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Relevance of morphological features for hepatocellular adenoma classification in pathology practice

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Abstract

Background: Gene mutations correlated with histological and immunohistochemical phenotypes of hepatocellular adenoma were recently identified. Based on these findings, four adenoma subtypes were distinguished. We classify hepatocellular adenoma (HCA) into subtypes based on histologic and immunohistochemical findings and verify the contribution of histological features in pathology practice.

Methods: Thirty hepatocellular adenomas were classified in subtypes. Sinusoidal dilatation, ductular reaction, pseudoportal tracts, pseudoglands, steatosis, inflammatory infiltrate and cellular atypia were analyzed, as well as liver fatty acid binding protein, β catenin, serum amyloid A, glutamine synthetase, and C-reactive protein antibodies.

Results: Histologically, eleven adenomas were classified as HNF1A inactivated (HHCA), five were β-catenin-activated (bHCA) and fourteen were inflammatory adenoma (IHCA). Steatosis was found in all HHCA and was predominantly severe. Sinusoidal dilatation and inflammatory infiltrate were present in all IHCA. Ductular reaction, pseudoportal tracts and cellular atypia were observed in 71.4, 85.7 and 42.8%, respectively. Pseudoglands were present in 60% and cellular atypia in 80% of bHCA. According to immunohistochemistry, 11 were HHCA; 1 was bHCA; 17 were IHCA, among which 5 were β-catenin activated IHCA; and 1 was unclassified UHCA (UHCA). Superior concordance between the histological and immunohistochemical classifications was found for HHCA (K = 0.854) and IHCA (K = 0.657).

Conclusion: Approximately 90% of adenomas may be diagnosed by subgroup based only on morphological features. When aberrant β catenin nuclear staining is not found, glutamine synthetase positivity is useful for diagnosis, although supplementary molecular analysis may be necessary.

Keywords: Hepatocellular adenoma, Morphology, Immunohistochemistry, Pathology

Background

The last decade was marked by great advances in the knowledge of hepatocellular adenoma (HCA) (Chen et al. 2002; Bluteau et al. 2002; Zucman-Rossi et al. 2006; Bioulac-Sage et al. 2007a, b). HCA is a rare benign liver neoplasm that occurs more frequently in women and is strongly associated with the use of oral contraceptives (OCs). Other associated risk factors include metabolic storage disease, obesity, metabolic syndrome and anabolic steroid use (Edmondson and Benton 1976; Bunchorntavakul et al. 2011; Bioulac-Sage et al. 2013). Molecular studies have advanced the understanding of HCA by identifying gene mutations, thereby expanding knowledge about the biological behavior of HCA and improving the accuracy of diagnosis and treatment (Chen et al. 2002; Bluteau et al. 2002; Zucman-Rossi et al. 2006; Bioulac-Sage et al. 2007a, b). Gene mutations have also been correlated with histological and immunohistochemical phenotypes, based on which four HCA subtypes were identified (Zucman-Rossi et al. 2006; Bioulac-Sage et al. 2007a, b).

Hepatocellular adenoma with mutation of hepatocyte nuclear factor 1A (HHCA) is one of the most common HCA subtypes. It is characterized by an inactivating mutation of hepatocyte nuclear factor 1A (HNF1A), with

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deregulation of fatty acid synthesis and decreased expression of liver type acid binding protein (LFABP), leading to steatosis in tumor cells (Pelletier et al. 2010).

Tumors carrying a CTNBB1 exon 3 mutation constitute a less common group of HCA exhibiting beta catenin mutation (bHCA). It is characterized by malignant transformation risk (Zucman-Rossi et al. 2006). Nuclear β catenin expression is observed in bHCA. Another antibody that reflects this mutation is glutamine synthetase (GS). Cellular atypia and pseudogland formation are the histological findings described (Zucman-Rossi et al. 2006; Dhingra and Fiel 2014). β catenin mutations are also observed in some cases of inflammatory HCA, which leads to an increased risk of malignant transformation (Dokmak et al. 2009).

