Human Pathology (2021) 112, 128–137

Human PATHOLOGY

www.elsevier.com/locate/humpath

Hepatocellular adenomas: review of pathological and molecular features

Aurélie Beaufrère MD [a,b], **Valérie Paradis MD, PhD** [a,b,*]

[a] *Université de Paris, INSERM U1149, Beaujon University Hospital, 92110, Clichy, France*
[b] *Pathology Department, Beaujon University Hospital, AP-HP, 92110, Clichy, France*

Received 3 October 2020; revised 16 November 2020; accepted 30 November 2020

Available online 9 December 2020

Keywords:
Hepatocellular adenoma;
HNF1α hepatocellular adenoma;
Inflammatory hepatocellular adenoma;
Beta-catenin hepatocellular adenoma;
Sonic hedgehog hepatocellular adenoma;
Unclassified hepatocellular adenoma;
Atypical hepatocellular adenoma

Summary Hepatocellular adenoma (HCA) is a rare benign liver neoplasm which predominantly occurs in women in the reproductive age group taking oral contraception**.** Since 2002, the terminology HCA has defined an heterogeneous group of neoplastic benign hepatocellular proliferations composed of different subtypes. The genotype-phenotype classification led to the description of 5 well-recognized subtypes based on morphological and immunophenotypical features, that are currently used in practice: *HNF1A* inactivated HCA, inflammatory HCA, β-catenin mutated HCA, sonic hedgehog HCA, and unclassified HCA. The main complications observed in HCAs are bleeding and malignant transformation. Risk of malignant transformation into hepatocellular carcinoma (HCC), more frequent in men, is also dependent to tumor size and HCA subtype, reaching 40% in β-catenin mutated HCA. The distinction of HCA from well-differentiated HCC remains difficult in some cases, leading to the diagnosis of so-called "atypical/borderline HCA". The management of HCA is now based on multidisciplinary approach including clinicians, radiologists, and pathologists integrating gender, tumor size, and HCA subtyping.

1. Hepatocellular adenoma: an evolving entity

Significant changes have been observed in the last twenty years in terms of epidemiology and clinical management thanks to the molecular advances provided by comprehensive genotype-phenotype analysis performed since 2002 (Fig. 1).

Hepatocellular adenoma (HCA) is a rare benign liver neoplasm predominantly occurring in women with in the reproductive age group taking oral contraception in a

Abbreviations: HCA, Hepatocellular adenoma; *CTNNB1*, catenin beta 1; *HNF1A*, Hepatocyte nuclear factor 1A; HHCA, *HNF1A* inactivated HCA; βHCA, β-catenin mutated HCA; IHCA, Inflammatory HCA; UHCA, unclassified HCA; LFABP, liver fatty acid binding protein; GS, glutamine synthetase; SAA, serum amyloid A; shHCA, Sonic hedgehog HCA; CRP, C reactive protein; βIHCA, β-catenin mutated inflammatory HCA; *GLI1*, GLI family zinc finger 1; *INHBE*, inhibin beta E subunit; PTGDS, prostaglandin D synthase; ASS1, argininosuccinate synthase 1; HCC, hepatocellular carcinoma; *TERT*, telomerase reverse transcriptase.

* Corresponding author. Pathology Department, Beaujon hospital, 100 av gal Leclerc, 92110, Clichy, France.
E-mail address: valerie.paradis@aphp.fr (V. Paradis).

https://doi.org/10.1016/j.humpath.2020.11.016
0046-8177/

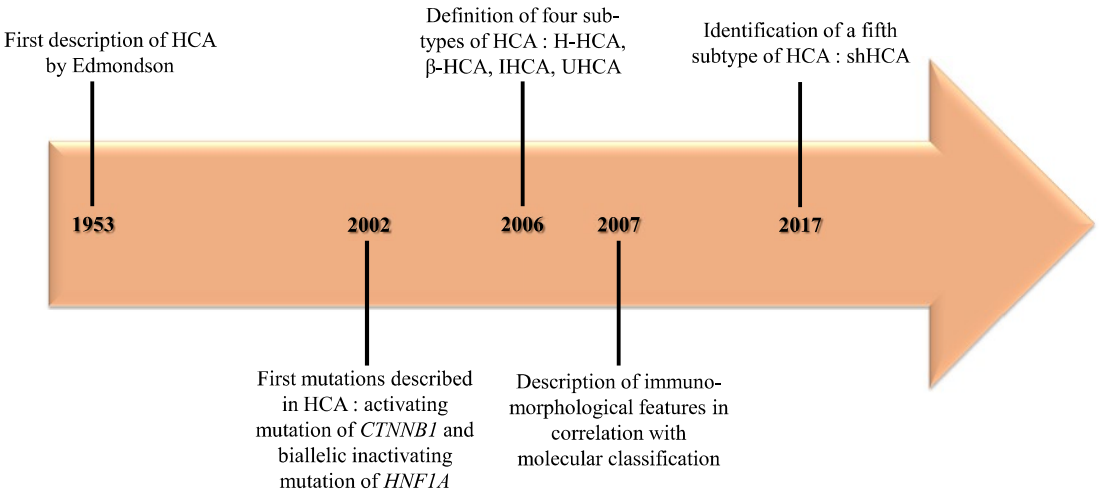

Fig. 1 Historical timeline of HCA.

normal background liver [1–4]. However, new associations are being recognized such as in men, related in some cases to the increase in the use of anabolic substances [5–8]. HCA is also increasingly recognized on a background of liver diseases such as non-alcoholic fatty liver diseases, vascular diseases and alcoholic cirrhosis [2,9]. Although the presence of HCA in the context of cirrhosis has been clearly demonstrated, this issue remains controversial [10,11].

HCAs have been described for the first time by Edmondson in 1953 [12] as hyperarterialized proliferations of well-differentiated, usually bland-looking, hepatocytes arranged in sheets and cords composed of one or two cells, with a preserved reticulin framework, and no portal tract [13].

Since 2002 and the first genotype-phenotype analysis, HCA has not been considered anymore as a "single tumor" but as an entity covering an heterogeneous group of neoplastic benign hepatocellular proliferations composed of different subtypes, characterized by specific molecular alterations and morphological features, clinical settings and complications [1,3,4,12–16]. Since 2002, when the first mutations described involved activating mutation of catenin (cadherin-associated protein) beta 1 (*CTNNB1)* and biallelic inactivating mutation of hepatocyte nuclear factor 1A (*HNF1A*), additional genomic abnormalities have been reported [14,15]. Then, in 2006, three subtypes have been fully characterized, including *HNF1A* inactivated HCA (HHCA), β-catenin mutated HCA (βHCA), and inflammatory HCA (IHCA) [13]. Importantly, in 2007, input of immunohistochemistry markers [liver fatty acid binding protein (LFABP), β-catenin, glutamine synthetase (GS), and serum amyloid A (SAA) to the morphological features has significantly improved and facilitated the recognition of the different HCA subtypes in clinical practice [17].

