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Differential Diagnosis of Clinical, Imaging and Pathological Features Between Focal Nodular Hyperplasia and Hepatocellular Carcinoma

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1. Abstract

1.1. Objective: To study the clinical, endoscopic and pathological features of Focal Nodular Hyperplasia (FNH) and hepatocellular carcinoma (HCC) in order to provide basis for differential diagnosis of FNH and HCC.

1.2. Methods: The clinical data of 56 patients with FNH and 260 patients with HCC treated in the Department of Hepatobiliary surgery, Renmin Hospital of Wuhan University from April 2015 to April 2021 were analyzed retrospectively. All patients underwent general laboratory examination, abdominal color ultrasound or contrast-enhanced ultrasonography, upper abdominal enhanced CT and MRI, which were surgically performed and finally pathologically confirmed.

1.3. Results: 1. The comparison of general conditions suggested that compared with HCC, patients with FNH had a younger age of onset and longer course of disease, most of which were unintentionally discovered during physical examination or other examinations, and a few patients had a history of oral contraceptives and lower Child-Pugh score (all P <0.05). 2. The comparison of main laboratory tests suggested that white blood cell count, alanine aminotransferase (ALT) and platelet count were higher in FNH patients, while erythrocyte count, aspartate aminotransferase (AST), total bilirubin, direct bilirubin, creatinine, AFP, CA199 and abnormal prothrombin were higher in HCC patients (all P <0.05). 3. The comparison of imaging features suggested that abdominal color Doppler ultrasound showed that there were more isoechoic lesions in FNH than in HCC, and more hypoechoic lesions in HCC than in FNH (all P < 0.05). Abdominal CT showed more isodense lesions in unenhanced phase, homogeneous enhancement in arterial phase, isodense lesions and high density lesions in portal venous and delayed phase and central scar enhancement in FNH than HCC, while low density lesions in unenhanced phase, inhomogeneous enhancement in arterial phase, low density lesions in portal venous and delayed phase in HCC, and the correct diagnosis rate of HCC on CT was higher than that of FNH (all P < 0.001). Abdominal MRI showed isointense or hyperintense on T2W1, isointense or hypointense on T1W1 on plain MRI, and central scar enhancement could be seen on contrast-enhanced MRI in FNH, while it showed hyperintense on T2W1 and hypointense on T1W1 in HCC (P < 0.001). 4. Histopathological features: central fibrous scar appeared in FNH, with arteries, bile ducts, inflammation occurring in the septum of the hepatic plate and thickness of hepatic plate <3 layers, while mitosis and nuclear heterogeneity appeared in HCC (P < 0.001).

1.4. Conclusion: In the differential diagnosis of FNH and HCC, more attention should be paid to the comprehensive judgment of clinical, imaging and pathological features so as to improve the rate of early diagnosis.

2. Introduction

Focal Nodular Hyperplasia (FNH) is the second most common benign tumor of the liver after hepatic hemangioma, accounting for about 8% of hepatic primary tumors [1-2], and its incidence is increasing year by year [3]. Hepatocellular carcinoma (HCC) is the most common malignant tumor of the liver, accounting for about 80% of primary malignant tumors of the liver [4], and it grows rapidly and can undergo metastasis at an early stage [5]. How to identify them in the early stage becomes a difficult problem because the clinical manifestations of the two are similar in the early stage, but the treatment and prognosis are different [6-7]. At present, the differential research on FNH and HCC mainly depends on imaging examination [8-13], while comprehensive analysis combined with the clinical manifestations and histopathological features of the patients were not performed. In this study, the clinical, imaging and pathological data of 56 patients with FNH and 260 patients with HCC confirmed by surgical resection in the Department of Hepatobiliary surgery of Renmin Hospital of Wuhan University were analyzed retrospectively in order to provide basis for early differential diagnosis between the two groups.