Recently, adenomas with mutation in exons 7 and 8 were described. They are associated with weak activation of the Wnt/β catenin pathway but not with high risk of malignant transformation. They may not show nuclear staining for beta catenin as well as demonstrate different patterns for GS staining (Pilati et al. 2014; Rebouissou et al. 2016).

Inflammatory hepatocellular adenoma (IHCA) is the most frequent adenoma and shows activation of the Janus kinase signal transducer (JAK)/activator of transcription (STAT)/interleukin 6 (IL6) pathway due to somatic mutation (Rebouissou et al. 2009; Nault and Zucman 2013). Hepatocyte tumor cells exhibit immunoexpression of inflammatory proteins (C-reactive protein and serum amyloid A). Morphological sinusoidal dilatation, inflammatory infiltrate, ductular reaction, and pseudoportal tracts are the main histological findings (Bioulac-Sage et al. 2007a, b; Dhingra and Fiel 2014).

The fourth adenoma subtype is unclassified (UHCA). It is characterized by a lack of known molecular alterations and does not show specific histological findings or protein expression (Bioulac-Sage et al. 2007a, b). The activation of sonic hedgehog signaling was recently demonstrated and did not have any specific immunohistochemical markers, it is associated with obesity and bleeding (Nault et al. 2017; Védie et al. 2018).

Reviews of the classification of HCA into subtypes have been published since 2007 but have mainly focused on the United States, Europe and Asia. These studies demonstrated some differences among these regions regarding epidemiologic data and subtype frequency, and showed the importance of an immunohistochemical panel for diagnosis (Kim et al. 2013; Bellamy et al. 2013; Lin et al. 2011; Larson and Guindi 2017).

In Brazil, immunomarkers for HCA subgroups classification are not available in most pathology laboratories, and similar studies have not been developed to the best of our knowledge. Thus, the current study aimed to classify HCA cases from the Federal University Hospital in Rio de Janeiro, Brazil, into subgroups both histologically and immunohistochemically, and to verify the contribution of morphological features to the diagnosis of hepatocellular adenoma subtypes in pathology practice.

Methods

Case selection and clinical data

The studied HCA obtained by surgical resection were retrieved from the pathology files of the Federal University Hospital (HUCFF-UFRJ), Brazil, between 2000 and 2015. This study was approved by the institutional ethical committee. The following data were retrieved from the medical records: age, gender, oral contraception use, metabolic disease and follow up. The size and number of nodules were obtained from imaging or pathology data.

Histological assessment

Slides stained with hematoxylin-eosin and reticulin were used for evaluation. All cases were reviewed by two pathologists with expertise in liver pathology (VLP, ACB). The following histological features were recorded as present or absent: steatosis, inflammatory infiltrate, sinusoidal dilatation, ductular reaction, pseudoportal tracts (thick wall arteries insert in collagen matrix), cellular atypia, pseudoglands, fibrosis, and reticulin loss. Steatosis and inflammatory cell infiltration were scored semiquantified. Steatosis were categorized as mild (> 5–33%), moderate (33–66%) or severe (> 66%); mononuclear inflammatory cell infiltration as mild (1–2 foci/high-power field), moderate (3–4 foci/high-power field) or severe (> 4 foci/high-power field).

Immunohistochemical analysis

Immunohistochemical staining was performed using the Novocastra Novolink polymer detection system (Leica Biosystems Newcastle Ltd., UK) and the following primary antibodies: mouse anti-human GS (MAB 302, 1:200, Merck Millipore, Darmstadt, GER); mouse anti-human LFABP (Ab7366, 1:40) and rabbit anti-human C-reactive protein (Ab32412, 1:400), both from Abcam (Cambridge, MA, USA); mouse anti-human β catenin (PA 0083, 1:400, Leica Biosystems Newcastle Ltd., UK); and mouse anti-human serum amyloid A (IS605,1:200, Dako, Carpinteria, CA, USA).