Table Pathomolecular features of the subtypes of HCA.

Subtype	Frequency Among HCA	Pathological features	Immunohistochemistry features	Molecular characteristics
HHCA	30–40%	Steatosis or clear cells, pericellular pattern at reticulin framework	Lack of LFABP	*HNF1A* inactivating mutation
IHCA	35–45%	Inflammation, sinusoidal dilatation, pseudo-portal tracts	CRP, SAA overexpression	*JAK/STAT* activation
βHCA	20%	Cytologic atypia, small-cell change, pseudoglandular architecture, and cholestasis	GS: diffuse and strong in case of exon 3 mutation with nuclear expression of β -catenin in some tumor hepatocytes	*CTNNB1* mutations
shHCA	4%	Hemorrhage, vessels abnormalities	ASS1 and PGTDS overexpression	*GLI1* activation
UHCA	5–10%	No specific features	All negative	No identified mutation

HCA, hepatocellular adenoma; HHCA, hepatocyte nuclear factor 1A (*HNF1A*) inactivated hepatocellular adenoma; LFABP, liver fatty acid binding protein; *HNF1A*, hepatocyte nuclear factor 1A; IHCA, inflammatory hepatocellular adenoma; CRP, C reactive protein; SAA, serum amyloid A; βHCA, betacatenin mutated hepatocellular adenoma; GS, glutamine synthetase; *CTNNB1*, catenin beta 1; shHCA, sonic hedgehog hepatocellular adenoma; PTGDS, prostaglandin D synthase; ASS1, argininosuccinate synthase 1; *GLI1,* GLI family zinc finger 1; UHCA, unclassified adenoma.

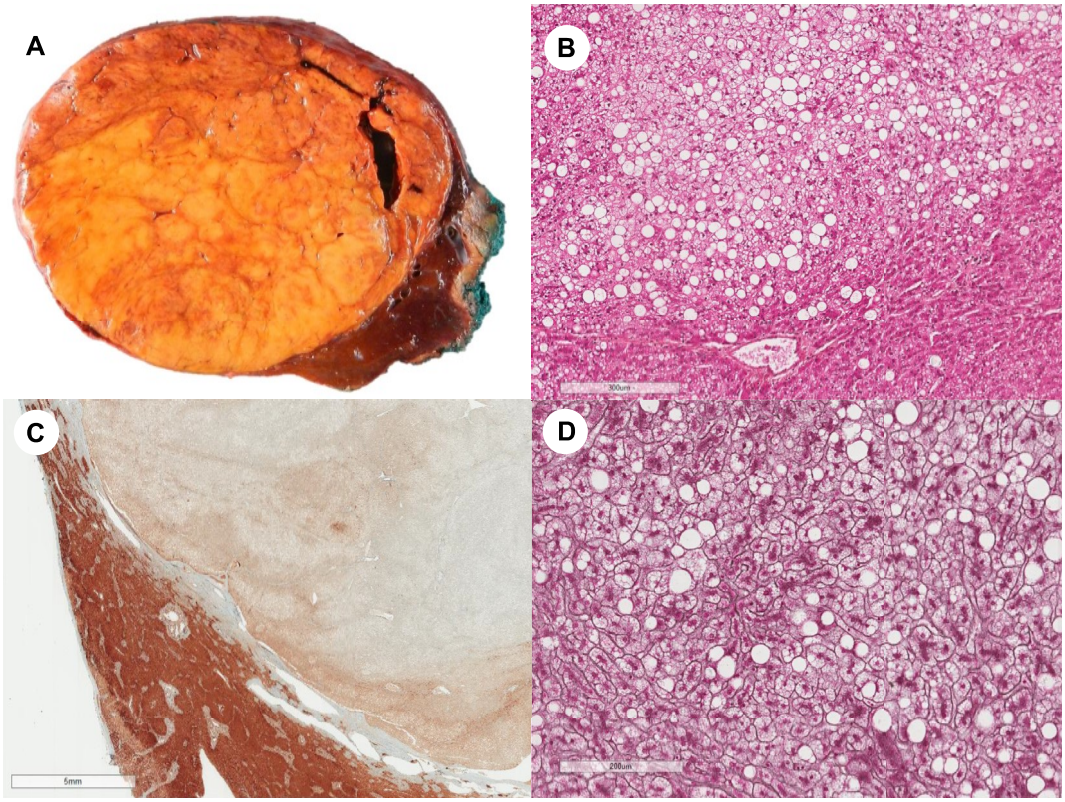

Fig. 2 Morphological and immunophenotypical features of HHCA. (A) Macroscopic examination: yellow well-demarcated tumor. (B) Microscopic examination (HES staining): presence of steatosis in the tumor cells. (C) Reticulin staining: pericellular pattern in which reticulin fibers can partially encircle small clusters of hepatocytes. (D) LFABP immunostaining: Lack of expression of LFABP in the tumor compared to its normal expression in normal hepatocytes. HHCA, *HNF1A* inactivated HCA; LFABP, liver fatty acid binding protein.

Finally, a fifth subtype of HCA, called sonic hedgehog HCA (shHCA) was reported in 2017 [4].

The aim of this work was to describe the pathomolecular characteristics of HCA subtypes and outline their implications in clinical management.

2. HCA subtypes: pathomolecular classification

2.1. Subtypes

The genotype-phenotype classification led thus to the description of 5 well-recognized subtypes based on morphological and immunophenotypical features (Table), that are currently used in practice:

o *HNF1A* inactivated HCA (HHCA)

The first subtypes of HCAs are defined by *HNF1A* mutation in 30%–40% of all HCAs [3,4]. *HNF1A* is a key transcription factor that controls several major metabolic pathways in hepatocytes. The gene defect was found to be somatic in 90% of cases and germline in the remaining 10% of cases [18,19]. It mostly occurs in women taking oral contraception as well as in young patients with *MODY3* diabetes [20–22]. Histologically, this subtype is characterized by the presence of steatosis, even though it could be of variable extent. The reticulin framework shows a pericellular pattern in which reticulin fibers can partially encircle small clusters of hepatocytes. Expression of LFABP, a molecule involved in lipid trafficking, is specifically absent in all HHCA (compared with its normal expression in normal hepatocytes), as a consequence of *HNF1A* inactivating mutation. Accordingly, LFABP immunoexpression serves as a relevant translational marker to specifically identify this subtype [2,4,23] (Fig. 2).

