Histol Histopathol (2014) 29: 243-249
DOI: 10.14670/HH-29.243

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Retrospective study of hepatocellular adenomas based on the phenotypic classification system: A report from China

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Summary. A molecular and pathological classification system for hepatocellular adenomas (HCAs) was recently introduced in Europe, resulting in four major identified subgroups. Asian countries have a considerably lower incidence of HCA as well as a different etiology. We aimed to characterize HCAs in a Chinese population based on this new classification system. A series of 30 patients with HCA were analyzed based on the phenotypic classification system using immunohistochemical analysis. Investigated antigens included liver-fatty acid binding protein (L-FABP), glutamine synthetase (GS), ß-catenin, serum amyloid A (SAA), and C-reactive protein (CRP). Of the 30 cases (20 female) included in this study, only one had a history of oral contraceptive use. We identified 9 (30%) hepatocyte nuclear factor (HNF)-1α-inactivated HCAs, 3 (10%) ß-catenin-activated HCAs, 11 (36.7%) inflammatory HCAs, and 7 (23.3%) unclassified HCAs. In the inflammatory HCA group, 2 cases demonstrated concurrent ß-catenin-activation. Homogeneous steatosis (6/9) and microadenomas (2/9) were more frequently observed in HNF1α-inactivated HCAs. A body mass index (BMI) of greater than 25 (5/11), alcohol use (4/11), and steatosis in background liver (3/11) were more frequent in inflammatory HCAs. ß-catenin-activated HCAs were larger than those of other subgroups. Despite obvious differences in etiology and gender proportion compared with Western countries, the clinical and pathological characteristics of HCA subgroups in China are similar to those in Europe. The phenotypic classification system could be reliably applied to Chinese patients as a meaningful tool for HCA management.

Key words: Hepatocellular adenoma, HCA subgroups, Phenotypic classification, Immunohistochemistry

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Introduction

Hepatocellular adenoma (HCA) is a rare, benign liver tumor that occurs primarily in women taking oral contraceptives (OCs). The incidence of HCA is approximately 3-4/100,000 in Europe and North America (Rooks et al., 1979), but lower in Asia. HCAs are rarely observed in men or children and have a male-to-female ratio of approximately 1:8-10 in Europe and North America (Bioulac-Sage et al., 2009; Farges and Dokmak, 2010).

It has been previously suggested that HCA is not a solitary disease, but a heterogeneous group of tumors with varying genetic and pathological characteristics (Bluteau et al., 2002; Zucman-Rossi et al., 2006; Rebouissou et al., 2009; Pilati et al., 2011; Nault et al., 2012). Four major subtypes have been identified to date: hepatocyte nuclear factor (HNF)-1α-inactivated (H-HCA), ß-catenin-activated (ß-HCA), inflammatory (I-

HCA), and unclassified HCA. I-HCA may concurrently be ß-catenin mutated. Authors from France and the Netherlands have described the pathological features of these different HCA subgroups (Bioulac-Sage et al., 2007, 2009, 2010; van Aalten et al., 2011). H-HCAs (35-40%) display marked steatosis, a lack of atypia, and an absence of inflammatory infiltrates. Liver adenomatosis (greater than 10 lesions) is most often found with H-HCA. ß-HCAs (10-15%) are frequently associated with pre-malignant and malignant features, including cytological atypia and concurrent hepatocellular carcinoma (HCC) within the lesion. I-HCAs (50%) are histomorphologically characterized by the presence of inflammatory infiltrates, thick-walled arteries, sinusoidal dilation and ductular reaction. Patients with a high body mass index (BMI) and excessive alcohol consumption (>40g/day) were overrepresented in the I-HCA group (Bioulac-Sage et al., 2007). Finally, less than 10% of HCAs remain unclassified.

Recently, a phenotypic classification of HCAs using immunohistochemistry has been proposed based upon the above-mentioned molecular characteristics (Bioulac-Sage et al., 2007, 2009). By immunohistochemical analysis of liver-fatty acid binding protein (L-FABP), glutamine synthetase (GS), ß-catenin, serum amyloid A (SAA) and C-reactive protein (CRP), this phenotypic classification successfully sorts HCAs in accordance with the pathological and clinical features of each subgroup, and reveals itself as a meaningful tool for HCA management.

