Research Article

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Diagnosis and Treatment of Hepatic Adenoma: A Retrospective Analysis

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ABSTRACT

Background and Aim: Hepatic adenoma (HA) is a rare type of liver tumor, and its clinical manifestations, diagnosis, treatment, and prognosis require further investigation. This study aims to summarize the experience of diagnosis and treatment of HA in a large single center.

Methods: A retrospective analysis was performed to evaluate the diagnosis, treatment, and prognosis of HA diagnosed by postoperative pathology at the First Affiliated Hospital of Zhejiang University School of Medicine between May 2009 and March 2022.

Results: Of the 44 patients included, 27 (61.4%) were women and 17 (38.6%) were men, and the average age was 34.3 years (range: 4-73 years). Most patients had no specific symptoms, 7 (15.9%) patients presented with abdominal discomfort, and 3 (6.8%) patients presented with ruptured hemorrhage. The final diagnosis was based on pathology after surgical resection. Forty-three patients had disease-free survival during follow-up, and one patient died of lung cancer.

Conclusion: HA is a rare liver neoplasm that commonly occurs in young females. HA should be confirmed by pathology as it has no specific clinical presentations, serological indicators, or imaging modalities for preoperative diagnosis. Postoperative prognosis is favorable.

Abbreviations: HE: Hematoxylin Eosin; HA: Hepatic Adenoma; MRI: Magnetic Resonance Imaging; HCC: Hepatocellular Carcinoma; OS: Overall Survival; HNF: Hepatocyte Nuclear Factor; CT: Computed Tomography; TAE: Transcatheter Arterial Embolization; TACE: Transcatheter Arterial Chemoembolization; DWI: Diffusion Weighted Images

Background

Hepatic adenoma (HA) is a rare benign tumor of the liver [1] and occurs mainly in the young and middle-aged [2]. It is reported that in women with a history of taking contraceptive drugs, the incidence of HA is 3/100 000, compared to just 0.3/100 000 in the general population [3]. Before the 1960s, there had been few reports of HA, and they have gradually increased in the past decades, which may be related to the invention and widespread use of contraceptives. It has been reported that some HAs have associated life-threatening risks such as carcinogenesis, rupture, and bleeding [4,5]. Early diagnosis of HA is difficult as there is no specific tumor marker and imaging examinations lack specificity. Pathological diagnosis is still the current gold standard. However, as HAs are difficult to distinguish from highly differentiated hepatocellular carcinoma, and some hepatocellular adenomas themselves have shown a tendency to become cancerous, auxiliary examinations are urgently needed to aid pathological diagnosis. Cheng et al. tried to improve the diagnostic accuracy of HA by establishing a deep learning model of hepatic nodule pathology [6], but this still requires further validation. Because of the rarity of HA, data regarding clinical features and clinical outcome are limited. We here present cases of HA in our center to summarize the clinicopathological characteristics and treatment experience.

Materials and Methods

Patients

The patients diagnosed with HA in the First Affiliated Hospital of Zhejiang University School of Medicine from May 2009 to March 2022 were analyzed. This study was approved by the Ethics Committee of Zhejiang University (ITT20210921A), and all patients provided informed consent prior to inclusion in the study.

Clinical Data

The clinical data of all patients were retrospectively obtained from the Electronic Medical Records System, and included age, sex, tumor pathology, tumor size, routine blood tests, liver function tests, hepatitis B virus surface antigen, serum tumor markers (alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19-9), imaging presentation, and time of recurrence. Follow-up data were obtained from clinical records or by telephone up to December 2022.

Pathology

Hematoxylin and Eosin (HE) staining and immunohistochemical staining for Glypican (GPC)-3, cytokeratin (CK)7, Reticular Fiber, Hepatocytes, CK19, β-Catenin and Glutamine synthetase were carried out. All immunohistochemical staining was performed using the BOND-III automated immunostainer (Leica Biosystems, Buffalo Grove, IL, USA).

Hepatic Imaging

Patients were evaluated using imaging modalities. Patients underwent ultrasound examination, computed tomography (CT) or magnetic resonance imaging (MRI). We recorded the following characteristics: lesion morphology, lesion number and lesion size.

Statistical Analysis

Statistical analyses were conducted using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). For the analysis of parametric data, group statistical significance was analyzed using the t test. Patient survival rate was analyzed by the Kaplan–Meier method using GraphPad Prism 8. Statistical significance was set at $P < 0.05$.

Results

Table 1: The baseline characteristics of HA.