o Inflammatory HCA (IHCA)

IHCAs account for 35–45% of all HCAs. The cardinal molecular feature of IHCAs is the activation of the JAK/STAT pathway, which may be related to various gene mutations, belonging to this pathway: *IL6ST* (coding for gp130, 77%), *STAT3* (4%), *GNAS* (3%), *FRK* (9%) and *JAK1* (1%) [3,24–28]. It mainly occurs in women, associated with high BMI and alcohol consumption [10,11]. These HCAs show pseudo-portal tracts with inflammation, large arteries and ductular reaction, together with variable degrees of sinusoidal dilatation and congestion. Steatosis may be present within tumor cells [3,25,29]. IHCAs exhibit overexpression of inflammatory proteins induced by STAT3

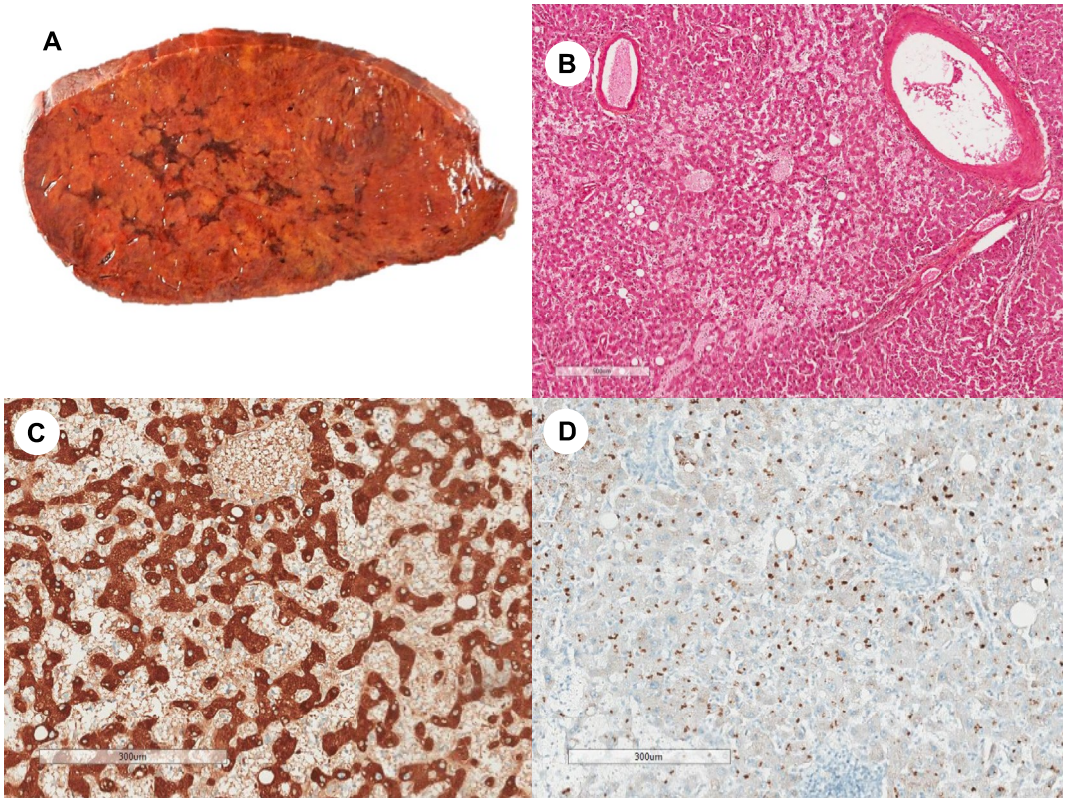

Fig. 3 Morphological and immunophenotypical features of IHCA. (A) Macroscopic examination: congestive well-demarcated tumor. (B) Microscopic examination (HES staining): sinusoidal dilatation and congestion associated with large arteries and a few lymphocytic infiltrate. (C) CRP immunostaining: intense cytoplasmic expression of tumor cells. (D) SAA immunostaining: cytoplasmic granular expression in tumor cells. SAA, serum amyloid A; CRP, C reactive protein.

activation, such as SAA and C reactive protein (CRP) by immunohistochemistry, that represent the molecular hallmark of this subtype [2,23]. CRP immunostaining appears to be more sensitive but less specific, since non-tumor hepatocytes in the adjacent normal liver may be focally positive [17] (Fig. 3).

- β-catenin mutated HCA (βHCA) and β-catenin mutated inflammatory HCA (βIHCA)

β-catenin-mutated HCAs constitute approximately 20% of all HCAs [3,12]. βHCA are divided in two groups according to the mutations observed in the *CTNNB1* coding for β-catenin: β-catenin exon 3 mutated HCA and β-catenin mutated HCA exon 7/8 [30].

Mutations of *CTNNB1* in exon 3 are observed in 10–15% of HCA. These mutations are canonical, leading to constitutive β-catenin activation. Levels of β-catenin activation are related to specific mutations, for example, large in-frame deletions led to high activity of β-catenin, whereas S45 exon 3 mutations are related to weak activity [30]. This subtype of HCA occurs more often in men than the other subtypes and can be occurred in a context of androgen use [6,8]. It is associated with a higher risk of malignant transformation particularly in large in-frame deletions, making its identification key in clinical practice [29–31]. Morphologically, cytological atypias, small-cell liver change, pseudoglandular/acinar architecture, and cholestasis are common features. Reticulin loss may be focally described. A strong and diffuse GS positivity was observed in the tumor as well as a nuclear expression of β-catenin in some tumor hepatocytes (Fig. 4). S45 mutations leading to moderate/intermediate level of beta-catenin activation, showed mostly a heterogeneous and diffuse staining with moderate or strong intensity [3,13,30].