3. Subjects and Methods

3.1. Research Object

The clinical data of 56 patients with FNH and 260 patients with HCC treated in the Department of Hepatobiliary surgery, Renmin Hospital of Wuhan University from April 2015 to April 2021 were collected. The patients were followed up for (1-73) months, with a median of 23.7 months. Excluding patients who could not be diagnosed definitely, 56 patients were enrolled in the FNH group, aged from 18 to 71 years old, with an average age of (37.14 ±13.62) years old, including 30 males and 26 females, and 260 patients were enrolled in HCC group, aged from 28 to 87 years old, with an average age of (59.7 ±10.29) years, including 215males and 45 females.

3.2. Research Methods

3.2.1. Inclusion Criteria: ① patients with FNH and HCC without distant metastasis were diagnosed for the first time in our hospital; ② all patients had complete medical records (including routine hematological examination, abdominal ultrasound or contrast-enhanced ultrasound, contrast-enhanced CT and contrast-enhanced MRI of the liver); ③ All surgical resection samples were confirmed as FNH or HCC by pathologic immunohistochemistry.

3.2.2. Exclusion criteria: ① patients with incomplete clinical and imaging data; ② HCC patients with distant metastasis and unable to perform surgery; ③ FNH patients who refused to operate; ④ Those lost to follow-up.

3.3. Data Collection

The clinical enrollment forms of FNH and HCC were designed to collect data on the main general conditions, main laboratory examinations, imaging features and histopathological features of the patients. A total of 66 differential indexes were selected, including 21 general conditions, 12 main laboratory examinations, 23 imaging features and 10 histopathological features.

3.4 Statistical Methods

After data collection, SPSS 27.0 software was used to analyze the data. The counting data were expressed as [n (%)] and the comparison between groups was performed by chi square test. If the measurement data obey the normal distribution, it is expressed by the mean ±standard deviation ($\bar{x} \pm s$), and the independent sample t-test is used for the comparison between groups. Those that followed non-normal distribution were expressed by quartiles, and comparisons between groups were performed using independent sample rank sum test. It is statistically significant with $P < 0.05$.

4. Results

4.1. Comparison of The General Situation Between the Two Groups

As shown in (Table 1) Patients with FNH had a younger age of onset and longer disease duration, most of which were unintentionally found during physical examination or other examinations. A few patients had a history of oral contraceptives, and had lower Child-Pugh score. The onset of patients with HCC was older, more common in males, shorter course of disease, more symptoms of abdominal pain, previous history of hepatitis or liver cirrhosis, and higher Child-Pugh score (all P < 0 05). There was no significant difference between the two groups in the clinical manifestations such as diarrhea and emaciation, history of hypertension, history of diabetes mellitus, family history of tumors, cardiovascular and cerebrovascular diseases, autoimmune diseases, and history of smoking and drinking.

4.2. Comparison of Major Laboratory Tests Between the Two Groups

As shown in (Table 2) There are significant differences between the two groups in the comparison of white blood cell count, red blood cell count, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, alpha-fetoprotein (AFP), CA199 and abnormal prothrombin. Most of the patients with FNH have higher white blood cell count, platelet count and ALT, while red blood cell count, AST, total bilirubin, creatinine, AFP, CA199 and abnormal prothrombin were higher in HCC group (all P < 0 05). However, there was no significant difference in hemoglobin and direct bilirubin between the two groups.

