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Clinicopathological Discrepancies in the Diagnosis of Hepatocellular Carcinoma in Explanted Livers, A Single Center Study on More Than 1500 Transplanted Livers

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Abstract

Background: Hepatocellular carcinoma is an unfortunate consequence in cirrhotic patients. Most of the cases are diagnosed by imaging modalities; however, some of them are missed and would be diagnosed only after thorough examination of the explanted liver following transplantation.
Objectives: In this study, we aimed to evaluate the frequency of incidental HCCs that are diagnosed after transplantation based on pathological examination of the explanted livers.
Methods: We evaluated all the explanted livers during 5 years from 2012 to 2016 with clinical and pathological diagnosis of HCC. In the meantime, all of the clinicopathological findings were investigated such as demographic information, AFP level, tumor size, and tumor location.
Conclusions: The frequency of incidental HCC in our center was around 20%, more than 80% of which were less than 2-cm in size (early HCC). Majority of the cases were male patients above 40 years age, with the underlying causes of Hepatitis B, C, and AIH as well as tyrosinemia and PFIC.

Keywords: Incidental Hepatocellular Carcinoma, Liver Transplantation, Explanted Liver

1. Background

Cirrhosis is the main predisposing factor in the development of hepatocellular carcinoma (HCC). Pretransplant imaging studies are very accurate and helpful for the diagnosis of HCC in cirrhotic patients (1); however, histomorphologic studies of the explanted livers are the gold standard for the identification of lesions that are not detected by imaging modalities (1). Diagnosis of HCC before transplantation can cause significant therapeutic changes in the patients; thus, it is very important to decrease the rate and the frequency of post-transplant incidental diagnosis of HCCs; however, there have been various reports on the incidental frequency of HCC in the explanted livers ranging from 4.2 to 40% in different centers in the world (2-5). Incidental hepatocellular carcinomas are tumors discovered in the explanted livers that had not been diagnosed by imaging modalities before transplantation (5, 6). It is very important for the pathologist to examine the explanted liver precisely by very thin (< 1 cm) slices to find even very small nodules (6, 7). In this study, we review our 5-year experience in 157 cases that were clinically or pathologically suspected to HCC.

2. Methods

During the study period (2012 - 2016) in 5 years, among more than 1500 liver transplants, we evaluated all the cases that had the diagnosis of HCC either clinically or pathologically. In these 5 years, all the explanted livers were examined by an expert pathologist. In the examination, every liver mass was precisely investigated in thin sections (< 1-cm in thickness) to find very small lesions different from surrounding cirrhotic nodules. Each lesion or any nodule was examined and sectioned thoroughly. The microscopic sections were seen by an expert hepatopathologist for the presence of any dysplastic focus, dysplastic nodule, or HCC nodules.

The size and location of the tumors were also recorded. In addition, demographic information and

alpha-fetoprotein levels were extracted from the patients' clinical chart and recorded.

3. Results

During the study period, there were 157 cases diagnosed with HCC either clinically or pathologically. In general, there were 43 (27.32%) cases with clinicopathological discrepancy in the diagnosis of HCC.

In these 157 cases, 10 cases were clinically suspected to HCC, which were not confirmed by pathologic examination. Table 1 shows the characteristics of these 10 cases. There were mostly cirrhotic nodules in 5 cases, which were diagnosed as HCC by imaging studies; however, thorough sectioning and histologic evaluation failed to show any evidence of HCC or dysplasia. There was 1 case suspected to HCC in a patient with cirrhosis, which after examination of the explanted liver turned out to be neuroendocrine tumor. Two other cases with the clinical diagnosis of HCC were discovered to have focal nodular hyperplasia and liver cell adenoma. The case with the diagnosis of FNH showed a discrete mass with typical central scar. It was completely prominent and different from the background cirrhotic liver. Fat accumulation in one case of NASH was also misdiagnosed as HCC nodule by imaging studies.