In addition to exon 3 abnormalities, non-canonical mutations in exons 7/8 have been more recently described leading to a weak activation of the WNT/β-catenin pathway, and then a lesser risk of malignant transformation [30,32]. Histologically, these HCAs do not exhibit specific features. Given their weak activation of the WNT/β-catenin pathway, GS expression in tumor hepatocytes is weaker and heterogeneous, with different described patterns: perivascular or weak, diffuse and heterogeneous staining, without any β-catenin nuclear staining. In most of the tumors, GS heterogeneous staining patterns were associated with a reinforcement rim at the periphery of the tumor. Nevertheless, further studies are needed to validate these

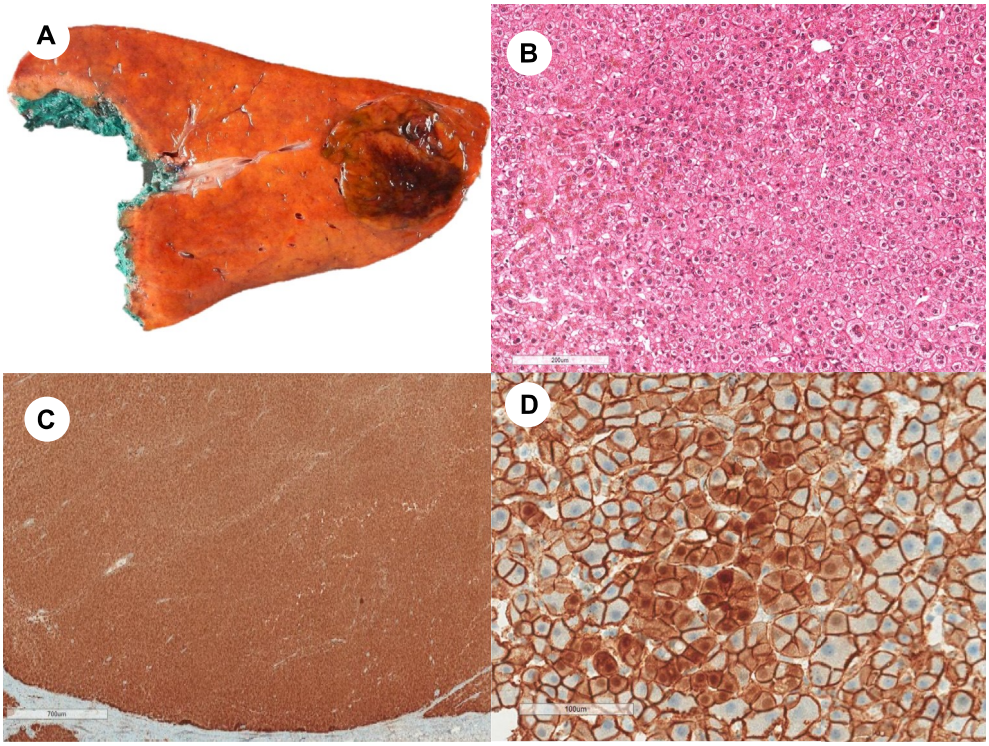

Fig. 4 Morphological and immunophenotypical features of β^{ex3}HCA. (A) Macroscopic examination: brown well-dermacated tumor. (B) Microscopic examination (HES staining): presence of cytological atypias associated with cholestasis. (C) Glutamine synthetase immunostaining: strong and diffuse positivity. (D) β-catenin immunostaining: nuclear expression of β-catenin in some tumor hepatocytes.

patterns and evaluate their performance to differentiate the mutation profiles. Accordingly, molecular analysis is required to accurately identify these HCAs so far [2,3,30].

While several mutations are exclusive (i.e HNF1A and *CTNNB1*), up to 50% of β-HCA also demonstrate activation of the JAK/STAT pathway and then display inflammatory features (βIHCA). In these cases, an expression of GS and SAA/CRP has also been observed [23,31] (Fig. 5).

o Sonic hedgehog HCA (shHCA)

This subtype has been recently described by Nault et al. in 2017 and represents approximately 4% of HCAs. It is defined by a GLI family zinc finger 1 (*GLI1)* overexpression due to a deletion leading to a fusion between inhibin beta E subunit (*INHBE)* and *GLI1*. These fusions constitutively activate the sonic hedgehog pathway into tumor hepatocytes. shHCAs occur more frequently in women and are associated with higher BMI and/or cumulative consumption of oral contraceptive. shHCAs have been associated with a high rate of microscopic or macroscopic hemorrhage and also clinically significant bleeding [4]. No specific morphological features have been described while prostaglandin D synthase (PTGDS) and argininosuccinate synthase 1 (ASS1) have been reported as overexpressed in shHCA (Fig. 6). However, it should be stressed that ASS1 may also be expressed in other HCA subtypes in a context of hemorrhage and may be rather considered as a marker of hemorrhage than a specific marker of shHCA. Accordingly, ASS1 is not yet included in the routine subtyping immunostaining panel so far. In the future, ASS1 would be very useful if it may be able to identify the HCA at risk of hemorrhage, especially in biopsy samples [33,34].

o Unclassified HCA (UHCA)

The last subtype of HCA (5−10% of all HCAs) is characterized by the lack of specific histological features without any specific molecular abnormality [3].

2.2. Complications

The main complications observed in HCAs are bleeding and malignant transformation [4,29,35−37]. Bleeding is the most commonly observed complication [35]. In the recent series of Nault et al., histologic hemorrhage was observed in half of tumors, and symptomatic bleeding in 14% of cases. Histologic hemorrhage is closely related to the molecular subtypes (β-^{ex7,8}HCA and shHCA showing the highest rate of hemorrhage), and to the tumor size with a cutoff of 50 mm. In addition, symptomatic bleeding is associated with shHCA subtype [4].

HCA may undergo malignant transformation into hepatocellular carcinoma (HCC) in around 5% of cases [23,30]. Risk of malignant transformation is associated