Table 1: Comparison of two groups of general conditions

Project	FNH group（n=56）	HCC group（n=260）	*t/ value*	*P* value
Age (years old)	37.14±13.62	59.7±10.29	11.695	<0.001
Male / female (number of cases)	30/26	215/45	22.430	<0.001
Course of disease (days)	227.77±600.78	56.22±120.42	4.247	<0.001
Clinical manifestation n（%）				
Physical examination	40(71.4)	123(47.31)	10.734	0.001
Abdominal pain	6(10.71)	101(38.85)	16.282	<0.001
Diarrhea	5(8.93)	17(6.54)	0.406	0.524
Emaciation	0(0.00)	11(4.23)	0.223[b]	0.113
Other	5(8.93)	8(3.07)	4.000	0.046
Previous history n（%）				
Hypertension	5(8.93)	51(19.61)	3.609	0.057
Diabetes	3(5.36)	22(8.46)	0.258[a]	0.612
Coronary heart disease	1(1.79)	4(1.54)	0.000[a]	1.000
Family history of tumor	1(1.79)	10(3.85)	0.912[a]	0.340
Cerebrovascular disease	1(1.79)	5(1.92)	0.000[a]	1.000
Autoimmune diseases	0(0.00)	3(1.15)	1.000[b]	0.556
Oral contraceptives	11(19.64)	0(0.00)	0.000[b]	<0.001
hepatitis	4(7.14)	110(42.30)	23.205[a]	<0.001
Liver cirrhosis	0(0.00)	68(26.15)	0.000[b]	<0.001
Other	5(8.93)	27(10.38)	0.107	0.743
Smoking history n（%）	9(16.07)	67(25.77)	2.372	0.125
Drinking history n（%）	7(12.50)	57(21.92)	2.533	0.111
Child-Pugh score	5.11±0.31	6.11±1.62	4.594	<0.001

Note: a is the chi-square value of continuity correction; b is Fisher test.

Table 2: Comparison of major laboratory tests between the two groups

Project	FNH (n=56)	HCC (n=260)	*Z* value	*P* value
White blood cell count (10^9/L)	5.615(4.425,10.243)	5.300(4.013,7.025)	-2.523	0.012
Red blood cell count (10^9/L)	3.755(3.055,4.343)	4.140(3.620,4.705)	-3.453	0.001
Hemoglobin (g/L)	130.0(120.0,140.0)	130.0(113.3,145.8)	-0.181	0.857
platelet count (10^9/L)	184.0(157.8,300.0)	144.0(100.25,199.8)	-4.741	<0.001
ALT(μmmol/L)	41.50(26.25,73.25)	30.00(20.25,51.00)	-2.307	0.021
AST(μmmol/L)	30.50(21.00,56.00)	38.00(26.00,63.00)	-2.433	0.015
Total bilirubin (μmmol/L)	11.50(10.50,14.95)	17.60(12.60,25.28)	-5.046	<0.001
Direct bilirubin (μmmol/L)	5.570(4.525,7.454)	6.500(4.500,10.10)	-1.888	0.059
Creatinine（μmol/L）	24.75(5.725,55.00)	45.00(6.500,65.00)	-11.74	<0.001
AFP(ng/mL)	1.600(1.300,3.350)	8.250(2.400,377.6)	-6.228	<0.001
CA199(ng/mL)	3.450(1.625,5.395)	11.86(3.000,34.89)	-5.304	<0.001
Abnormal prothrombin（μg/L）	26.50(20.00,43.50)	80.05(28.00,2830)	-5.797	<0.001

Notes: ALT is alanine aminotransferase; AST is aspartate aminotransferase; AFP for alpha-fetoprotein.; CA199 is carbohydrate antigen 199.