Asian countries have a far lower prevalence of oral contraceptive use than Europe and North America, which presumably results in the lower HCA incidence and different sex ratio between these areas. In Chinese patients, only 11% of HCAs are attributed to OC use (Lin et al., 2011). To date, there have been no reports evaluating the clinical and pathological features of HCAs in a Chinese population based on the recent European phenotypic classification system. In this study, we aimed to characterize a series of 30 HCA cases in our hospital based on this new classification system.

Materials and methods

Patients

A series of 30 patients who had been pathologically diagnosed with HCA between January 2002 and December 2011 in Zhongshan Hospital were included for this retrospective study. All patients underwent surgery (hepatectomy or transplantation, in 28 or 2 cases, respectively). The clinical data regarding OC use, individual and familial history, body mass index and symptoms, among other factors, were collected.

Histopathological and immunohistochemical analyses

Formalin-fixed and paraffin-embedded tissue blocks were retrieved from the Department of Pathology at Zhongshan Hospital. For each case, a representative HCA nodule, as well as a portion of non-neoplastic liver, was selected for study. When multiple nodules were present, only one representative lesion was included. 4-μm sections were cut and stained with hematoxylin and eosin for routine histopathology. Microscopic features (e.g., cytology, steatosis, and inflammatory infiltration) were noted by the liver pathologist before subsequent classification.

Immunohistochemical stains for five antibodies, including L-FABP, GS, ß-catenin, SAA, and CRP, were performed on both tumoral and adjacent non-tumoral tissues to apply the HCA phenotypic classification. Briefly, after microwave antigen retrieval, tissues were incubated with primary antibodies (L-FABP, rabbit polyclonal, Abcam, 1:50 dilution; GS, mouse monoclonal, BD Biosciences, 1:200 dilution; ß-catenin, mouse monoclonal, BD Biosciences, 1:200 dilution; SAA, mouse monoclonal, Abcam, 1:100 dilution and CRP, rabbit monoclonal, Abcam, 1:200 dilution) overnight at 4°C, followed by a 30-min incubation with the secondary antibody. The reaction was visualized with diaminobenzidine, and tissues were counterstained with hematoxylin. Positive and negative controls were routinely included. Additional immunostaining for cytokeratins 7 and 19, α-smooth muscle actin, and CD34 were performed to better visualize bile ducts, arteries and sinusoidal capillarization.

The pathological diagnoses and differentiation between HCA and HCC were made according to the WHO criteria. Briefly, a typical adenoma was composed of benign hepatocytes arranged in regular plates that were usually one or, at most, two cells thick. The parenchyma lacked biliary structures or portal triads, and the tumor cells were similar to normal hepatocytes. In HCC, tumor cells grew in cords of variable thickness and formed numerous acinar structures. Different architectural patterns (trabecular, acinar, or compact pattern) and cytological variants frequently occur in combination. HCAs were immunohistochemically negative for markers of heat shock protein 70 (HSP70) and glypican 3 (GPC3). Glutamine synthetase expression was limited to centrilobular regions, except for ß-catenin-activated HCA subtype. Reticulin staining showed that reticular fibers were present. In contrast, HCCs were positive for at least 2 of the 3 markers (GS, GPC3, HSP70). When present, GS was diffusely positive in HCC. Capillarized sinusoids (CD 34+) were almost always found, and reticulin staining showed attenuated or absent reticular fibers.

Samples with cytological abnormalities (e.g., cell enlargement, nuclei that were large, irregular, or hyperchromatic, or normal to mildly increased nuclearcytoplasmic ratio) but no architectural changes were described as having "cytological atypia".

H-HCA was defined as absence of L-FABP expression in the tumor. ß-HCA was defined as strong and diffuse expression of GS, with nuclear ß-catenin expression as a supplementary parameter. I-HCA was

defined as strong and diffuse expression of SAA/CRP. Nodules without any of these above-mentioned phenotypic markers were reported as unclassified HCAs.

Ethics

Ethical approval was obtained from the Research Ethics Committee of Zhongshan Hospital, and written informed consent was obtained from each patient.

Statistical analysis

Continuous variables were summarized as the mean and standard deviation for normal variance, or as the median with ranges in the case of non-normal variance. The Kruskal-Wallis test and Fisher's exact test were used for statistical analysis. A p-value of less than 0.05 was considered statistically significant.