	Cases(n=44)	Male(n=17)	Female(n=27)	P-value
Age (Mean ± SD)	36.41±14.51	39.82±16.91	34.26±12.65	0.25
No symptom, n (%) Symptom	34(77.3)	15(88.2)	19(70.4)	0.17
Abdominal discomfort	7(15.9)	1(5.9)	6(22.2)	0.15
Ruptured hemorrhage	3(6.8)	1(5.9)	2(7.4)	0.85
Location of tumors, n (%)				0.90
Left lobe	17(38.6)	6(35.3)	11(40.7)	0.72
Right lobe	18(40.9)	7(41.2)	11(40.7)	0.98
Both side	9(20.5)	4(23.5)	5(18.5)	0.70
Lesion number, n (%)				0.59
solitary	33(75)	12(70.6)	21(77.8)	0.60

multiple	11(25)	5(29.4)	6(22.2)	0.92
Tumor size, n (%)				(0.19)
≤2cm	5(11.4)	2(11.8)	3(11.1)	0.89
2-5cm	11(25.0)	7(41.2)	4(14.8)	0.04
5-9cm	18(40.9)	4(23.5)	14(51.9)	0.09
≥10cm	9(20.5)	3(17.6)	6(22.2)	0.80
Blood test				
WBC (Mean ± SD)	6.12 ±1.68	5.74 ±1.85	6.39 ±1.53	0.23
N%, median	59.40(52.65,64.05)	60.25(50.75,64.23)	58.60(55.8,63.45)	0.65
IB, (Mean ± SD)	8.18 ±4.13	9.51 ±4.28	7.23 ±3.83	0.08
TB, median	13.30(7.60,16.00)	13.75(10.63,17.53)	13.30(7.55,16.00)	0.18
DB, median	4.40(3.00,5.95)	4.50(2.93,5.88)	5.00(2.80,6.30)	0.96
CEA, median	1.50(1.08,2.03)	1.90(1.30,2.98)	1.30(0.85,1.60)	0.01
Ca199, median	5.35(2.15,13.58)	3.85(2.05,14.75)	5.70(2.40,13.75)	0.57
Ca125, median	12.20(9.20,18.23)	11.60(9.25,14.40)	12.80(9.35,22.35)	0.39
AFP, median	2.55(1.88,3.53)	3.10(2.35,3.93)	2.10(1.75,3.15)	0.02

Patients and Clinical Presentation

A total of 44 patients were diagnosed with HA, 27 were female (61.4%) and 17 were male (38.6%). Their average age was 37 years (36.41±14.51 years). The majority of HAs were found during routine physical examinations, only 7 (15.9%) patients presented with abdominal discomfort and 3 (6.8%) patients presented with ruptured hemorrhage (6.7%). Liver function and routine blood levels as well as tumor markers were normal in these patients (Table 1). HAs were found in the right liver lobe in 18 patients (40.9%) and in the left liver lobe in 17 patients (38.6%). Regard to the size of the tumor, the maximum diameter measured by ultrasound was 20.3×13.4 cm, nine patients (20.5%) had lesions >10 cm in diameter and 18 patients (40.9%) had lesions sized between 5 cm and 9 cm. Thirty-three patients (75%) presented with a solitary mass and 11 patients (25%) presented with multiple masses.

Figure 1: A typical CT scan in a HA patient.

A. Plain scan;

B. Arterial phase;

C. venous phase.

Imaging Manifestations

Almost all patients underwent ultrasound examination, CT, or MRI. B ultrasound results showed that the echo level in the lesion was different, the boundary was unclear, and the blood flow signal could be seen in some lesions. There were 3 cases of ruptured HA, 2 of which showed obvious blood flow signals in the lesion. CT examination showed obvious enhancement in the arterial phase, and delayed enhancement in the portal and venous phases (Figure 1). MRI showed equal intensity or slightly lower signal intensity on T1-weighted images (T1WI), equal intensity or slightly higher signal intensity on T2-weighted images (T2WI), and equal intensity or slightly higher signal intensity on Diffusion Weighted Images DWI, (Figure 2). However, the diagnostic accuracy of CT was 23.3%, MRI was 40.6% and 4.9% in the ultrasound imaging group (Table 2). MRI had a higher diagnostic accuracy than CT and B ultrasound.