4.3. Comparison of Abdominal Imaging Features Between the Two Groups

As shown in (Table 3) Abdominal color Doppler ultrasound showed that the isoechoic appearance in the FNH group was more than that in the HCC group, while the hypoechoic appearance in the HCC group was more than that in the FNH group ($P < 0.05$). Most of the patients in FNH group showed low density lesions or isodense lesions on CT, homogeneous enhancement in arterial phase, high density or isodense lesions in portal venous phase and delayed phase, and scar enhancement in part of the center, showing the characteristics of "fast in and slow out", and the correct diagnosis rate of CT was 7.14% ($P < 0.001$). Patients in HCC group showed more low density or isodense lesions in CT plain scan phase, inhomogeneous enhancement in arterial phase, low density lesions in portal vein phase and delayed phase, no central scar enhancement, showing the enhancement characteristics of "fast in and fast out", and the correct diagnosis rate of CT was 40.08% ($P < 0.001$). Patients in FNH group showed hyperintense or isointense on T2W1 and isointense or hypointense on T1W1 on MRI plain scan. The characteristics of contrast-enhanced MRI are similar to CT, and center scar enhancement can be seen in the center, and The diagnostic rate of MRI is 14.29% ($P < 0.001$). Patients in HCC group showed hyperintense on T2W1 and hypointense on T1W1on plain MRI, and the MRI diagnosis rate was 68.8%($P<0.001$).

Table 3: Comparison of abdominal imaging features between the two groups

Project	FNH（n=56）	HCC（n=260）	χ^2 value	*P* value
Color ultrasound n（%）				
Low echo	32(57.14)	204(78.46)	11.076	0.001
Iso-echo	13(23.21)	30(11.53)	5.343	0.020
High echo	11(19.64)	26(10.00)	2.325	0.127
CT n（%）				
Low density	29(51.78)	193(74.23)	11.107	0.001
Iso-density	15(26.79)	33(12.69)	7.104	0.008
High density	12(21.43)	34(13.08)	2.584	0.108
Homogeneous enhancement in the arterial phase	54(96.43)	13(5.00)	230.536	<0.001
Inhomogeneous enhancement in the arterial phase	2(3.57)	247(95.00)	225.096[b]	<0.001
Hypodense foci in portal phase	3(5.36)	235(90.38)	174.638[b]	<0.001
Iso-density foci in portal phase	19(33.93)	23(8.85)	25.153	<0.001
Hyperdense foci in portal phase	34(60.71)	7(2.69)	137.378	<0.001
Central scar enhancement in portal phase	11(19.64)	0(0.00)	0.000[a]	<0.001
Hypodense in delayed phase	3(5.36)	241(92.96)	194.825[b]	<0.001
Iso-density in delayed phase	15(26.79)	19(7.31)	18.206	<0.001
Hyperdense in delayed phase	38(67.86)	0(0.00)	0.000[a]	<0.001
Central scar enhancement in the delayed phase	8(14.29)	0(0.00)	0.000[a]	<0.001
CT diagnosis n（%）	4(7.14)	112(40.08)	24.085[b]	<0.001
MRI n（%）				
Hyperintense on T2W1	42(75.00)	242(93.08)	16.544	<0.001
Iso-intense on T2W1	14(25.00)	18(6.92)	16.544	<0.001
Hyperintense on T1W1	21(37.50)	8(3.08)	65.504	<0.001
Iso-intense on T1W1	18(32.14)	25(9.62)	17.200	<0.001
Hypointense on T1W1	17(30.36)	227(87.31)	80.491	<0.001
Central scar enhancement	8(14.29)	0(0.00)	0.000a	<0.001
MRI diagnosis n（%）	8(14.29)	177(68.8)	54.932	<0.001

Note: a is the chi-square value of continuity correction; b is Fisher test.

4.4. Comparison of Histopathological Characteristics Between the Two Groups

As shown in (Table 4) A total of 63 lesions with diameters of (1.1-9.5) cm were found in 56 patients with FNH, three of which were multiple lesions, and a total of 279 lesions with diameters of (1.5-15) cm were found in 260 HCC patients, 17 of which were multiple lesions. The lesions of patients in both groups were sent for pathological examination after surgically removed, and the lesions of left lobe, right lobe and caudate lobe in FNH group were 30, 25 and 8 cases respectively, while those in HCC group were 147 cases, 106 cases and 26 cases respectively. Central fibrous scar appeared more often in the FNH group, with arteries, bile ducts, inflammation occurring in the septum of the hepatic plate and the thickness of hepatic plate <3 layers ($P < 0.001$), while it showed mitosis and nuclear heterogeneity more often in HCC, with multiple ≥ 3 layers of liver plate thickness ($P < 0.001$). However, there was no significant difference in lesion location, boundary and capsule integrity between the two groups.

