trabecular proliferation of benign hepatocytes without portal tracts that display unpaired thin arteries throughout the tumour). Moreover, histological subtyping based on a set of morphological and immunophenotypical characteristics, directly related to the genomic analysis, can help in the diagnosis of HCA (Fig. 2).[1]

Key point

Molecular subtypes correlate with specific imaging, histological and clinical features.

HHCA

Morphologically, HHCAs are characterised by prominent steatosis, usually of marked intensity, associated with the absence of expression of LFABP, a gene controlled by HNF1A, in tumour hepatocytes, in contrast with highly LFABP expression in non-tumour hepatocytes.[18] To note, steatosis may be mild in some HHCAs, while it can be significant in other subgroups, especially in IHCA.

b^{ex3}HCA

Morphologically, b^{ex3}HCA are characterised by the presence of cellular atypia, pseudoglandular formation and cholestasis.[11] Tumour hepatocytes exhibit a strong homogeneous GS positivity (a β-catenin target gene product) as well as a nuclear expression of β-catenin in some tumour hepatocytes. Although both markers have a very good specificity for β-catenin mutations, sensitivity is insufficient, especially for β-catenin as a biomarker, since very few nuclei may be β-catenin positive.[11] Importantly, HCA with mutations in exon 3, causing S45 residue substitution, are associated with a lower activation of the WNT/β-catenin pathway, GS immunostaining reveals a lower overexpression with a heterogeneous positivity of moderate or strong intensity. In these cases, it is possible that very few β-catenin nuclei will be observed.[20] Sometimes the interpretation of GS on tumour biopsy is difficult. In these cases molecular analysis could help to determine the molecular subgroup.

b^{ex7,8}HCA

Morphologically, these HCA may be unremarkable or classified as IHCA when they are associated with JAK/STAT activation.[21] Given their weak activation of the WNT/β-catenin pathway, positivity for GS is observed in tumour hepatocytes, showing different patterns: perivascular or weak, diffuse and heterogeneous staining, without any β-catenin nuclear staining.[20] However, due to the faint modification of GS staining in the tumour, identification of this subgroup using immunohistochemistry remains difficult, particularly on biopsy.

IHCA

Morphologically, IHCAs are characterised by the presence of clusters of small arteries surrounded by extracellular matrix and inflammatory infiltrates associated with foci of sinusoidal dilatation (Fig. 1).[23] Tumour hepatocytes exhibit cytoplasmic expression of SAA and CRP, two proteins of the acute phase of inflammation induced by STAT3 activation (Fig. 1K and L).[18] CRP immunostaining appears to be more sensitive but less specific, since non-tumour hepatocytes in the adjacent normal liver may be positive. As previously mentioned, IHCA may show some degree of steatosis, and features of HCA related to additional β-catenin mutations.[18]

shHCA

shHCA have recently been identified. Initially considered as unclassified, no specific morphological features are recognised, except high potential for bleeding.[13] Accordingly, these HCAs often contain haemorrhagic foci, while no specific immunostainings are currently available.

UHCA

So far, a very limited number of HCA remain unclassified; *i.e.* without any specific morphological and/or

immunophenotypical characteristics. Based on immunohistochemistry, UHCAs are LFABP positive, SAA & CRP negative, GS negative or focally positive, nuclear β-catenin negative.[13]

HCA subtyping improves imaging diagnosis

On imaging, HCA is no longer a unique entity and imaging features reflect the tumour subtypes. Although CT may suggest some subtypes, MRI is much more accurate because of its ability to diagnose fat and telangiectatic features.

HHCA are characterised by the presence of a diffuse and homogeneous signal dropout on chemical shift T1-weighted sequences, corresponding to fat, leading to a high (87% to 91%) sensitivity and (89% to 100%) specificity of MRI.[38,39] On the other sequences, they appear homogeneous, with a variable signal on T2-sequences depending on the presence of fat suppression or not. They are usually moderately hypervascular and often show washout on portal and/or delayed phase MRI, using extracellular MRI contrast agents.[38,39] They are hypointense on hepatobiliary-phase MRI using hepatospecific contrast agents.

IHCA are characterised by their telangiectatic features, which appear as a strong hyperintense signal on T2-weighted MRI scans. This signal may be either diffuse or a rim-like band in the periphery of the lesion, with persistent enhancement on delayed phase (Fig. 1).[38–40] Combining these two findings provides a high (85% to 88%) sensitivity and (88% to 100%) specificity of MRI. Moreover, IHCAs are markedly hypervascular and heterogeneous. Some of the IHCAs are iso-or hyperintense on hepatobiliary MR phase using hepatospecific contrast agents, mimicking that of FNH.[41–43] Clinicians should be aware that some IHCA also harbour activating mutations of β-catenin in exon 3 and are at risk of malignant transformation. Consequently, identification of IHCA at MRI could not rule out a mixed inflammatory- activated β-catenin tumour. Overall MRI is accurate for HHCA and IHCA subtyping, with a sensitivity of approximately 90%.