LFABP, serum amyloid A (SAA), C-reactive protein (CRP), and GS immunoreactivity were observed in the cytoplasm and were recorded as positive or negative. For GS, staining was recorded as positive when it was moderate to strong, diffuse or patchy. Perivenular positivity alone was not considered in the evaluation. Only nuclear β catenin was recorded as positive.

Briefly, the presence of diffuse steatosis and negative LFABP immunostaining indicated HHCA. Pseudoglands, cellular atypia, diffuse or patchy immunoexpression of GS

and/or nucleus-positive β catenin indicated bHCA. Inflammatory infiltrate, sinusoidal dilatation, ductular reaction, SAA and CRP positivity indicated IHCA. However, if IHCA also showed immunoexpression of GS and/or nuclear β catenin, the coexistence of β catenin mutation was considered (b-IHCA). Tumors with none of the above phenotypic markers or with marked necrosis and/or hemorrhage were considered UHCA (Zucman-Rossi et al. 2006; Bioulac-Sage et al. 2011).

Statistical analysis

Categorical variables were summarized as the frequency and percentage. Continuous variables were compared using the chi-squared test or Fisher's exact test. A P value of less than 0.05 was considered statistically significant. The concordance between histological and immunohistochemical classifications was investigated using the Kappa test, where values of less than 0.2 indicated no agreement; 0.2 to 0.40 indicated slight agreement; 0.4 to 0.6 indicated moderate agreement; 0.6 to 0.8 indicated good agreement; and values greater than 0.8 indicated excellent agreement (Landis and Kock 1977).

Results

Thirty HCA from 23 patients were studied. Only one male patient was included in the analyses. The median age of the study subjects was 35 years, and the male patient was 57 years old. Seventy-seven percent of the patients used OC; 28% had diabetes mellitus; and 43% were obese, including the male patient. Adenomatosis was found in 3 patients, one of whom had glycogen storage disease, type 1. Most of the HCA specimens measured ≤5 cm (45.8%), followed by tumors greater than 10 cm (33.3%) and those > 5–10 cm (20.9%). Follow-up data were available for 19 patients, with the follow-up period ranging from 3 to 132 months, with an average of 36 months. There were no reports of recurrence or metastasis.

Histological classification

Eleven HCA specimens (36.6%) were classified as HHCA (Fig. 1), representing the second most frequent subtype. Steatosis was observed in all specimens, with a predominantly severe intensity (63.6%). Inflammatory infiltrate were found in a few tumors, while cellular atypia, sinusoidal dilatation, ductular reaction, pseudoportal tracts and reticulin loss were absent (Table 1). bHCA (Fig. 1) was considered in 5 adenomas (16.7%). Two showed both the morphological findings, i.e.pseudoglands and cellular atypia, whereas in the others, only one of these criteria was met. Steatosis, sinusoidal dilatation, ductular reaction, and pseudoportal tracts were not found in any tumor (Table 1).

Fourteen cases of HCA (46.7%) were classified as IHCA, which was the most common subtype (Fig. 1). Steatosis was observed in 64.3% of cases; however, in contrast to HHCA, none of these cases were severe. Sinusoidal dilatation and inflammatory infiltrate were present in all IHCA. Ductular reaction, pseudoportal tracts and cellular atypia were observed in 71.4, 85.7 and 42.8%, respectively (Table 1). Focal loss of reticulin was observed in only one tumor. No adenomas were classified as UHCA according to the histological criteria.

Considering all the analyzed histological variables, only steatosis and its intensity were associated with HHCA ($p = 0.002$ and $p < 0.0001$, respectively), while inflammatory cell infiltration and its intensity, ductular reaction, sinusoidal dilation and pseudoportal tracts were strongly associated with IHCA ($p < 0.0001$), as were pseudoglands and cellular atypia ($p = 0.003$) and with bHCA (Table 1).

