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Clinico-Radiological Profiling of Combined Hepatocellular Carcinoma and Cholangiocarcinoma (Biphenotypic) Tumors

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ABSTRACT

Background: Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is an uncommon primary liver malignancy and little is known about the clinical and imaging characteristics.
Objective: To define the features of cHCC-CC on contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CT) in this study.
Methods: 45 patients with pathologically proven cHCC-CC had undergone preoperative CEUS and 43 patients who had additional CT scan in our institution were studied for retrospective review of the imaging studies and clinical data.
Results: cHCC-CC accounted for 6.4% of all primary liver malignancy. Enhancement pattern resembling cholangiocarcinoma (CC) was noted in 53.3% (24/45) of patients on CEUS and in 30.2% (13/43) of patients on CT. Enhancement pattern resembling hepatocellular carcinoma (HCC) was observed in 42.2% (19/45) of patients on CEUS and in 58.1% (25/43) of patients at CT. The percentage of tumors showing CC enhancement pattern (27.9%, 12/43) was comparable with that of tumors showing HCC enhancement pattern (44.2%, 19/43) on both CEUS and CT ($p = 0.116$).
Conclusions: The cHCC-CC tumors display enhancement patterns resembling CC or HCC in comparable proportion on both CEUS and CT.

KEYWORDS Combined hepatocellular-cholangiocarcinoma, Contrast-enhanced ultrasound, Computed tomography

INTRODUCTION

Combined hepatocelluar-cholangiocarcinomas (cHCC-CC) are uncommon form of primary hepatic carcinoma, accounts for 1.0–6.7% of all primary liver cancers in Asia and 2.4–14.2% in Western countries [1, 2]. It was first defined by Allen and Lisa [3]. Due to the relative rarity of this tumor type, little is known about the risk factors, imaging appearance or prognosis. Risk factors overlap with hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) [4]. The clinical characteristics of cHCC-CC were similar to those of HCC [5], but overall survival was more similar to or poorer than that of CC [2]. Multimodal treatment with an initial aggressive therapeutic approach can improve survival [5]. Preoperative diagnosis is crucial for appropriate management. Few studies have evaluated the radiological characteristics of cHCC-CC on computed tomography (CT) or magnetic resonance imaging (MRI) with limited number of patients [6–10]. To our knowledge, no Indian study has reported the imaging features of cHCC-CC on contrast-enhanced ultrasound (CEUS) up to now. The presence of imaging features of both HCC and CC in the same tumor may alert the radiologist to the possibility of cHCC-CC, which occurs in minority of cases though [4, 10].

The main tumor markers of interest for cHCC-CC are carbohydrate antigen 19–9 (CA19-9) and α–fetoprotein (AFP), which are useful adjuncts to imaging in patients with CC and HCC respectively [11]. Simultaneous elevation of both CA 19–9 and AFP has been suggested as highly concerning for cHCC-CC tumors [12]. Other reports suggest that discordance between serum tumor marker elevation and imaging morphology may be suggestive [13]. However, these results were based on clinical data from very limited number of patients and the imaging features of CEUS not included. Therefore, the purpose of this study was to retrospectively evaluate the demographics, clinical presentation, and imaging features on CT and CEUS in patients with cHCC-CC tumors, in the hope of defining features of the uncommon malignant hepatic tumor that may improve preoperative diagnosis and better guide clinical management decisions.

METHODOLOGY

This is a Retrospective observational record-based study conducted at a tertiary care hospital in central India. Records were reviewed for the cases dating from January1st 2001 to December 31st 2015. Pathology databases of our hospital recorded 716 patients with liver cancer, including 46 patients with mixed type (biphenotypic) of cHCC-CC which accounted for 6.4% of all primary liver cancer. One case of cHCC-CC without available CEUS imaging was excluded. Patients with available cross sectional imaging were included in the study. Clinical information was retrospectively found from our hospital information system. Serum tumor markers reported were drawn before treatment and within 1 week of the imaging examination. Normal values were 0–20 ng/ml for AFP and 0-22U/ml for CA19-9. Cirrhosis was confirmed histopathologically through examination of resected liver specimen.