The other subtypes of β-catenin mutated HCA ($b^{ex7,8}$HCA, b^{ex3}HCA) are less distinctive on imaging and cannot be differentiated from HCC and sometimes FNH.[41,43] Imaging features of the recently described shHCA have not been explored yet. We expect tumours containing haemorrhage on MRI.

HCA molecular subtyping impact on surgical indications?

Classically, HCAs have been considered an indication for surgical resection because of their potential for bleeding and malignant transformation.[44] However, further knowledge of this condition has showed that bleeding and malignant transformation were mainly observed in lesions >5 cm and rarely in lesions less than this size[10]). It has also been shown that malignant transformation is 10 times more frequent in males, especially in the presence of steroid intake.[11,12] These features have led to the management of hepatic adenomas based on size and gender, with resection of HCAs >5 cm in females and of all HCAs in males.[3] Recent molecular subtyping of adenomas has revolutionised the field and further refined indications for resection of HCAs.[1] In several reference centres, it has also revived the use of preoperative biopsies for more personalised management.[45] Therefore, liver surgeons must be fully educated on the molecular subtypes of hepatic adenomas, with knowledge that HCA molecular subtypes: (i) drive the prognosis and natural history of these lesions; (ii) have a good correlation with imaging; (iii) can be studied on biopsy specimens using specific immunochemistry; (iv) obesity is a risk factor of IHCA and shHCA; (v) HHCA have a low potential for malignant transformation; (vi) b^{ex3}HCA have a high potential for malignant transformation; (vii) less than 10% are not characterised by imaging or immunohistochemistry, (viii) among them a subgroup (shHCA) have a high risk of bleeding; (ix) all are favored by oral contraceptives in females; (x) the size and gender rule (higher risk of bleeding and malignancy in lesions >5 cm and of malignancy in males) remains valid.

The incidental finding of a liver "mass, tumour, nodule" in a young woman with no medical history is a common reason for consulting a liver surgeon, and a stressful one for the patient. The duties of the surgeon are threefold: i) make sure a firm diagnosis is reached, ii) avoid unnecessary resection of asymptomatic harmless lesions and iii) resect symptomatic lesions and those with harmful potential.

Harmless hepatocellular lesions include FNH and small adenomas. FNH has posed a differential diagnosis problem for many years, but this is no longer an issue because of MRI with hepato-specific contrast agents and the use of contrast enhanced ultrasound in small lesions. The vast majority of FNHs are now diagnosed without the need for a biopsy, and do not require any intervention. Small HCAs may also be treated conservatively, but require indefinite follow-up imaging.[10] Border-sized lesions (4–5 cm) pose more difficult problems. If the lesion has features of HHCA at imaging, a biopsy is not required and lesions can be observed. In other cases, a biopsy should be recommended and if a mutation in exon 3 of *CTNNB1* is demonstrated, resection should be performed. Resection of lesions >5 cm should be discussed. Although the use of tumour size to assess the risk of complications is controversial in the literature, some studies have reported that tumour bleeding (mostly assessed at histology) and malignant transformation are associated with tumour size.[9,10] In contrast, in our recent multicentric series of 511 HCA, the tumour size was not associated with the risk of malignant transformation.[13] We observed

malignant transformation in 8% of HCA lesions <5 cm and 13% in HCA >5 cm. Moreover, the rate of histological haemorrhage was significantly higher in tumours >5 cm, but symptomatic bleeding at presentation did not differ according to tumour size. Future studies are warranted to confirm that pre-resection biopsy for molecular typing could guide the decision of whether to resect and what type of resection to perform.[3] For example, b^{ex3}HCA may require an oncologic resection (*i.e.* with a margin of normal liver) as it may be difficult to differentiate it with a well-differentiated HCC on biopsy and sometimes on the whole specimen.[11,13] The evolution of adenomas after oral contraceptive removal is variable and unpredictable. However, it may be useful to test it in marginal lesions sized between 4–5 cm, as surgery may be avoided if a size decrease is observed.[19]

Multiple adenomas and adenomatosis pose a dilemma. In such cases, imaging remains paramount.[46] Biopsy and/or resection of the largest adenoma if >3–5 cm is often proposed, for prognostic reasons and prevention of complications. Again, molecular subtyping is important for planning treatment and surveillance.[19] In most cases, the largest tumour harboured *CTNNB1* exon 3 mutations. Liver transplantation is only indicated in exceptional circumstances, mostly for malignant transformation of HCA.[47]

Key point

β-catenin exon 3 mutated HCAs are at risk of malignant transformation and sonic hedgehog HCAs are at risk of bleeding.