4.5. Typical images and pathological pictures of FNH

As shown in (Figure 1).

Table 4: Comparison of histopathological features between the two groups

Project	FNH（n=63）	HCC（n=279）	χ^2 value	*P* value
Lesions in left lobe n（%）	30(47.62)	147(52.69)	0.529	0.467
Lesions in right lobe n (%)	25(39.68)	106(37.99)	0.062	0.803
Lesions in caudal lobe n(%)	8(12.70)	26(9.32)	0.656	0.418
Borderline clear n（%）	56(88.89)	239(86.66)	0.451	0.502
Complete capsule n（%）	53(84.13)	222(79.57)	0.578	0.410
Central fibrous scar n（%）	17(26.98)	0(0.00)	79.224	<0.001
mitosis figures n（%）	0(0.00)	279(100.00)	0.000a	<0.001
Nuclear heterogeneity n（%）	0(0.00)	279(100.00)	0.000a	<0.001
Thickness of liver plate ≥ 3 layers n（%）	2(3.17)	215(77.06)	117.819b	<0.001
Hepatic plate thickness n（%）	57(90.48)	12(4.30)	236.986	<0.001

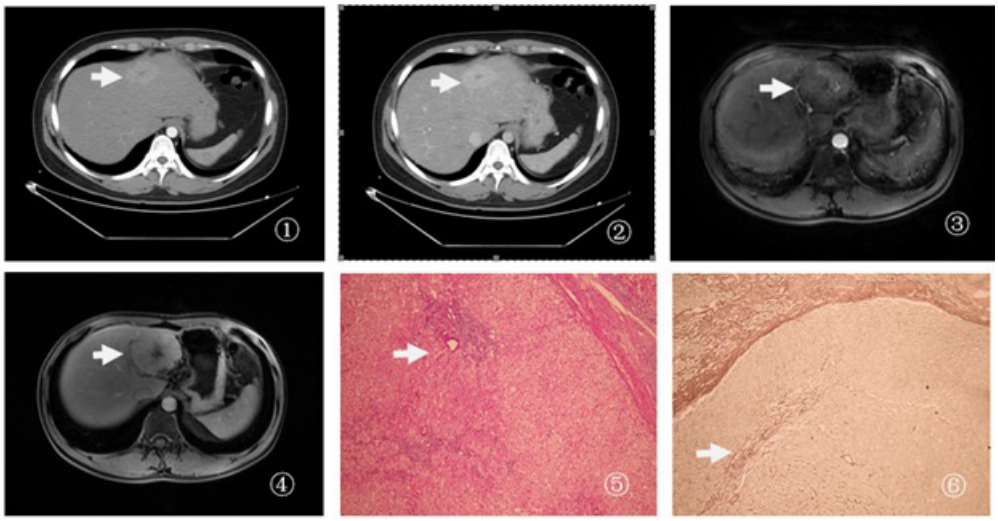

Figure 1: Typical images and pathological pictures of FNH

Notes: Patients in FNH group showed homogeneous enhancement in arterial phase, high density lesions in portal venous phase and scar in part of the center on CT (see picture 1 and 2). Patients in FNH group showed enhancement in arterial phase and portal venous phase and scar in part of the center on MRI (see picture 3 and 4). On pathological sections, the proliferating fibrovascular pattern was radially distributed to the surrounding liver tissue, and there was proliferation of small bile ducts between the interstitium and parenchyma with lymphocytic infiltration (see picture 5). Reticular fibers stained positive (see picture 6).