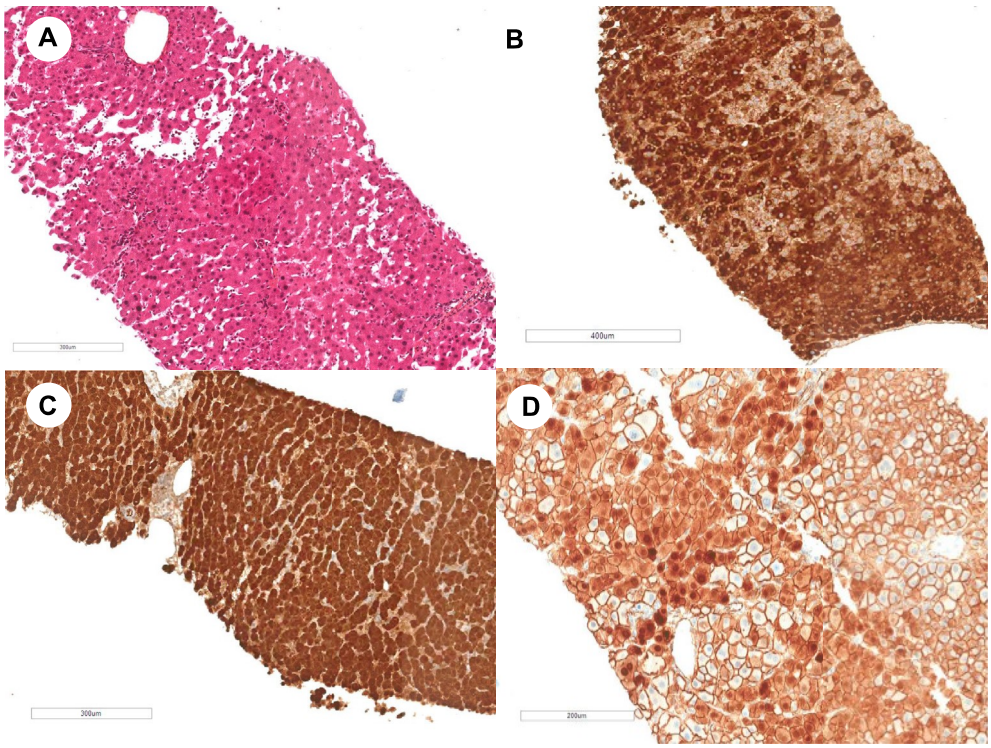

Fig. 5 Morphological and immunophenotypical features of βIHCA on a biopsy sample. (A) Microscopic examination (HES staining): sinusoidal dilatation and congestion associated with cytological atypias. (B) CRP immunostaining: intense cytoplasmic expression of tumor cells. (C) Glutamine synthetase immunostaining: strong and diffuse positivity. (D) β-catenin immunostaining: nuclear expression of β-catenin in numerous tumor hepatocytes.

with sex male, large tumor size (>50 mm), and β^{ex3}-HCA or β^{ex3}-IHCA [3,4,38]. The risk of malignant transformation into HCC may reach 40% in β-HCA, an incidence higher than for other molecular HCA subtypes [13,29,39,40]. In HCC arising within pre-existing HCA, the *CTNNB1* exon 3 mutation is the earliest genetic alteration, whereas mutations in the promoter of *TERT* seem to be involved in the final step of transition between HCA and HCC [32,39,41]. Recently, a multicentric study collected a series of 13 H-HCA with malignant transformation, and reported the malignant transformation was most frequently seen in female patients with multiple lesions compared to a control group exclusively composed of βHCA. To note, the mean size of the HHCA with malignant transformation was 8.9 cm, suggesting that tumor size may also contribute to the malignant progression [42].

3. Borderline/atypical HCA

As HCA may progress to malignancy, borderline hepatocellular lesions may be expected, and in that case, the distinction of HCA from well-differentiated HCC is challenging. Those HCAs are not really recognized as a definite pathomolecular subtype but reflect uncertain diagnosis between HCA and HCC [43–47]. Various terms, including "atypical hepatocellular neoplasm", "hepatocellular neoplasm of uncertain malignant potential," and "well-differentiated hepatocellular neoplasm with atypical or borderline features" have been proposed [32,40,45–47]. According to the definition used, diagnosis of these lesions is based on clinical and/or morphological and/or molecular data. The morphological criteria in favor of atypical HCA include cytologic atypias, small cell liver change, increased cell thick plates, presence of pseudoglands, abnormal reticulin network, and pigmented nodule, that are not enough evident for an unequivocal diagnosis of HCC [2,43,48] (Fig. 7). Additional markers, such as glypican 3 and heat shock protein 70, are usually not helpful as they are commonly negative in well-differentiated HCC [49]. Molecular analysis of *TERT* promoter mutations, as a marker of malignancy, may be useful. For instance, *TERT* promoter mutations have been reported in 17% of borderline lesions compared with 50–60% of HCC [44,50]. Finally, the use of reticulin staining can be so far the most useful staining in order to distinguish atypical HCA from HCC.

4. Management

In recent years, the development of the pathomolecular classification of HCAs identifying different subtypes associated with specific clinical behavior led to refine patient management taking into account the potential risks of complications (bleeding, malignant transformation). The management of HCA is primarily based on gender and

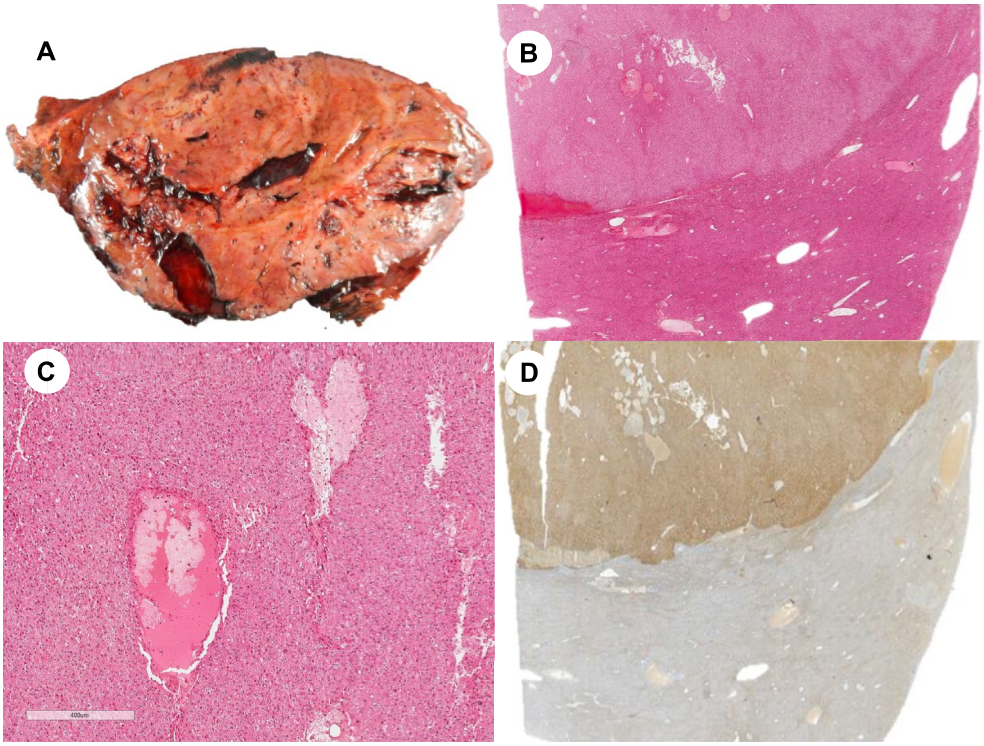

Fig. 6 **Morphological and immunophenotypical features of shHCA**. (A) Macroscopic examination: Tumor with numerous hemorrhage areas. (B) Microscopic examination (HES staining): well-dermarcated tumor. (C) Microscopic examination (HES staining): microscopic hemorrhage areas. (D) PTGDS immunostaining: overexpression in tumor cells. shHCA, sonic hedgehog hepatocellular adenoma; PTGDS, prostaglandin D synthase.