Over the past two decades major advances have occurred in liver surgery, with increased safety and reduced bleeding. A major advance has been the advent of laparoscopic liver surgery.[48] This is a very tempting option in young patients with benign disease. However, the availability of these techniques must not change the indications for resection or lead to unnecessary resection of well-characterised, small asymptomatic and harmless lesions.[48]

In summary, surgery for benign liver disease should be associated with zero mortality and no transfusions. Therefore, it should be performed in specialised units. Indications should be precisely discussed. Therefore, all benign incidental hepatocellular lesions must be discussed at multidisciplinary liver tumour boards that include specialised radiologists, pathologists, hepatologists and surgeons.[3] The indications for resection of HCAs are greatly helped by the recent development of molecular subtypes.[13]

Candidate therapeutic targets emerging from basic research

Surgical resection is the cornerstone of HCA management.[3] However, surgical resection of all tumours is not always possible owing to the massive liver involvement in adenomatosis or because of an at-risk localisation of the tumour for surgery.[46,47] These cases and the rare cases of malignant transformation could benefit from the use of biotherapy adapted to tumour biology. Several pathways were deregulated in HHCA, including activation of the mTOR pathway.[16] However, it is unknown if HHCA is dependent of mTOR pathway activation and if mTOR inhibitors, such as temsirolimus or everolimus, could be useful to treat this molecular subtype. Additional data in preclinical models are warranted, to test new treatments targeting pathways that are deregulated after the complete inactivation of *HNF1A*.

In contrast, several lines of evidence have underlined the possibility to target the constitutive activation of the IL6/JAK/STAT pathway in IHCA. However, biotherapy should be tailored to the type of genes mutated in the IL6/JAK/STAT pathway to efficiently block this pathway.[49] In preclinical models, ruxolitinib, a JAK1 and JAK2 inhibitor, is the most efficient biotherapy for blocking *ILS6T* and *JAK1* activating mutations, whereas dasatinib, a src inhibitor, is more efficient for inhibiting *FRK* and *STAT3* activating mutations.[49,21,25]

Unfortunately, no drugs that inhibit *CTNNB1* mutations have shown both efficacy and safety. Additional efforts are still required to identify a potent treatment that inhibits activated β-catenin in benign and malignant liver tumours.[50]

Finally, smoothened (SMO) inhibitors are currently used to treat basal cell carcinoma characterised by an upstream activation of the sonic hedgehog pathway.[51] However, shHCA are characterised by *INHBE-GLI*1 fusion, a genetic alteration situated downstream of the SMO receptor.[13] Consequently, SMO inhibitors, such as vismodegib, are predicted to be inefficient for preventing the aberrant activation of sonic hedgehog, induced by *INHBE*/*GLI1* fusion.[13] Specific inhibitors targeting GLI1 such as GANT58, GANT61 or arsenic, are currently under development and could be tested in the future to treat sonic hedgehog HCA.[52]

Conclusion

In the last fifteen years, major advances in basic and translational research have refined our understanding of the pathogenesis of HCAs.[11] We have moved from a uniform homogeneous disease to a heterogeneous complex disease, linking molecular subclasses with tumour phenotype and clinical behaviour, and developing a new nosology for these benign liver tumours.[13] Moreover, the risk factors are not simply linked with HCA occurrence, but with specific occurrence of molecular subtypes. Histological, immunohistochemical and imaging features are currently used to guide clinical care by several teams worldwide, underlying the robustness of genotype/phenotype correlation.[1,39,53] In conclusion, EASL has defined general guidelines on diagnosis and patient management. However, because HCA is a rare disease, the level of evidence derived from the

literature to guide treatment is low. Obviously, no randomised controlled trial will be conducted to test the impact of molecular classification on clinical care, because HCA is an orphan disease. In the future, the introduction of molecular subtyping should be evaluated in prospective cohorts of patients to refine therapeutic decisions according to a more precise assessment of the risk of malignant transformation or bleeding, based on the natural history of each HCA subtype.