Immunohistochemical classification

Eleven HCA (36.7%) cases were classified by immunohistochemistry as HHCA. Immunostaining for LFABP, GS and β catenin was negative in all tumors (Fig. 1). The histological diagnosis was confirmed by immunohistochemistry in 90.9% of cases. In two HCA there was not agreement between histological and immunohistochemical classifications, one of which was positive for LFABP, SAA and CRP and was reclassified as IHCA. Interestingly however, steatosis was moderate in this tumor, and it did not show any morphological IHCA features. The opposite situation also occurred, i.e., one IHCA specimen was LFABP and SAA negative but showed weak and diffuse CRP staining and was reclassified as HHCA. This specimen showed moderate steatosis, mild inflammatory cell infiltration, and focal sinusoidal dilatation. We emphasize that in both tumors, non-tumoral hepatic tissue was used as the internal control for the reaction, and it is possible that genetic analysis might elucidate the true HCA subtype in both cases due to their phenotypic profile common to HHCA and IHCA.

Seventeen tumors (56.6%) were classified as IHCA by immunohistochemistry, most of them were positive for both SAA and CRP (13/17) (Fig. 1). Five adenomas were also GS+ and were classified as b-IHCA, although these tumors did not show any nuclear β catenin positivity. The histological and immunohistochemical subtypes were concordant in 13 cases of IHCA (76.5%). Among the four adenomas that did not have histological diagnosis of the IHCA, after immunohistochemical appraisal, one was reclassified as HHCA, as discussed above; two as b-IHCA (GS+,CRP+,GS+) and one as IHCA (GS- and CRP+). We point out that the last three adenomas were morphological classified as bHCA.

Finally, one HCA was classified as bHCA (GS+,CRP-, SAA -), although it did not show nuclear β catenin