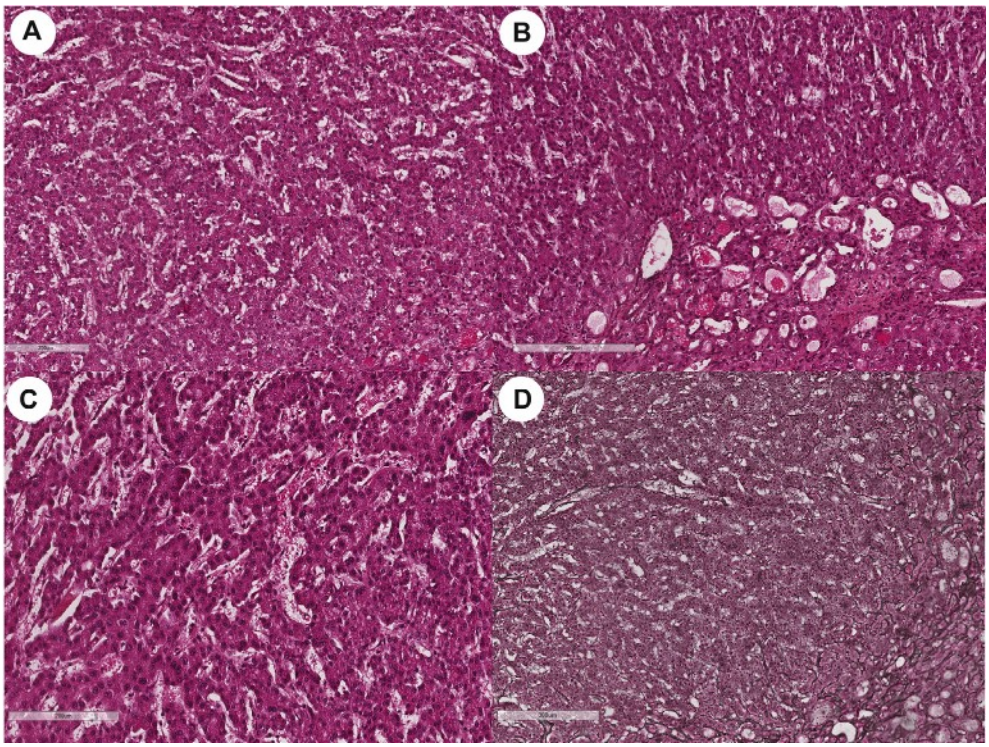

Fig. 7 **Morphological features of a borderline HCA**. (A) HES staining: focal increased cell thick plates. (B) HES staining: presence of pseudoglands. (C) HES staining: focal cytologic atypias. (D) Reticulin staining: focal loss of the reticulin framework.

tumor size followed by molecular subtyping of HCA [3,5,51–54]. According to the clinical guidelines established by EASL, a resection is recommended in (1) in men and in any instance of proven β-catenin mutation irrespective of tumor size, (2) in women, for nodules equal or greater than 5 cm and those continuing to grow after a period of 6 months observation after lifestyle change including removal of oral contraception, (3) bleeding HCA with hemodynamic instability after embolization and if residual viable lesion on follow-up imaging is present [5,37]. HCA with borderline features on biopsy should be also resected [43].

On imaging, some HCA subtypes show specific features. Overall MRI is accurate for HHCA and IHCA subtyping, with a sensitivity of approximately 90%. βHCA or βIHCA are less distinctive on imaging and cannot be differentiated from HCC. Imaging features of the recently described shHCA have not been explored yet, even if hemorrhage can be detected on imaging [3,55]. In practice, if the lesion displays undoubtedly features of HHCA at imaging, a biopsy could be avoided [3]. In other cases, a biopsy should be recommended for more personalized management and for exclude malignancy [3,5,56].

Multiple HCA and adenomatosis pose a clinical management dilemma. Multiple adenomas are more frequently found in patients with metabolic syndrome or obesity. In patients with multiple adenomas, the occurrence of complications is not related to the number of lesions [3,37,51]. Imaging remains paramount in case of multiple HCAs [57]. Biopsy and/or resection of the largest adenoma if $>$ 3–5 cm is often proposed. Liver transplantation is only indicated in exceptional circumstances, mostly for malignant transformation of HCA [3,51,58].

5. Conclusion

Major advances in the understanding of HCAs have been realized during the last twenty years leading to move from a “single tumor” to a heterogeneous entity including five pathomolecular subtypes. The identification of these different subtypes and their specific clinical behavior have allowed to adapt the management of these tumors.

References

[1] Bioulac-Sage P, Blanc JF, Rebouissou S, Balabaud C, Zucman-Rossi J. Genotype phenotype classification of hepatocellular adenoma. World J Gastroenterol 2007;13:2649–54. https://doi.org/10.3748/wjg.v13.i19.2649.

[2] Bioulac-Sage P, Sempoux C, Balabaud C. Hepatocellular adenoma: classification, variants and clinical relevance. Semin Diagn Pathol 2017;34:112–25. https://doi.org/10.1053/j.semdp.2016.12.007.

[3] Nault J-C, Paradis V, Cherqui D, Vilgrain V, Zucman-Rossi J. Molecular classification of hepatocellular adenoma in clinical practice. J Hepatol 2017;67:1074–83. https://doi.org/10.1016/j.jhep.2017.07.009.

[4] Nault J-C, Couchy G, Balabaud C, et al. Molecular classification of hepatocellular adenoma associates with risk factors, bleeding, and malignant transformation. Gastroenterology 2017;152:880–94. https://doi.org/10.1053/j.gastro.2016.11.042. e6.

[5] European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the management of benign liver tumours. J Hepatol 2016;65:386–98. https://doi.org/10.1016/j.jhep.2016.04.001.

[6] Gupta S, Naini BV, Munoz R, et al. Hepatocellular neoplasms arising in association with androgen use. Am J Surg Pathol 2016;40:454–61. https://doi.org/10.1097/PAS.0000000000000576.

[7] Socas L, Zumbado M, Pérez-Luzardo O, et al. Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature. Br J Sports Med 2005;39:e27. https://doi.org/10.1136/bjsm.2004.013599.

[8] Paustian L, Chao MM, Hanenberg H, et al. Androgen therapy in Fanconi anemia: a retrospective analysis of 30 years in Germany. Pediatr Hematol Oncol 2016;33:5–12. https://doi.org/10.3109/08880018.2015.1129567.