The molecular mechanisms underlying HCA development and its consequence in clinical practice have been elucidated. This success story supports the translational research performed in malignant liver tumours.[54]

Back to the clinical vignette

1) Did we need to perform a biopsy of the tumour?
   In this clinical vignette, imaging features were neither characteristic of HHCA nor IHCA and therefore histologic subtyping was required. Based on the tumour size (6 cm), the subcapsular localisation that has been associated with a higher risk of bleeding,[55] and the clinical context (planned bariatric surgery), the multidisciplinary committee recommended an upfront laparoscopic tumour resection. Histological analysis of the surgical specimen confirmed the diagnosis of HCA without any signs of malignancy. If surgical resection had not been performed, then histological diagnosis from tumour biopsy would have been indicated.
   However, the role of tumour biopsy for the diagnosis of HCA is not clearly defined. It is usually restricted to large HCA in poor surgical candidates and doubtful cases on imaging, particularly for assessing activation of β-catenin, which requires surgical resection. Doubtful cases on imaging comprise either uncertain diagnosis between HCA and other hepatocellular tumours (FHN, HCC, *etc.*), or HCA diagnosis and subtyping when typical MRI imaging criteria are lacking. Indications of tumour biopsy should be discussed at a multidisciplinary tumour board in a reference centre.
2) Did we need to perform a molecular subtyping of the adenoma?
   In our clinical vignette, analysis of the surgical specimen revealed a well-limited liver nodule, mostly yellowish with a darker periphery (Fig. 1). Histologically, the nodule corresponded to a very well differentiated trabecular proliferation of steatotic hepatocytes covering around 80% of the nodule. In the periphery, the hepatocytes were not steatotic and numerous clusters of small arteries surrounded by inflammatory cells were observed. Using immunohistochemistry, the nodule was LFABP positive and focally SAA positive (mostly in the periphery). GS was focally positive. All these features were consistent with a diagnosis of HCA, inflammatory subtype, mostly steatotic. Non-tumour liver was normal except for the presence of mild steatosis (30%).
   EASL guidelines do not recommend a systematic molecular subtyping of HCA for all patients. However, HCA subtyping explained the diversity of HCA phenotypes. In our case, imaging findings were atypical with a predominent steatotic lesion, which did not fully match the classical imaging features of HHCA. Therefore molecular subtyping was helpful.
   In biopsy samples, typical morphological criteria may not be seen. Therefore molecular subtyping is useful, especially to identify activation of the β-catenin pathway, associated with a higher risk of malignant transformation, which could guide surgical resection.
   In our multicentric study, HHCA of less than 5 cm were never associated with malignant transformation and may be diagnosed by imaging. In contrast, 21% of HCA of less than 5 cm after exclusion of HHCA are at risk of complications (bleeding for shHCA and malignant transformation for b^{ex3}HCA). The role of biopsy with molecular classification should be evaluated in prospective cohorts of patients to improve treatment decision and follow-up.
3) Are imaging features sufficient to subtype the adenoma?
   In this clinical vignette, some findings were suggestive of inflammatory subtype, including obesity, serum CRP increase and imaging features at the periphery of the lesion (strong hyper T2 and persistent enhancement) (Fig. 1). However, the lesion was mostly steatotic, potentially suggesting an HHCA and a definite subtyping could not be reached using imaging features in this case. Histological analysis with immunohistochemistry confirmed the diagnosis of IHCA containing fat.
   It is well accepted that MRI is the reference imaging modality to confidently diagnose HCA. The high diagnostic accuracy of MRI is related to the strong genotype-phenotype correlation. MRI allows subtyping with high sensitivity and specificity in the two most common subtypes, HNF1A HCA and IHCA, enabling a non-invasive diagnosis. However, we must highlight that mixed inflammatory and β-catenin tumours exist. The β-catenin component could not be diagnosed by MRI and precise diagnosis requires immunohistochemistry and/or molecular biology of the tumour for identification.

4) What type of treatment could we propose?
EASL guidelines recommend resecting all HCA in men and stopping oral contraception and re-evaluating tumour size in women, at a 6-month interval after lifestyle changes.
In this clinical vignette, after six months of oral contraception withdrawal, the tumour did not decrease in size. We then decided to perform a laparoscopic tumour resection given the tumour size (6 cm) and the subcapsular localisation that has been associated with a higher risk of bleeding.[55] Because a decrease in HCA size has also been described after weight loss in a small series of patients,[56] an alternative strategy could have been employed in our patient: (i) to rule out the two HCA subtypes at higher risk of malignant transformation (b^{ex3}HCA and b^{ex3}IHCA) and bleeding (shHCA) at tumour biopsy, (ii) to stop oral contraception and perform bariatric surgery (iii) to re-evaluate the lesion by MRI six months later. Resection would have been performed if the tumour had remained stable or increased in size. Conservative treatment would have been proposed if the HCA had regressed.

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Conflict of interest

The authors declare no conflict of interest relating to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors contributions

Writing and approval of this review (JCN, VP, VG, DC, JZR).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2017.07.009.

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