There were also 33 cases (21.09%) with the clinical diagnosis of cirrhosis and no pretransplant impression of tumor, which histologic evaluation of the explanted liver showed HCC. Table 2 shows details and characteristics of these 33 patients. They consisted of 12 cases of hepatitis B related cirrhosis, 8 cases with cryptogenic cirrhosis, 4 cases of HCV related cirrhosis, 3 cases of tyrosinemia, 2 cases of autoimmune hepatitis related cirrhosis, 2 patients with progressive familial intrahepatic cholestasis (PFIC), one Budd-Chiari syndrome, and one case of nonalcoholic steatohepatitis related cirrhosis (NASH). It is worthy to note that two cases had the diagnosis of small cell dysplasia and one case had the pathologic diagnosis of dysplastic nodules (true precursors of HCC), which were also considered as HCC nodule in this study. It is also worth mentioning that we included all the cases with dysplasia in this study after thorough examination of the explanted livers.

Size of tumor in 33 incidental HCCs was 1.6 ± 0.98 cm. The size in other cases (with pretransplant diagnosis of HCC) was 3.78 ± 3.79 cm. The difference between these two sizes was statistically significant (P value < 0.05).

Level of alpha-fetoprotein (AFP) in 33 incidental HCC cases with no pretransplant diagnosis was 29.4 ± 45.1 ng/mL. This level for the HCCs with pretransplant diagnosis was $751.5 \pm 3895.0.3$ ng/mL; in 10 cases with the clinical diagnosis of HCC, which had not been confirmed by pathology, it was 34 ± 71.08 ng/mL. There was a statistically significant difference between incidental HCCs and HCCs with pretransplant diagnosis (P value < 0.05).

4. Discussion

Diagnosis of HCC before transplantation is mostly based on imaging studies including CT scan and MRI methods. However, there are often missed cases, so imaging methods may underestimate the presence and the number of HCCs in cirrhotic livers. Therefore, histological examination of the explanted livers is an essential step in the diagnosis of HCCs especially small HCCs under the size of 2-cm (2, 6, 7).

The reported frequency of incidental HCCs in explanted cirrhotic livers has been from less than 10% to about 50% (1-3). In the current study, among 157 clinically and pathologically diagnosed HCCs, there were 21.01% incidental HCCs that have been diagnosed only after examination of the explanted livers. More than 80% of these incidental HCCs have been small with the size of less than 2-cm (1.6 ± 0.98). It is significantly less than the size of 114 HCCs diagnosed before transplantation (3.78 ± 3.79); in other words, only 14% of the latter cases were less than or equal to 2-cm in size. Therefore, it seems that the diagnosis of these small lesions is difficult in the preoperative period because there are some similarities in imaging methods with regenerative nodules in cirrhotic livers (1-3, 6).

More than 80% of incidental HCCs has been in patients above 40 years of age, most of which were male that emphasizes more precise pretransplant investigation especially in older male cirrhotic patients. However, this is also true in children with tyrosinemia and PFIC (8).

Most of the cases with incidental HCC failed to show high levels of AFP, i.e. more than 66% showed AFP levels below 10 ng/mL, which is another misleading factor to underestimate the diagnosis of HCC before transplantation. On the other hand, in about 40% of our 10 pretransplant diagnosed HCCs, the level of AFP was high. Previous studies showed the average AFP level of 19.5 ng/mL for incidental HCCs, while our findings showed the mean AFP level of 29.4 ng/mL (3).

Development of HCC in cirrhosis can also be dependent on the underlying cause, as higher risks have been reported in tyrosinemia and hepatitis B and C related cirrhosis and lower risks in AIH (autoimmune hepatitis) (8-11). In our study, majority of patients had tyrosinemia, hepatitis B, and C and cryptogenic cirrhosis; however, 2 cases of AIH and 2 patients with PFIC also showed incidental HCCs discovered in the explanted livers. We had also incidental dual malignancies in the cryptogenic cirrhosis, which have been previously reported by our group (11).