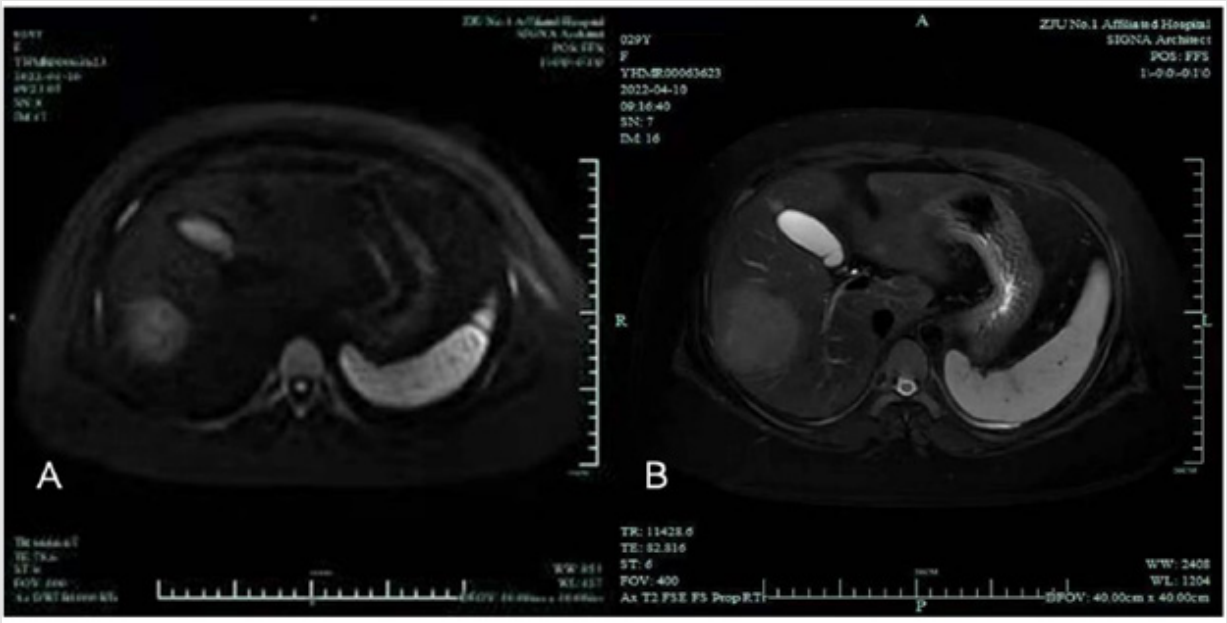

Figure 2: A typical MRI scan in a HA patient.

A. DWI;

B. T2WI.

Table 2: Accuracy of imaging diagnosis of hepatic adenoma.

Imaging methods	Cases(n)	Simultaneous diagnostic accuracy(n/%)
US	41	2(4.9)
CT	30	7(23.3)
MRI	22	13(40.6)

Pathological Findings

Pathological analyses of 41 liver resections were performed. The pathological characteristics of HA were absence of portal and central veins, bile ducts or connective tissue, and scattered thin-walled vascular channels within the mass (Figure 3). Histopathological features included focal loss of reticulin, focal cytological atypia in <5% of the tumor and/or focal architectural atypia. In our study, one patient showed focal well-differentiated Hepatocellular Carcinoma (HCC), and five patients indicated the potential to transform into HCC. Pathology can be identified by specific antibodies or alternative markers using immunohistochemistry. A lot of research has been conducted on the immune classification of HA. Immunohistochemically, the positive expression rate of CD34 was 92.7%, followed by GPC-3, CK7, Reticular Fiber, Hepatocytes, CK19, and β-Catenin with expression rates of 80.5%, 78%, 68.3%, 68.3, 65.9%, and 63.4, respectively.

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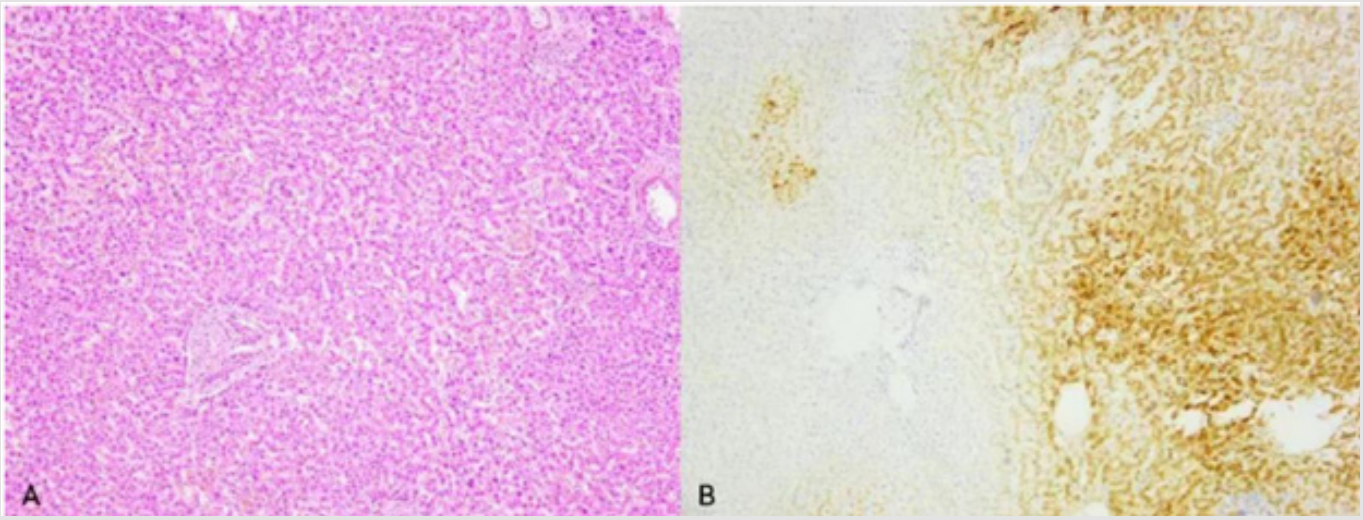