All the 45 tumors were excised and underwent tissue diagnosis. The final diagnosis of biphenotypic primary liver carcinoma depended on a combination of H and E stain findings [14] and proof of both hepatocellular and biliary differentiation immunohistochemical markers. Sub-classification was done according to the 2010 World Health Organization Tumors of the Digestive System classification [15]. CT findings were evaluated in consensus by 2 radiologists who were blinded to CEUS findings and pathological results of the tumors. A per-patient analysis was performed. Characteristics of the patients expressed as median and range or count and proportion. Comparison of CEUS and CT was done by using the chi-squared test for categorical variables.

RESULTS

Clinico-pathologic features

Mean age of patients was 52.8 year (range: 28–74 year) and 40 being male (88.9%). Thirty patients (66.7%) had cirrhosis. The etiology of cirrhosis was viral hepatitis B infection in 24 patients, combination of viral hepatitis B infection and alcoholism in 5 patients. Nine patients had chronic hepatitis B without cirrhosis (20%). Of the 45 patients with cHCC-CC tumors, 6 presented incidentally, 10 discovered on cirrhosis screening, 22 presented with abdominal pain, 2 with jaundice, 2 with tarry stool, 1 with edema feet. Of the 22 patients presented with abdominal pain, 4 patients had a palpable mass. In two patients, the presentation is unknown. All 45 patients had AFP assay which was abnormally elevated in 28 patients (62.2%) and normal in 17 patients. Forty five patients had serum assays of CA19-9 which was elevated in 10 patients (22.2%) and normal in 35 patients. Both AFP and CA19-9 were simultaneously elevated in 7 patients (15.6%). The average size of cHCC-CC was 5.3 cm and over half of them were less than 5 cm. Most patients had single tumor and over half of them were located in the right lobe of liver.

Radiological features

The enhancement appearances of cHCC-CC on CEUS in 45 patients are shown in Table 1.

Table 1: Enhancement patterns of combined hepatocellular-cholangiocarcinoma on CEUS (n = 45)

	Arterial Phase	Portal Phase	Delayed phase
Peripherally hyperdense [No. (%)]	12 (27.9)	13 (30.2)	7 (16.3)
Partially hyperdense [No. (%)]	24 (55.8)	5 (11.6)	6 (13.9)
Globally hyperdense [No.(%)]	2 (0.5)	-	-
Isodense [No.(%)]	-	-	1 (0.2)
Hypodense [No.(%)]	5 (11.6)	25 (58.1)	29 (67.4)

Tumors showing peripheral hyperenhancement in the arterial phase followed by marked washout in the portal phase in 9 patients were defined as CC pattern. Tumors showing heterogeneous (8 tumors) or homogeneous (7 tumors) hyperenhancement in the arterial phase followed by early (washout begins earlier than 60s) and marked wash out during the portal phase were judged as CC pattern. Tumors showing heterogeneous (13 tumors) or homogeneous (6 tumors) hyperenhancement in the arterial phase followed by both slow (washout begins later than 60s) and mild wash out in the portal or late phase were judged as HCC pattern. The enhancement pattern of 2 patients was judged as indeterminate because one tumor showed heterogeneous hyperenhancement in the arterial phase followed by isoenhancement in the portal and the late phase, and another tumor displayed hypoenhancement in the arterial phase, remained hypoenhancement in the portal and the late phase. The average time of washout emergence on CEUS was 58.18s (median:53s, range:22s~129s). The percentage of tumors showing CC enhancement pattern (53.3 %) was similar to that of tumors showing HCC enhancement pattern (42.2 %) on CEUS (p = 0.291). Forty three patients had unenhanced CT scan. Forty of the tumors were hypodense and 3 were hyperdense. Hepatic capsular retraction was revealed in 4 cases (9.3 %). Three patients had intrahepatic biliary dilatation (7.0 %). Five patients had malignant portal veins thrombus (11.6 %) and 5 had regional lymphadenopathy (11.6 %). Intrahepatic metastasis was observed in 7 patients (16.3 %).

Enhancement appearances of cHCC-CC on CT in 43 patients are shown in Table 2.