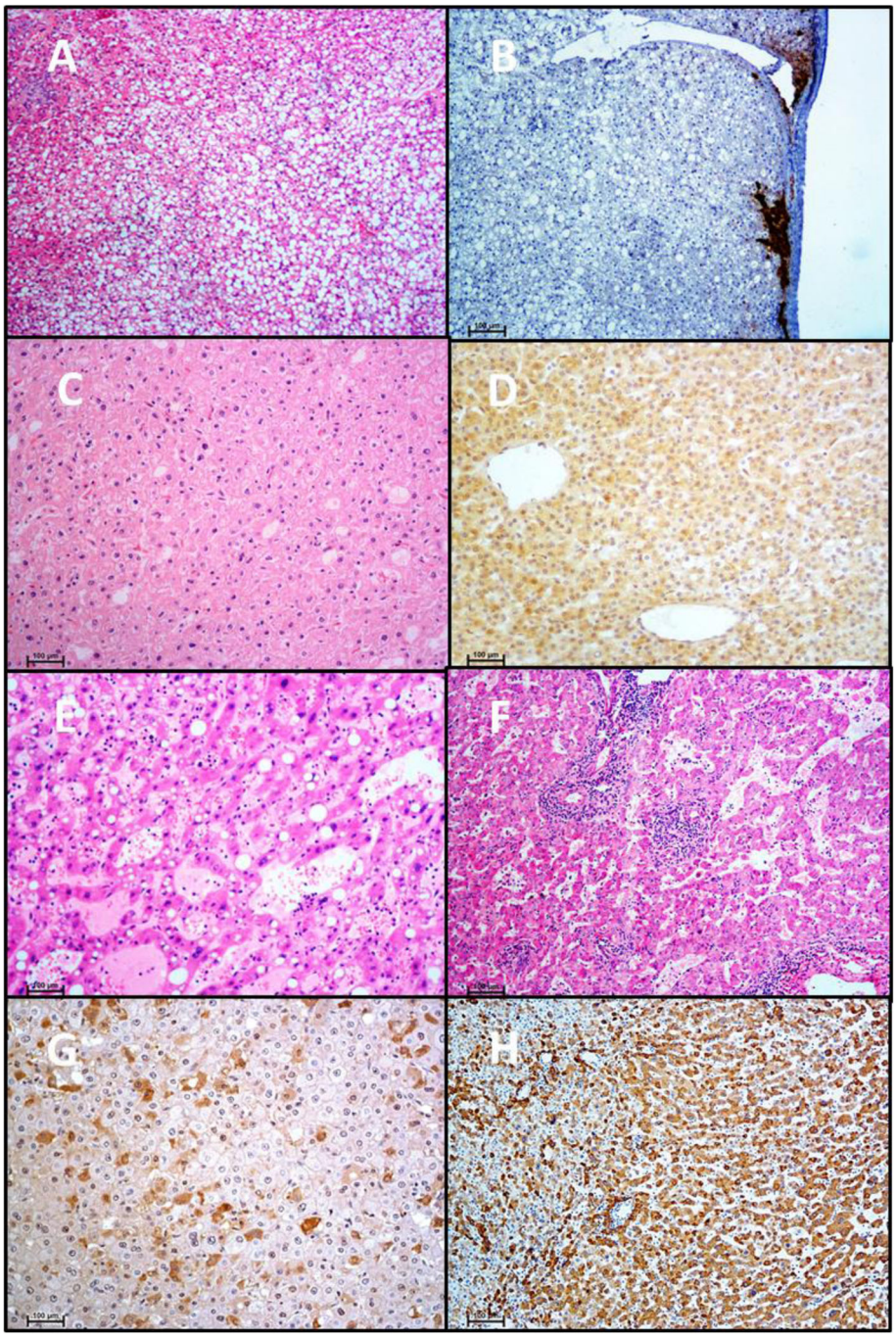

Fig. 1 **a** HHCA - HE: diffuse steatosis; **b** HHCA - LFABP immunostaining negative; **c** bHCA - HE: pseudoglands (**d**) bHCA - diffuse immunoexpression of GS; **e** IHCA - HE: sinusoidal dilatation, mild steatosis; **f** IHCA - HE: patchy inflammation, sinusoidal dilatation and pseudoportal tract formation; **g** IHCA - SAA immunoexpression; **h** IHCA - CRP immunoexpression

expression. (Fig. 1). Histology showed only pseudoglands. Another case histologically classified as bHCA did not express any markers and was subsequently reclassified as UHCA.

Concordance analyses between histological and immunohistochemical classifications were performed considering only HHCA, bHCA and IHCA because UHCA was not histologically diagnosed. Under these conditions, the agreement was good, with $K = 0.70$ and $p < 0.0001$. However, when we analyzed each HCA subtype separately, the concordance for HHCA was excellent ($K = 0.854$ and $p < 0.0001$); that for bHCA was slight ($K = 0.365$ and $p =$

Table 1 Histological features of the hepatocellular adenomas by histological classification

Histological features	HHCA $n = 11$	bHCA $n = 5$	IHCA $n = 14$	p value
steatosis mild	1(9.1%)	0	6(42.9%)	**< 0.0001**
steatosis moderate	3(27.3%)	0	3(21.4%)	
steatosis severe	7(63.6%)	0	0	
atypia	0	4(80%)	6(42.8%)	**0.003**
I. infiltrate mild	2(18.2%)	0	9(64.3%)	**< 0.0001**
I. infiltrate moderate	0	0	4(28.6%)	
I. infiltrate severe	0	0	1(7.1%)	
sinusoidal dilatation	0	0	14(100%)	**< 0.0001**
ductular reaction	0	0	10(71.4%)	**< 0.0001**
pseudoportal tracts	0	0	12(85.7%)	**< 0.0001**
fibrosis	2(18.2%)	0	3(21.4%)	0.82

HHCA= hepatocellular adenoma with HNF1A mutation, *bHCA*= hepatocellular adenoma with beta catenin mutation, *IHCA*= inflammatory hepatocellular adenoma, I. infiltrate= inflammatory infiltrate. 0 = absent

0.011); and that for IHCA was good (K =0.657 and $p <$ 0.001).