Figure 3: HE staining and immunohistochemical images.

A. HA with thick-walled blood vessels and lymphocyte infiltration (40×).

B. GS staining, the left normal liver tissue was negative and the right liver adenoma tissue was positive.

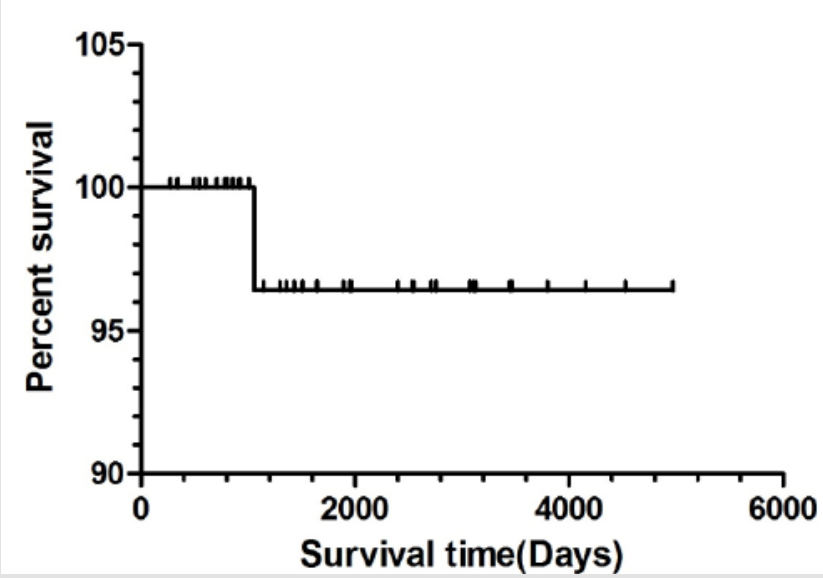

Figure 4: The OS of HA patients.

Treatment and Follow-Up

All the patients underwent surgical resection, including open surgery and laparoscopic surgery. Follow-up was completed in 44 patients. Overall survival (OS) is shown in (Figure 4) and no recurrences were observed. During the follow-up period, a 55-year-old male patient died of lung cancer after HA resection. There was no significant difference between the patients who underwent laparoscopic surgery in terms of OS.

Discussion

This study analyzed a total of 44 patients with HA, and it was found that HAs usually occur in young females. Regarding clinical manifestations, 77.3% of patients had no symptoms, and abdominal discomfort and ruptured hemorrhage were the most common complaints. There are no specific serological indicators or imaging modalities for the preoperative diagnosis of HA, and the diagnosis is established by pathology. Complete surgical resection was necessary for HA in these patients, and the postoperative prognosis was favorable. According to the degree of hepatocyte steatosis, inflammatory cells, bile duct proliferation, or dystrophic blood vessels, HA is classified into four subtypes[1]: hepatocyte nuclear factor 1A (HNF-1A) inactivated HA (H-HA), inflammatory HA (I-HA), β-catenin activated HA (β-HA) and unclassified HA (U-HA), with underlying molecular changes in the following 3 different pathways: HNF-1A, interleukin-6/the Janus kinase/signal transducer and activator of transcription (IL-6/JAK/STAT), and β-catenin signaling (Table 3).

Table 3: Immunohistochemical statistics of hepatic adenomas.