Table 1. Pathologic Diagnosis of 10 Cases with Clinical Diagnosis of HCC That Were Not Confirmed

Number	Sex	Age	AFP level, ng/mL	Pathologic Diagnosis
1	F	16	17	Cirrhotic nodule
2	F	46	1.7	Nonalcoholic steatohepatitis
3	F	38	8.2	Cirrhotic nodule
4	M	47	33.7	Neuroendocrine Tumor
5	M	20	1.3	Focal Nodular hyperplasia
6	M	58	234.9	Cholangiocarcinoma
7	M	66	8.5	Cirrhotic nodule
8	F	59	24.5	Cirrhotic nodule
9	F	62	8.2	Cirrhotic nodule
10	F	55	8.5	Liver cell adenoma

Table 2. Characteristics of 33 Cases of Incidental HCC Diagnosed in the Explanted Liver After Transplantation

	Sex	Age	Underlying Cause of Cirrhosis	AFP level, ng/mL (Nl = 10 ng/mL)	Size of the tumor, cm	Location	Pathologic Diagnosis in the Explanted Liver
1	M	61	Autoimmune Hepatitis	7.2	1.5	Left	Small cell Dysplasia
2	M	60	Hepatitis B	4.99	2	Right	HCC
3	F	30	Hepatitis B	2.9	0.5	Right	HCC
4	M	60	Cryptogenic	8.2	1.5	Right	HCC
5	M	59	Cryptogenic	2.6	2	Right	HCC
6	M	54	Cryptogenic	6.9	0.5	Left	HCC
7	M	62	Cryptogenic	48	2	Right	HCC
8	M	66	Hepatitis C	74.1	2	Right	HCC
9	M	12	Progressive familial intrahepatic cholestasis	8.3	1	Right	HCC
10	F	65	Hepatitis B	8.5	1	Right	HCC
11	F	4	Tyrosinemia	55.3	0.4	Right	HCC
12	F	64	Hepatitis B	124.6	2.5	Right	HCC
13	M	5	Tyrosinemia	8.5	2	Left	HCC
14	F	54	Cryptogenic	8	1.5	Right	HCC
15	F	47	Cryptogenic	1.5	2	Right	HCC
16	M	5	Tyrosinemia	12.2	1	Left	HCC
17	M	56	Hepatitis B	1.6	1.5	Right	HCC
18	M	40	Hepatitis B	4.6	1.2	Right	HCC
19	F	51	Cryptogenic	0.8	1	Right	HCC
20	M	17	Autoimmune Hepatitis	3	2	Right	HCC
21	F	47	Budd-Chiari Syndrome	98.7	1	Right	HCC
22	M	62	Cryptogenic	3.8	0.5	Right	HCC
23	M	60	Hepatitis B	6.8	3	Right	Dysplastic nodule
24	M	48	Hepatitis B	8.8	0.5	Both lobes, Multiple	HCC
25	M	67	Cryptogenic	2.3	0.5	Right	HCC
26	M	62	Hepatitis C	43.2	1.5	Right	HCC
27	M	46	Hepatitis B	3.5	1	Left	HCC
28	M	53	Hepatitis B	32	5	Both lobes, Multiple	HCC
29	M	59	Hepatitis B	4	1.2	Right	HCC
30	M	43	Hepatitis C	61	2	Right	HCC
31	F	54	Hepatitis C	2	1	Right	Small cell Dysplasia
32	M	46	Hepatitis B	188	4	Right	HCC
33	F	9	Progressive familial intrahepatic cholestasis	14.7	2	Right	HCC

As a conclusion, diagnosis of HCC in the explanted livers needs thorough examination and there is high level of suspicion especially in older male patients with cirrhosis. Our experience in the largest liver transplantation center

in the country shows that incidental HCCs should be suspected in every explanted livers especially in cryptogenic cirrhosis, hepatitis B, hepatitis C, and tyrosinemia related cirrhosis even with low levels of AFP.

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Footnote

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