Table 1. Clinical and pathological data of 30 cases of HCA.

Characteristics		Value
Age (year); median (extremes)		27.5 (16-69)
Sex		
	Female	20
	Male	10
BMI; mean±SD		22.5±3.3
	BMI<25	23
	BMI≥25	7
Mode of discovery		
	Abdominal pain	4
	Abdominal discomfort	2
	By chance	24
Number of HCA		
	solitary	23
	Multiple	7
Tumor size (cm); median (extremes)		7.8 (2.5-21)
	Tumor size<5cm	9
	Tumor size≥5cm	21

Results

General analysis

Clinical and pathological features are summarized in Table 1. Of the 30 patients included in this series, the sex ratio (female: male) was 2:1, the median age was 27.5 years with a range of 16-69 years. The mean BMI was 22.5±3.3; six males and one female had a BMI of greater than 25. Oral contraceptive use was only found in one patient: a 41-year-old woman who used OC for 4 years in her twenties. No other exposure to estrogenic, androgenic or anabolic steroids was reported in any of the patients. Four patients (all male) reported excessive alcohol intake. Two patients suffered from concomitant glycogen storage disease, a known risk factor for HCA. Other diseases known to be associated with HCA, such as familial adenomatous polyposis coli, aplastic anemia, and vascular disorders, among others, were not found in our series. Three patients had a history of hepatitis B virus (HBV) infection but all were HBsAg-negative.

Four patients (13.3%) presented with acute abdominal pain. Two of them had tumor rupture and hemoperitoneum, and one of them developed hemorrhagic shock. Abdominal discomfort was the presenting complaint in two additional cases. The remaining cases were discovered incidentally during radiological examination for routine check-ups or unrelated disorders.

Preoperative transcatheter arterial chemoembolization (TACE) was performed in 2 cases for palliation, and embolization in one ruptured tumor case with hemoperitoneum and hemorrhagic shock. Twenty-three patients had solitary lesions and underwent hepatectomy to have them removed. Seven patients had multiple HCA nodules in their livers. Two of them had concomitant glycogen storage disease and underwent

Table 2. Clinical and pathological characteristics according to subtype classification of hepatocellular adenomas.

Characteristics		H-HCA(n-9)	ß-HCA(n=3)	I-HCA(n=11)	Unclassified HCA(n=7)
Patients					
	Female/male	8/1	2/1	4/7	6/1
	BMI; median (extremes)	20.7 (17.7-24.1)	16.9 (16.9-23.7)	24.1 (17.9-29.4)	22.4 (19.0-27.0)
	BMI≥25	0	0	5	2
	Excessive alcohol consumption	0	0	4	0
Tumor					
	Number of HCA (solitary/multiple)	7/2	3/0	8/3	5/2
	Tumor size (cm); median (extremes)	4 (3-18)	12 (10-12.5)	5 (4-14)	8 (2.5-21)
	Steatosis (focal)	6	0	1 (1)	2 (2)
	Sinusoidal dilatation	1	1	4	2
	Inflammatory infiltration	0	0	4	0
	Macroscopical hemorrhage	2	2	0	3
	Cytological atypia	0	1	4	1
	HCA with HCC	0	1	0	2
Background liver					
	Steatosis (partial/diffuse)	1/0	0/0	1/2	0/1