5. Discussion

FNH is a rare benign tumor-like space occupying lesion of the liver [14-15], the pathogenesis of which is still unclear. Studies have reported that FNH is mainly formed by arterial hyperplasia in the hepatic parenchyma or by congenital vascular abnormalities, inflammation, trauma and other factors, with a good long-term prognosis. HCC is one of the most common malignant tumors in clinic, the pathogenesis of which is related to hepatitis, cirrhosis, aflatoxin and other factors, with a high degree of malignancy and poor prognosis. It has been reported that the fatality rate of liver cancer has decreased year by year in recent years through early intervention which can improve the survival rate [16]. FNH and early HCC have no obvious clinical symptoms, which makes the differential diagnosis difficult, easy to misdiagnose, miss diagnosis, affecting the prognosis of patients. At present, there are few literatures on the differentiation between FNH and HCC, mainly focusing on imaging, without comprehensive analysis of patients' general conditions, laboratory examination and pathological characteristics. The purpose of this study is to comprehensively consider the clinical indicators and improve the rate of early differential diagnosis.

In this study, it was found that FNH was more common in young and middle-aged men with a slow onset. Most patients were found through physical examination, and a few patients had a history of oral contraceptives and no background of hepatitis or cirrhosis. However, there were more males than females in this study, which was inconsistent with the literature reports [17], which may be related to the small sample size. HCC is more common in middle-aged and elderly men with acute onset, abdominal pain, and background of hepatitis or cirrhosis, which is similar to that reported in the literature [18-20].

Abdominal imaging examination is an important means for preoperative diagnosis of liver tumors. In this study, abdominal ultrasound showed that it was isoechoic or hypoechoic in FNH, and hypoechoic in HCC. In contrast-enhanced CT, most of the FNH patients showed the enhancement characteristics of "fast in and slow out", but there were still some patients with atypical manifestations, no central scar enhancement or capsule enhancement, while in the HCC group, the contrast-enhanced CT showed the enhancement characteristics of "fast in and out", often accompanied by portal vein thrombosis, tumor hemorrhage, necrosis and so on. Patients in FNH group showed hyperintense or isointense on T2W1 on MRI plain scan while it showed isointense or hypointense on T1W1. The characteristics of enhanced scan are similar to those of CT, with central scar enhancement seen in typical patients. In the HCC group, Patients in HCC group showed hyperintense on T2W1 on plain MRI while it showed hypointense on T1W1.

Pathological examination is the gold standard for the diagnosis of liver tumors. FNH usually has a clear lesion boundary but no capsule, which can expand on the surface of the liver, but rarely has a pedicle. It is brown on the section and lighter in color than that of the adjacent normal liver. The central stellate scar with radial fibrous septum divides the mass into several small nodules as one of its characteristics [21]. Typical FNH generally has three characteristics: abnormal nodular structure, malformed blood vessels and bile duct hyperplasia, but atypical FNH generally has no central scar and is easy to be misdiagnosed as HCC. The general morphology of HCC can be massive or nodular, dispersed in each leaf, or diffuse in the liver tissue. Most of the massive HCC are spherical, with grayish white section and clear but irregular boundary, while the boundary of diffuse HCC is unclear. Fast-growing tumors are prone to ne-

crosis and bleeding in the center, and some tumors are surrounded by "satellite" nodules. Cancer cells are polygonal with large nuclei, obvious nucleoli and abundant cytoplasm, which are arranged into nests or cords, and there are abundant liver sinusoids between cancer nests, which cancer cells tend to grow into [22]. In this study, it was found that central fibrous scar appeared in FNH, with arteries, bile ducts, inflammation occurring in the septum of the hepatic plate and thickness of hepatic plate <3 cell layers, while mitosis and nuclear heterogeneity appeared in HCC, and the thickness of liver plate ≥ 3 cell layers.

In conclusion, for the differential diagnosis of FNH and HCC, it is necessary to pay attention to the comprehensive judgment of clinical, imaging and histopathological features in clinical work. However, the sample size of this study was small, which may result in bias. In the future, large sample and prospective studies are still needed to verify the research results.

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