[9] Sempoux C, Balabaud C, Paradis V, Bioulac-Sage P. Hepatocellular nodules in vascular liver diseases. Virchows Arch 2018;473:33–44. https://doi.org/10.1007/s00428-018-2373-6.

[10] Calderaro J, Nault JC, Balabaud C, et al. Inflammatory hepatocellular adenomas developed in the setting of chronic liver disease and cirrhosis. Mod Pathol 2016;29:43–50. https://doi.org/10.1038/modpathol.2015.119.

[11] Sasaki M, Kondo F, Sawai Y, et al. Serum amyloid A-positive hepatocellular neoplasms in the resected livers from 3 patients with alcoholic cirrhosis. Histol Histopathol 2013;28:1499–505. https://doi.org/10.14670/HH-28.1499.

[12] Bioulac-Sage P, Sempoux C, Balabaud C. Hepatocellular adenomas: morphology and genomics. Gastroenterol Clin N Am 2017;46:253–72. https://doi.org/10.1016/j.gtc.2017.01.003.

[13] Zucman-Rossi J, Jeannot E, Nhieu JTV, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. Hepatology 2006;43:515–24. https://doi.org/10.1002/hep.21068.

[14] Chen Y-W, Jeng Y-M, Yeh S-H, Chen P-J. P53 gene and Wnt signaling in benign neoplasms: beta-catenin mutations in hepatic adenoma but not in focal nodular hyperplasia. Hepatology 2002;36:927–35. https://doi.org/10.1053/jhep.2002.36126.

[15] Bluteau O, Jeannot E, Bioulac-Sage P, et al. Bi-allelic inactivation of TCF1 in hepatic adenomas. Nat Genet 2002;32:312–5. https://doi.org/10.1038/ng1001.

[16] Le Bail B, Chiche L, Balabaud C, Bioulac-Sage P. Collision of hepatocellular nodules in vascular livers: a medical challenge. Clin Res Hepatol Gastroenterol 2018;42:e83–5. https://doi.org/10.1016/j.clinre.2017.11.001.

[17] Bioulac-Sage P, Rebouissou S, Thomas C, et al. Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. Hepatology 2007;46:740–8. https://doi.org/10.1002/hep.21743.

[18] Rebouissou S, Imbeaud S, Balabaud C, Boulanger V, Bertrand-Michel J, Tercé F, et al. HNF1alpha inactivation promotes lipogenesis in human hepatocellular adenoma independently of SREBP-1 and carbohydrate-response element-binding protein (ChREBP) activation. J Biol Chem 2007;282:14437–46. https://doi.org/10.1074/jbc.M610725200.

[19] Pelletier L, Rebouissou S, Paris A, Rathahao-Paris E, Perdu E, Bioulac-Sage P, et al. Loss of hepatocyte nuclear factor 1alpha function in human hepatocellular adenomas leads to aberrant activation of signaling pathways involved in tumorigenesis. Hepatol Baltim Md 2010;51:557–66. https://doi.org/10.1002/hep.23362.

[20] Haring MPD, Vriesendorp TM, Klein Wassink-Ruiter JS, de Haas RJ, Gouw ASH, de Meijer VE. Diagnosis of hepatocellular adenoma in