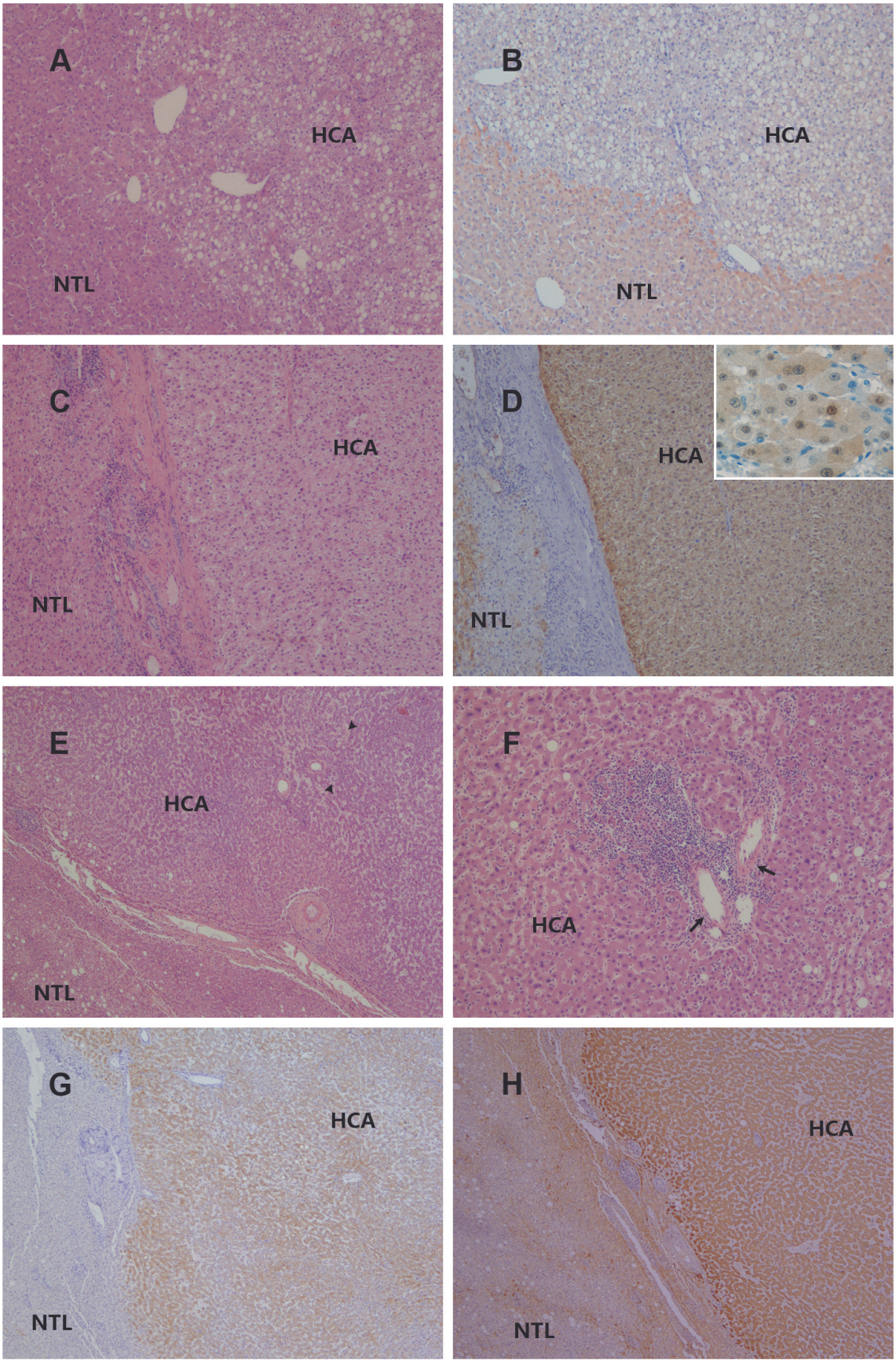

Fig. 1. Characteristic features of adenoma subtypes with hematoxylin-eosin and immunohisto-chemistry stain. **A, B.** Hepatocyte nuclear factor (HNF)-1α-inactivated hepatocellular adenoma (HCA). **A.** Marked steatosis in HNF1α-inactivated HCA (hematoxylin-eosin [HE]). **B.** Lack of liver-fatty acid binding protein (L-FABP) in HCA, in contrast to the non-tumor live. **C, D.** ß-catenin-activated HCA. **C.** Increased cellularity in HCA, in contrast to the non-tumor liver (HE). **D.** Homogeneous glutamine synthetase (GS) staining in HCA, in contrast to the non-tumor liver, ß-catenin cytoplasmic and nuclear overexpression in HCA (inset). **E-H.** Inflammatory HCA. **E, F.** Sinusoidal dilatation (arrow head) and inflammatory infiltrates around a thick artery (arrow) in HCA (HE). **G.** Overexpressed serum amyloid A (SAA) outlines the HCA. **H.** C reactive protein (CRP) overexpression in HCA, in contrast to the non-tumor liver. A-D, F, x 100; E, G, H, x 50; inset in D, x 400

liver transplantation; two other patients had more than 10 nodules, which could be diagnosed as liver adenomatosis, and both of these patients had 2 major lesions excised to prevent rupture; the remaining three patients, who had 3, 4, and 2 HCA nodules in right lobe, underwent partial or right-hemi liver resection including all the HCA nodules.