Discussion

The present series consisted almost exclusively of female patients; among the 23 patients studied, only one was male. Seventy-seven percent of the patients had a history of OC use. In the literature, the prevalence of HCA in men ranges from 11 to 50% (Dokmak et al. 2009; Kim et al. 2013). It is important to verify whether HCA in men is as uncommon as in the series investigated herein in other Brazilian studies.

The increase in obesity in some western countries is considered one of the reasons for the large number of HCA cases in male patients (Chang et al. 2013). In this study the obesity, associated or not with metabolic syndrome, was a risk factor for eight patients. Interestingly, no tumor recurrence or malignant transformation was found in any patient.

Adenomatosis was found in three patients, two used OCs, one of whom was also obese, and the third had glycogen storage disease type 1. In a previous series, IHCA was found to be more frequent in patients with glycogen storage disease, as observed in our study. However, whether glycogen storage disease shares the same inflammatory metabolic pathways as IHCA remains unclear (Sakellariou et al. 2012). The other two HCA cases were classified as HHCA, which is described as the most common subtype in patients with adenomatosis without glycogen storage disease (Zucman-Rossi et al. 2006). Adenomatosis is also associated with prolonged use of OCs in women between the 3rd and 4th decades, in addition to maturity onset diabetes of the young type 3 (MODY3), caused by mutations in HNF1 alpha (Dhingra and Fiel 2014; Nault and Zucman 2013).

LFABP was negative in the liver in both cases of HHCA with adenomatosis. However, one of these specimens was SAA positive, which was obtained from a patient with obesity, a condition that is most frequently associated with IHCA. In this case, genetic analysis might elucidate the possible association between HHCA and IHCA.

In the classification based on microscopic findings, IHCA was identified most frequently (46.7%), followed by HHCA (36.6%) and bHCA (16.7%). According to immunohistochemistry, IHCA and HHCA occurred most frequently (56.6 and 36.6%, respectively). These results agree with those of other studies in which IHCA and HHCA were identified as the main subtypes, representing approximately 90% of HCA cases (Rebouissou et al. 2009; Bellamy et al. 2013; Greaves and Bhattacharya 2008). Concerning bHCA and UHCA, we found fewer cases than other studies (Bellamy et al. 2013; van Aalten et al. 2011; Shafizadeh et al. 2014). Some authors have noted that the different diagnostic criteria applied for hepatocellular carcinoma may explain why they did not find any cases of bHCA (Shafizadeh et al. 2014). Similar findings are also reported in French series, however they compared IHCA associated with β catenin mutation and not with bHCA exclusively (Bioulac-Sage et al. 2012; Balabaud et al. 2013). We believe that these studies may not be comparable because they involved different methodologies; that is, the French study was performed using biopsies, while Shafizadeh et al. did not describe the tissue samples they analyzed.

When we analyzed HCA with possible mutation of β catenin in our series, regardless of its association with IHCA, the frequency was approximately 20%. The frequency of UHCA identified in the present study was also below the rate reported in the literature (Shafizadeh et al. 2014; Bioulac-Sage et al. 2012). Some authors observed that half of UHCA cases resemble bHCA, the difference being the lack of abnormal GS expression (Fonseca et al. 2013). Overall agreement between the histological and immunohistochemical classifications was good in the present study. The agreement between different subtypes was excellent for HHCA. This allowed the diagnosis of the HHCA subtype based only on histological features. The single case of HHCA that was revised to IHCA was positive for LFABP, CRP and SAA. On the opposite, in a study conducted by other authors only 67% were LFABP negative and were morphologically classified as HHCA (Bellamy et al. 2013; Margolskee et al. (2016) reported cases of HHCA with double-phenotype (LFABP- and GS+). Recently, molecular study demonstrated malignant transformation in some hepatocellular adenomas LFABP negative. However, in most of these adenomas the steatosis did not found (Putra et al. 2019).