men before onset of diabetes in HNF1A-MODY: watch out for winkers. Liver Int 2019;39. https://doi.org/10.1111/liv.14235. 2042–5.
[21] Jeannot E, Poussin K, Chiche L, et al. Association of CYP1B1 germ line mutations with hepatocyte nuclear factor 1alpha-mutated hepatocellular adenoma. Canc Res 2007;67:2611–6. https://doi.org/10.1158/0008-5472.CAN-06-3947.
[22] Jeannot E, Mellottee L, Bioulac-Sage P, Balabaud C, Scoazec J-Y, Tran Van Nhieu J, et al. Spectrum of HNF1A somatic mutations in hepatocellular adenoma differs from that in patients with MODY3 and suggests genotoxic damage. Diabetes 2010;59:1836–44. https://doi.org/10.2337/db09-1819.
[23] Nault J-C, Bioulac-Sage P, Zucman-Rossi J. Hepatocellular benign tumors-from molecular classification to personalized clinical care. Gastroenterology 2013;144:888–902. https://doi.org/10.1053/j.gastro.2013.02.032.
[24] Rebouissou S, Amessou M, Couchy G, et al. Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours. Nature 2009;457:200–4. https://doi.org/10.1038/nature07475.
[25] Bioulac-Sage P, Rebouissou S, Sa Cunha A, et al. Clinical, morphologic, and molecular features defining so-called telangiectatic focal nodular hyperplasias of the liver. Gastroenterology 2005;128:1211–8. https://doi.org/10.1053/j.gastro.2005.02.004.
[26] Paradis V, Benzekri A, Dargère D, et al. Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. Gastroenterology 2004;126:1323–9. https://doi.org/10.1053/j.gastro.2004.02.005.
[27] Nault JC, Fabre M, Couchy G, et al. GNAS-activating mutations define a rare subgroup of inflammatory liver tumors characterized by STAT3 activation. J Hepatol 2012;56:184–91. https://doi.org/10.1016/j.jhep.2011.07.018.
[28] Pilati C, Amessou M, Bihl MP, et al. Somatic mutations activating STAT3 in human inflammatory hepatocellular adenomas. J Exp Med 2011;208:1359–66. https://doi.org/10.1084/jem.20110283.
[29] Bioulac-Sage P, Laumonier H, Couchy G, et al. Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. Hepatology 2009;50:481–9. https://doi.org/10.1002/hep.22995.
[30] Rebouissou S, Franconi A, Calderaro J, et al. Genotype-phenotype correlation of CTNNB1 mutations reveals different ß-catenin activity associated with liver tumor progression. Hepatology 2016;64:2047–61. https://doi.org/10.1002/hep.28638.
[31] Saldarriaga J, Bisig B, Couchy G, et al. Focal β-catenin mutation identified on formalin-fixed and paraffin-embedded inflammatory hepatocellular adenomas. Histopathology 2017;71:989–93. https://doi.org/10.1111/his.13283.
[32] Pilati C, Letouzé E, Nault J-C, et al. Genomic profiling of hepatocellular adenomas reveals recurrent FRK-activating mutations and the mechanisms of malignant transformation. Canc Cell 2014;25:428–41. https://doi.org/10.1016/j.ccr.2014.03.005.
[33] Nault J-C, Couchy G, Caruso S, et al. Argininosuccinate synthase 1 and periportal gene expression in sonic hedgehog hepatocellular adenomas. Hepatology 2018;68:964–76. https://doi.org/10.1002/hep.29884.
[34] Henriet E, Abou Hammoud A, Dupuy J-W, et al. Argininosuccinate synthase 1 (ASS1): a marker of unclassified hepatocellular adenoma and high bleeding risk. Hepatology 2017;66:2016–28. https://doi.org/10.1002/hep.29336.
[35] van Aalten SM, de Man RA, IJzermans JNM, Terkivatan T. Systematic review of haemorrhage and rupture of hepatocellular adenomas. Br J Surg 2012;99:911–6. https://doi.org/10.1002/bjs.8762.
[36] Dokmak S, Paradis V, Vilgrain V, et al. A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. Gastroenterology 2009;137:1698–705. https://doi.org/10.1053/j.gastro.2009.07.061.
[37] Dokmak S, Aussilhou B, Rasoaherinomenjanahary F, et al. Hemorrhage of hepatocellular adenoma: a complication that can be treated by conservative management without surgery. HPB (Oxford) 2018;20:1198–205. https://doi.org/10.1016/j.hpb.2018.06.1796.
[38] Farges O, Ferreira N, Dokmak S, Belghiti J, Bedossa P, Paradis V. Changing trends in malignant transformation of hepatocellular adenoma. Gut 2011;60:85–9. https://doi.org/10.1136/gut.2010.222109.
[39] Védie A-L, Sutter O, Ziol M, Nault J-C. Molecular classification of hepatocellular adenomas: impact on clinical practice. Hepat Oncol 2018;5. https://doi.org/10.2217/hep-2017-0023. HEP04.
[40] Evason KJ, Grenert JP, Ferrell LD, Kakar S. Atypical hepatocellular adenoma-like neoplasms with β-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas. Hum Pathol 2013;44:750–8. https://doi.org/10.1016/j.humpath.2012.07.019.
[41] Nault JC, Mallet M, Pilati C, et al. High frequency of telomerase reverse-transcriptase promoter somatic mutations in hepatocellular carcinoma and preneoplastic lesions. Nat Commun 2013;4:2218. https://doi.org/10.1038/ncomms3218.
[42] Putra J, Ferrell LD, Gouw ASH, et al. Malignant transformation of liver fatty acid binding protein-deficient hepatocellular adenomas: histopathologic spectrum of a rare phenomenon. Mod Pathol 2020;33:665–75. https://doi.org/10.1038/s41379-019-0374-x.
[43] Choi W-T, Kakar S. Atypical hepatocellular neoplasms: review of clinical, morphologic, immunohistochemical, molecular, and cytogenetic features. Adv Anat Pathol 2018;25:254–62. https://doi.org/10.1097/PAP.0000000000000189.
[44] Joseph NM, Umetsu SE, Shafizadeh N, Ferrell L, Kakar S. Genomic profiling of well-differentiated hepatocellular neoplasms with diffuse glutamine synthetase staining reveals similar genetics across the adenoma to carcinoma spectrum. Mod Pathol 2019;32:1627–36. https://doi.org/10.1038/s41379-019-0282-0.
[45] Bedossa P, Burt AD, Brunt EM, et al. Well-differentiated hepatocellular neoplasm of uncertain malignant potential: proposal for a new diagnostic category. Hum Pathol 2014;45:658–60. https://doi.org/10.1016/j.humpath.2013.09.020.
[46] Balabaud C, Bioulac-Sage P, Ferrell L, et al. Well-differentiated hepatocellular neoplasm of uncertain malignant potential. Hum Pathol 2015;46:634–5. https://doi.org/10.1016/j.humpath.2014.10.029.
[47] Kakar S, Evason KJ, Ferrell LD. Well-differentiated hepatocellular neoplasm of uncertain malignant potential: proposal for a new diagnostic category–reply. Hum Pathol 2014;45:660–1. https://doi.org/10.1016/j.humpath.2013.09.019.
[48] Souza LN, de Martino RB, Thompson R, Strautnieks S, Heaton ND, Quaglia A. Pigmented well-differentiated hepatocellular neoplasm with beta-catenin mutation. HBPD INT 2015;14:660–4. https://doi.org/10.1016/s1499-3872(15)60381-2.
[49] Di Tommaso L, Franchi G, Park YN, et al. Diagnostic value of HSP70, glypican 3, and glutamine synthetase in hepatocellular nodules in cirrhosis. Hepatology 2007;45:725–34. https://doi.org/10.1002/hep.21531.
[50] Cancer Genome Atlas Research Network. Electronic address: wheeler@bcm.edu, Cancer Genome Atlas Research Network. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. Cell 2017;169:1327–41. https://doi.org/10.1016/j.cell.2017.05.046. e23.
[51] Herman P, Fonseca GM, Kruger JAP, Jeismann VB, Coelho FF. Guidelines for the treatment of hepatocellular adenoma in the era of molecular biology: an experience-based surgeons' perspective. J Gastrointest Surg 2020. https://doi.org/10.1007/s11605-020-04724-1.
[52] Klompenhouwer AJ, IJzermans JNM. Malignant potential of hepatocellular adenoma. Liver Int 2017;37:966–7. https://doi.org/10.1111/liv.13449.
[53] Krause K, Tanabe KK. A shifting paradigm in diagnosis and management of hepatic adenoma. Ann Surg Oncol 2020;27:3330–8. https://doi.org/10.1245/s10434-020-08580-w.

[54] Tsilimigras DI, Rahnemai-Azar AA, Ntanasis-Stathopoulos I, et al. Current approaches in the management of hepatic adenomas. J Gastrointest Surg: Off J Soc Surg Aliment Tract 2019;23. https://doi.org/10.1007/s11605-018-3917-4.

[55] Ba-Ssalamah A, Antunes C, Feier D, et al. Morphologic and molecular features of hepatocellular adenoma with gadoxetic acid-enhanced MR imaging. Radiology 2015;277:104–13. https://doi.org/10.1148/radiol.2015142366.

[56] Bioulac-Sage P, Cubel G, Taouji S, et al. Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. Am J Surg Pathol 2012;36:1691–9. https://doi.org/10.1097/PAS.0b013e3182653ece.

[57] Chiche L, Dao T, Salamé E, et al. Liver adenomatosis: reappraisal, diagnosis, and surgical management: eight new cases and review of the literature. Ann Surg 2000;231:74–81. https://doi.org/10.1097/00000658-200001000-00011.

[58] Chiche L, David A, Adam R, et al. Liver transplantation for adenomatosis: European experience. Liver Transplant 2016;22:516–26. https://doi.org/10.1002/lt.24417.