The median size of the largest nodule in each case was 7.8 cm (range 2.5-21). In 21 cases, the size of the excised nodules exceeded 5 cm. Intra-tumoral hemorrhage was present in 7 cases (23.3%).

Analysis according to subgroups

Immunohistochemical analysis identified 9 HNF1α-inactivated HCAs (30%), 3 ß-catenin-activated HCAs (10%), 11 inflammatory HCAs (36.7%), and 7 unclassified HCAs (23.3%). In the inflammatory HCA group, two adenomas also demonstrated ß-catenin-activation. Table 2 summarizes the clinical and pathological features of each subgroup. Fig. 1 shows the representative histology and immunohistochemical findings.

HNF1α-Inactivated HCA (H-HCA)

Homogeneous steatosis was a common finding in H-HCAs (6/9, p=0.032), and no HCCs or cytological atypia were detected in this subgroup. The two adenomatosis cases were classified into this subgroup with micronodules (diameter ≤1 cm) present in the remaining liver following resection.

Inflammatory HCA (I-HCA)

Sinusoidal dilation (4/11) and inflammatory infiltration (4/11) were present in the I-HCA group; the nontumoral liver was more frequently steatotic (3/11) in this group relative to others. Heterogeneous steatosis was observed in one I-HCA nodule. Two cases in this group (1 male) also demonstrated ß-catenin-activation but no cytological atypia. The median BMI of patients with I-HCA was 24.1 (range 17.9-29.4) compared to a median BMI of 20.7 (range 17.7-24.1) in the H-HCA group. The difference between subgroups did not reach statistical significance. Four patients with excessive alcohol intake fell exclusively into this subgroup. The I-HCA subgroup had a majority of male patients (7/11).

ß-catenin-activated HCA (ß-HCA)

Two of the three cases of ß-HCA were found to have cytological atypia or coexisting HCC. Patients with ß-HCA had a complete absence of steatosis. The median size of tumors in the ß-HCA subgroup was 12 cm (range 10-12.5 cm) compared to others, but this difference did not reach statistical significance.

Unclassified HCA

Seven HCAs were unclassifiable (23.3%) because they were negative for CRP, SAA, ß-catenin, GS, with a normal L-FABP staining pattern. The two cases with glycogen storage disease fell into the unclassified group, as they presented with neither cytological atypia nor HCC.

Discussion

This is the first report addressing the clinical and pathological features of HCA subgroups in a Chinese population based on the newly suggested phenotypic classification system. We demonstrated that despite obvious differences in etiology and gender proportion compared with Western countries, the clinical and pathological characteristics of HCA subgroups in China were similar to those in Europe. In our study, H-HCA (30%) and I-HCA (36.7%) formed the two main subgroups. Histologically, H-HCA displays marked homogeneous steatosis without inflammation or cytological atypia. Microadenomas may be discovered in a resected specimen from the removal of a single HCA of this subtype. Obesity and excessive alcohol consumption is frequently seen in patients with I-HCA. Inflammatory infiltrates and sinusoidal dilation are frequently observed in this subtype. The proportion of ß-HCA (10%) is similar to that reported by Zucman-Rossi and colleagues (Zucman-Rossi et al., 2006). In our series, 2 of the 3 ß-catenin-activated HCAs are found to have cytological atypia or HCC, but this does not include the two I-HCAs that show ß-catenin activation. Besides, 2 of the 7 unclassified HCAs are also found to have HCC, which need further investigation.