Table 2: Enhancement patterns of combined hepatocellular-cholangiocarcinoma on CT (n=43)

Enhancement appearance	Number (%)
Arterial phase	
Peripheral hyperenhancement	9 (20.0)
Heterogeneous hyperenhancemen	22 (48.9)
Homogeneous hyperenhancement	13 (28.9)
Hypoenhancement	1 (0.2)
Isoenhancement	0 (0)
Portal phase	
Peripheral hyperenhancement	0 (0)
Heterogeneous hyperenhancement	1 (0.2)
Homogeneous hyperenhancement	0 (0)
Slight hypoenhancement	17 (37.8)
Marked hypoenhancement	25 (55.6)
Isoenhancement	2 (0.4)
Delayed phase	
Peripheral hyperenhancement	0 (0)
Heterogeneous hyperenhancement	1 (0.2)
Homogeneous hyperenhancement	0 (0)
Slight hypoenhancement	8 (17.8)
Marked hypoenhancement	35 (77.8)
Isoenhancement	1 (0.2)
Emergence of-washout	
< 60 seconds	28 (62.2)
60–120 seconds	13 (28.9)
> 120 seconds	2 (4.4)
No washout	2 (4.4)

Tumors showing stable persistent peripherally hyperenhancement from the arterial phase to the late phase in 8 patients were defined as CC pattern. Tumors showing progressive delayed enhancement from the arterial phase to the late phase in 5 patients were also judged as CC pattern. Tumors showing hyperenhancement (24 heterogeneous, 1 homogeneous) in the arterial phase followed by washout in the portal or the late phase in 25 patients were defined as HCC pattern. Tumors showing hypoenhancement from the arterial phase to the late phase in 4 patients and 1 tumor showing hyperenhancement in the arterial phase and the portal phase followed by isoenhancement in the late phase were judged as indeterminate pattern. The percentage of tumors showing CC enhancement pattern (30.2%) was less than that of tumors showing HCC enhancement pattern (58.1%) on CT (p = 0.009). 12 of 43 patients displayed CC enhancement pattern on both CEUS and CT (27.9 %), while 44.2 % (19/43) of patients demonstrated HCC enhancement pattern at both CEUS and CT. The percentage of tumors showing CC enhancement pattern was comparable with that of tumors showing HCC enhancement pattern (p = 0.116).

In 7 patients with simultaneous elevation of both AFP and CA19-9, CC enhancement pattern was observed in 5 patients on CEUS and 1 patient at CT. HCC enhancement pattern was noted in 2 patients on CEUS and 6 patients at CT respectively. Correlations between AFP & CA19-9 enhancement patterns of CEUS and CT are shown in Table 3

Table 3: Correlation between AFP & CA19-9 and enhancement patterns of CEUS and CT

	CEUS pattern (n = 45)			CT pattern (n = 43)		
	CC	HCC	Indeterminate	CC	HCC	Indeterminate
AFP normal	10	7	-	5	9	3
AFP elevated	14	12	2	8	16	2
CA19-9 normal	19	14	2	11	17	5
CA19-9 elevated	5	5	-	2	8	-

AFP was elevated and CA19-9 normal in 9 of 45 (20.0%) patients showing CC enhancement pattern on CEUS and in 7of 43 (16.3%) patients showing CC enhancement pattern on CT (p = 0.651). In 3 patients with elevated CA19-9 and normal AFP, HCC enhancement pattern was noted in 3 patients on CEUS and in 2 patients at CT, CC enhancement pattern was observed 1 patient at CT. Elevated tumor markers (AFP or CA19-9) were in discordance with imaging findings in 19 of 45 (42.2%) patients on CEUS and in 16 of 43 (37.2%) patients at CT (p = 0. 0.631). Simultaneous elevation of tumor markers (AFP and CA19-9) or tumor marker elevation (AFP or CA19-9) in discordance with enhancement pattern on CEUS was demonstrated in 26 of 45 patients, which was significantly more than simultaneous elevation of tumor markers (AFP and CA19-9) alone (7/45, p = 0.000). Simultaneous elevation of tumor markers (AFP and CA19-9) or tumor marker elevation (AFP or CA19-9) in discordance with enhancement pattern on CT was observed in 23 of 43 patients, which was significantly more than simultaneous elevation of tumor markers (AFP and CA19-9) alone (7/43, p = 0.000).

DISCUSSION

Combined hepatocellular-cholangiocarcinoma accounts for 0.4–14.2 % of all primary liver carcinomas, with not only local incidence varying considerably between regions [11, 13], but also the different inclusion criteria for classification in previous literature. In present study, most patients with cHCC-CC had cirrhosis (66.7 %) or chronic hepatitis B (20 %). The mean age of patients was 52.8 year and 88.9 % of patients were male. Our data demonstrated that cHCC-CC developed more frequently in a middle-aged male population with chronic hepatitis and cirrhosis mostly related to chronic hepatitis B, indicating the clinical characteristics of cHCC-CC are similar to those of HCC [5, 16]. However, this is inconsistent with two reports from Western countries [10, 13], which published data of 27 patients and 29 patients, cirrhosis was seen in 0% and 20%, positive hepatitis B or C detected in 15% and 10% of the patients respectively.