	Cases		Male(n=15)		Female(n=26)	
	Count(n/%)	Positive(n/%)	Count	Positive(n/%)	Count	Positive(n/%)
CD34	38/92.7	34(89.5)	14	12(85.7)	24	22(91.7)
P53	12/29.3	4(33.3)	5	2(40)	7	2(28.6)
AFP	23/56.1	1(4.3)	8	1(12.5)	15	0(0)
CK19	27/65.9	10(37)	14	6(42.9)	13	4(30.8)
Ki67	15/36.6	9(60)	4	2(50)	11	7(63.6)
Reticular Fiber	28/68.3	25(89.3)	10	8(80)	18	17(94.4)
β-Catenin	26/63.4	22(84.6)	9	6(66.7)	17	16(94.1)
Hepatocyte	28/68.3	28(100)	11	11(100)	17	17(100)
CK7	32/78	25(78.1)	13	12(92.3)	19	13(68.4)
GPC-3	33/80.5	2(6.1)	12	1(8.3)	21	1(4.8)
masson	9/22	9(100)	3	3(100)	6	6(100)
CD10	4/9.8	3(75)	1	0(0)	3	3(100)
HMB45	4/9.8	0(0)	1	0(0)	3	0(0)
CD31	2/4.9	2(100)	1	1(100)	1	1(100)
D-PAS	6/14.6	1(16.7)	1	1(100)	5	0(0)
PAS	7/17.1	6(85.7)	2	2(100)	5	4(80)
GS	13/31.7	11(84.6)	5	4(80)	8	7(87.5)
Arginase-1	5/12.2	5(100)	1	1(100)	4	4(100)

Note: A total of 41 people, including 26 women and 15 men, underwent immunohistochemical analysis.

In our study, we carried out immunohistochemistry on 26 samples, and 22 were positive (84.6%), indicating that β-HA was the most common subtype, which is in line with previous research [7]. At present, the diagnosis of HA prior to surgery is still difficult. As a rare liver tumor, the diagnosis of HA is mainly based on pathological biopsy results after clinical puncture or surgical resection [8]. The diagnostic methods and treatment methods for HA are still controversial. The reasons for misdiagnosis include the lack of accurate identification of tumor markers and specific test indicators of HA, and low specificity of imaging findings such as B-ultrasound and CT. MRI has a significant advantage in the examination and diagnosis of HA, which can distinguish and identify typical H-HAs and I-Has [9]. However, all current imaging techniques cannot identify β-HAs and U-HAs. Furthermore, the diagnostic accuracy is low.

In our study, MRI showed the greatest diagnostic sensitivity of 40.6%. Establishment of the deep learning model based on artificial intelligence may be a good method to improve the diagnosis of HA [6]. Most patients with HA had no obvious symptoms, some felt discomfort in the upper abdomen and poor appetite. The two most serious complications are malignancy and bleeding. Julien et al. found that the size of the HA is not the only factor causing bleeding [4]. They observed that certain gene mutations and alcohol consumption were independent risk factors for bleeding. At present, the treatment of HA mainly includes follow-up observation, surgical resection, vascular embolization and ablation. However, surgery is still considered to be the best way to treat HA, and it has a good therapeutic effect on bleeding and malignant transformation [10]. A French group suggested that transcatheter arterial embolization (TAE) could be used as a preoperative treatment to reduce tumor volume.

For HAs larger than 5 cm, it was previously believed that the probability of bleeding was greater when taking contraceptives for a long time, and some gene mutations and alcohol consumption are risk factors for tumor rupture. For these high-risk tumors, surgical treatment is recommended. The surgical methods include traditional open surgery, laparoscopic-assisted surgery, and Da Vinci robot-assisted laparoscopic surgery, and there is no significant difference in the prognosis of these surgical methods. The efficacy of transcatheter arterial chemoembolization (TACE) and TAE still requires further study and validation. Three patients in our center received TACE treatment; however, all underwent subsequent surgical treatment. The specific treatment plan is also related to the location of the liver lesion, the size of the lesion, the HA subtype, patient preference, and the professional practice of the center where the treatment is performed. To date, there is no report on transplantation for HA.

In our cohort, 44 patients underwent surgical resection, and the only patient to receive a liver transplantation in our center was a 4-year-old female with congenital portal vein malformation. There are some limitations in this study. First, due to the low incidence of HA, the sample number of this study was small. Second, the follow-up time was not adequate, and these patients still need longer follow-up time to evaluate the prognosis after treatment. Third, almost all the patients in our study were taking contraceptives, and this is different from Western countries [5]. HA is a rare liver neoplasm that commonly occurs in young and middle-aged females. HA needs to be determined by pathology, as there are no specific clinical presentations, serological indicators, or imaging modalities for preoperative diagnosis. Furthermore, postoperative prognosis is favorable.

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