Although there were more female cases in our series, the female to male ratio (2:1) was much lower than in Europe and North America (8-10:1) (Bioulac-Sage et al., 2009; Farges and Dokmak, 2010). A previous systematic review by Haoming Lin and colleagues reported that the male to female ratio of HCA patients in China was 1.65 (119:72) (Lin et al., 2011). Taken together, a higher proportion of males is a common feature of HCA in Chinese populations. In Western countries, HCA mainly occurs in young women using OC. OC use was present in 80-90% of female patients with HCA in France and the Netherlands (Bioulac-Sage et al., 2009; van Aalten et al., 2011). In our study, OC use was found in only one 41-year-old patient in her twenties, which is not likely to be relevant to the occurrence of HCA. This finding is also consistent with a review by Haoming Lin and colleagues (Lin et al., 2011), which reported a much lower prevalence (8/72) of long-term OC use among female patients in China compared to Western countries. We speculate that the scarcity of OC use is the reason for the relatively lower occurrence of HCA in young women in China, which consequently leads to the higher male to female ratio. However, with regards to the clinical and

pathological features of the disease, we did not find any obvious differences between our series and those observed in France and the Netherlands, whether analyzed as a whole or in subgroups. Considering the large differences in etiology and sex proportion between European and Asian countries, this result implies that different pathogenic factors may act via a common mechanism resulting in several different pathway abnormalities, consequently causing HCA. This speculation is supported by the observations that HCA cases that are obviously attributable to OC use may be sorted into different subtypes (Rebouissou et al., 2008).

Another noteworthy finding is that the unclassified HCAs (23.3%) accounted for a larger proportion in our series than those from France and the Netherlands (Bioulac-Sage et al., 2010; van Aalten et al., 2011). It is unclear whether the higher number of unclassified HCAs is associated with a higher male to female ratio in China, whether it is just a result of the limited sensitivity and specificity of the immunohistochemical analysis, or perhaps another unknown reason. This question awaits further investigation.

A history of HBV infection may add concerns for a diagnosis of HCC. Chronic HBV infection causes persistent inflammation and cirrhosis, which could lead to HCC (Liaw et al., 1989; Ahn et al., 2005). HCA is defined to occur in normal or nearly normal livers, but in rare cases it can occur in cirrhotic livers (Seo et al., 2012). In such cases, the clinical and pathological data should be carefully evaluated. In our study, three cases showed serologic marker patterns indicating immunity against chronic HBV infection. There was no underlying inflammation or cirrhosis in the adjacent liver parenchyma. Two of these cases were classified as HNF 1α-inactivated HCA, and the third was classified as an inflammatory HCA. None of the cases showed evidence of ß-catenin activation. The case classified as inflammatory presented mild cytological atypia.

Interpretation of immunohistochemical analyses can be perplexing. Categorizing samples as either H-HCA or I-HCA is feasible in most cases because of their homogeneous staining patterns. However, the heterogeneous and sometimes focal nuclear staining pattern of ß-catenin sometimes hinders the identification of ß-HCAs, making additional molecular analyses necessary. This issue has already been mentioned by European authors (Bioulac-Sage et al., 2009; van Aalten et al., 2011), and was confirmed by our data.

Presently, HCA management is primarily based on clinical parameters (van der Windt et al., 2006). Patients are advised to discontinue hormone treatments (OC pills and androgens), which can alone cause lesions to regress (Steinbrecher et al., 1981). Surgical resection is recommended for HCAs greater than 5 cm in size, HCAs that do not regress after withdrawal of hormones, HCAs with malignant transformation or evidence of ß-catenin activation, and HCAs in men (van Aalten et al., 2012). In conservatively treated patients, regular radiologic surveillance is the most appropriate strategy.

With the prevalence of HBV infection and the high incidence of HCC in China (Tanaka et al., 2011), surgeons are more prone to excising suspicious liver nodules. HCA subtyping may provide us with better tools to define patient management guidelines once HCA are discovered (Bioulac-Sage et al., 2011). For example, the identification of ß-HCA may lead to treatment of excision as it indicates an increased risk of malignant transformation, and genetic counseling may be proposed for H-HCA patients with associated diseases. However, a reliable diagnosis of HCA and its subtypes prior to surgery is in demand, and to date, this is still not an easy task because of the drawbacks mentioned previously. A multidisciplinary team of radiologists, surgeons, pathologists and hepatologists with combined expertise on these matters may help to make better disease management decisions.

In summary, we applied the phenotypic classification of HCAs to validate its use in Chinese patients. In this population, OC use is much less prevalent and the sex proportion of patients with HCA is far different from that in Western countries. Our study suggests that this classification system could be reliably applied to HCAs in China, which may benefit the clinical management of this disease.

Acknowledgements. The authors gratefully acknowledge Haiying Zen for making tissue slices, and Aiwu Ke for his advice on manuscript editing.

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Accepted July 19, 2013