In our study, 27.9% of the cases showed arterial peripheral hyperenhancement on CT, which is lower than previous reports by Ebied et al (50%) and Fowler et al (51.9 %) [8, 10]. On the contrary, 60.5% of our patients displayed heterogeneous or homogeneous hyperenhancement in the arterial phase that is higher than in the study by Ebied et al. (33.3%). Patients with cHCC-CC in the present study demonstrated more HCC enhancement pattern (58.1%) and less CC enhancement pattern (30.2%) than reported by Fowler et al (31.0%, 41.4% respectively). An explanation of these discrepancies may be the tumor size, which was much smaller in our study (median size 4.5cm) as compared with the data reported by Ebied et al (median size 7cm) and by Fowler et al (median size 7.5cm). As the tumor grows larger, a relatively smaller blood supply is available, leading to necrosis and more fibrous stroma formation in the central portion of the tumor, which constitute the pathological background of CC enhancement pattern on contrast-enhanced CT [17]. Capsular retraction and biliary ductal dilatation have been considered important ancillary features of CC. Less patients with cHCC-CC revealed capsular retraction (9.3%) and biliary ductal dilatation (7.0%) on CT in our data than reported by Ebied et al (26.7%, 16.7%) and by Fowler et al (41.4%, 34.5%). We favor to interpret these inconformity in the light of the differences in tumor size and the underling liver diseases, namely, the tumors of our patients were much smaller and more patients had cirrhosis than in the previous series mentioned above.

Imaging characteristics of cHCC-CC on CEUS has not been reported up to now. Our study demonstrated that 95.6% of the tumor showed washout enhancement pattern on CEUS, indicating malignant nature of the tumor. Imaging features of cHCC-CC may display as CC enhancement pattern or HCC enhancement pattern. The percentage of the two types of enhancement pattern on CEUS showed no statistical difference in our series. CC enhancement pattern and HCC enhancement pattern are likely present in a comparable proportion in patients with cHCC-CC on CEUS.

Serum tumor markers of potential utility in cHCC-CC are CA 19–9 and AFP, which are associated with CC and HCC respectively. When both are simultaneously elevated or elevated in discordance with presumptive imaging findings (i.e., elevated CA 19–9 with imaging findings of HCC pattern, or elevated AFP with imaging findings of CC pattern), cHCC-CC should at least be suggested [4, 12]. However, this point of view was based on few studies with very limited number of patients (less than 15 patients) [6, 12, 18] and needs to be evaluated in more patients. Previous reports demonstrated that elevated serum AFP levels were found in 33%–78% and elevated CA19-9 in 20%–36% of patients with cHCC-CC [6, 12, 18]. In our series, AFP was abnormally elevated in 62.2% and CA19-9 in 22.2% of patients, which is comparable to previous reports. AFP and CA19-9 were simultaneously elevated in 15.6% of patients in the present study, indicating a much low sensibility if this criterion alone was used for suggestion of cHCC-CC. In our study, simultaneous elevation of tumor markers (AFP and CA19-9) or tumor marker elevation (AFP or CA19-9) in discordance with enhancement pattern on CEUS or on CT was demonstrated in significantly more patients (51.1 %, 53.3 % respectively) than simultaneous elevation of tumor markers (AFP and CA19-9) alone (15.6 %, p = 0.000), indicating that when both the results of tumor makers and imaging features of CEUS or CT were taken into consideration, the possibility of cHCC-CC may be suggested in significantly more patients.

CONCLUSIONS

Combined hepatocelluar – cholangiocarcinomas (biphenotypic) is an uncommon primary liver malignancy with background population characteristics similar to HCC. Imaging features of CC or HCC presents in comparable proportion in cHCC-CC on both CEUS and CT. Combination of simultaneous elevation of tumor makers (AFP and CA19-9) and tumor mark elevation in discordance with presumptive imaging findings on CEUS or CT may lead significantly more patients to be suspicious of the diagnosis of cHCC-CC.

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