The good agreement between the histological and immunohistochemical diagnoses of IHCA also reinforces the histological diagnosis of this subtype. The divergent cases were mainly due to GS expression, indicating mutation of β catenin. A single case initially classified as IHCA was LFABP negative and SAA positive only in a few tumor cells; considering this immunophenotype was reclassified as HHCA. However, the possibility of a double phenotype cannot be ruled out because in addition to moderate steatosis, this specimen also showed mild inflammatory cell infiltration and sinusoidal dilatation.

Although our subtype classification did not consider double-subtype phenotypes among HHCA and IHCA and because mutations common to both have not been described, we believe that this situation may occur. In these cases, genetic analysis may clarify this question. It was described HCA with a similar immunohistochemical pattern, although molecular analysis was not performed (Bellamy et al. 2013). The identification of IHCA with β catenin mutation based only on morphology is a major challenge in IHCA. Therefore, in such cases, GS is an important marker.

The agreement for bHCA was weak, and only one tumor morphologically classified as bHCA did not show positive staining for any antibody, except GS; the other three were GS+,SAA+ and CRP+ and these cases were reclassified as b-IHCA. Finally, the last adenoma morphologically classified as bHCA was negative for all antibodies and were considered as UHCA.

We found no nuclear β catenin staining in HCA, although GS was diffusely positive in some HCA cases. However, we do not know whether this profile resulted from mutation of other β catenin exons or components of the Wnt pathway or from the few cells with nuclear β catenin staining, which represented less than 5% of the total tumor area (Margolskee et al. 2016). A challenge in the interpretation of GS staining occurs when staining is weak and focal, making it difficult to consider such staining truly positive (van Aalten et al. 2011; Joseph et al. 2014); which is why we considered GS positivity in the cases with diffuse expression and moderate/strong intensity. Some authors recommend that all GS expression patterns should be described in the pathologist's report (Hale et al. 2016).

Conclusion

It was possible to diagnose most of HCA subgroups based on morphological features; moreover, GS analysis is highly useful for the diagnosis of adenomas with β catenin mutation mainly when aberrant nuclear β catenin staining is not found, though molecular analyses may also be necessary.

Abbreviations

bHCA: β-catenin-activated hepatocellular adenoma; bIHCA: β-catenin-activated inflammatory hepatocellular adenoma; CRP: C-reactive protein; GS: Glutamine synthetase; HCA: Hepatocellular adenoma; HHCA: HNF1A inactivated hepatocellular adenoma; HNF1A: Hepatocyte nuclear factor 1A; IHCA: Inflamatory hepatocellular adenoma; LFABP: Liver type acid binding protein; OCs: Oral contraceptives; SAA: Serum amyloid A; UHCA: Unclassified hepatocellular adenoma

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Authors' contributions

CAV collected and analyzed the data and the results, performed morphological and immunohistochemistry studies and drafted the manuscript. ACB performed morphological and immunohistochemistry studies, developed the table and critical reviewed the manuscript. AS offered histological and immunohistochemical support. ODR contributed to the critical revision of the manuscript and developed the figures. VLP conceived and designed the study, performed the morphological and immunohistochemical studies, and contributed to the interpretation of the data, critical revision of the manuscript and study supervision. All the authors read and approved the final manuscript.

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Availability of data and materials

All data are available upon request to the corresponding author.

Ethics approval

This study was approved by the Ethics Committee of Clementino Fraga Hospital, Federal University of Rio de Janeiro with a waiver of informed consent (CAAE No 51496515.3.0000.5257).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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