

# Diffuse Cirrhosis-like Hepatocellular Carcinoma

## *A Clinically and Radiographically Undetected Variant Mimicking Cirrhosis*

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**Abstract:** A rare variant of hepatocellular carcinoma (HCC) is encountered that produces small cirrhosis-like nodules diffusely throughout the liver (CL-HCC), instead of a larger evident mass. This pattern remains undetected as carcinoma clinically and radiographically and is unexpectedly discovered after liver transplantation in the explanted native liver. We studied 10 such cases (9 males and 1 female, age 35 to 80 y) from 4 medical centers. The pretransplant clinical, laboratory, and radiographical studies were reviewed to determine the cause and stage of liver disease,  $\alpha$ -fetoprotein (AFP) levels, and detectability of a mass on imaging. All 10 cases had underlying cirrhosis of varying etiology [3 hepatitis C virus (HCV), 3 alcoholic hepatitis, 1 hepatitis B virus, 1 autoimmune, and 2 mixed HCV/alcoholic hepatitis and hemochromatosis/HCV] and underwent orthotopic liver transplantation with no preoperative clinical suspicion of HCC. Ultrasound and/or dynamic imaging showed cirrhosis and no definite HCC. AFP levels were only mildly elevated in only 3 of 10 cases (144, 150, and 252 ng/mL). Grossly, there were innumerable (from about 20 to > 1000) small CL-HCC nodules (0.2 to 0.6 cm) scattered among cirrhotic nodules. Histologically, these were well or moderately differentiated HCC, often with pseudoglandular pattern, perinodular sclerotic rims, cholestasis, frequent Mallory bodies, and small vessel invasion. In addition to the usual HCC immunophenotype, CL-HCC showed frequent ubiquitin and cytoplasmic and membranous CD10 positivity, relatively low Ki-67 proliferative index and absence of AFP immunohistochemically. CL-HCC warrants recognition as a unique HCC variant that evades pretransplant detection despite massive tumor burden, mimics cirrhotic nodules, and shows some uncommon pathologic and immunophenotypical characteristics.

**Key Words:** hepatocellular carcinoma, cirrhosis-like, undetected, variant, diffuse

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Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and usually arises in the setting of chronic liver disease and cirrhosis from varied etiologies. Patients with such settings who are at risk of developing HCC require screening and surveillance to detect HCC at an earlier stage for treatment eligibility, qualification for curative procedures including orthotopic liver transplantation (OLT), and better survival.<sup>2</sup> Recommendations for HCC detection offered by the American Association for the Study of Liver Diseases<sup>1</sup> include  $\alpha$ -fetoprotein (AFP) and ultrasonography initially, and if > 1 cm nodule is found, dynamic imaging studies such as computed tomography (CT) or magnetic resonance (MR) and depending on the result, confirmatory biopsy of the mass. Development of HCC in patients gives them increased priority for OLT, but the upper limits of the tumor size and number have to be met under one of multiple prevailing criteria for acceptable outcome.<sup>1,21</sup> We describe a variant of HCC that is present diffusely through most of the liver and remains largely undiscovered preoperatively. As this variant displays small nodules and blends-in with the coexistent cirrhotic nodules, we refer to it as “cirrhosis-like HCC” (CL-HCC), defining both its pervasiveness and imitation of cirrhosis. By examining 10 cases of this rare variant, we attempt to describe the macroscopic, microscopic and immunophenotypical characteristics and discuss its mimicry to cirrhosis, and potential reasons for nondetectability.

### MATERIALS AND METHODS

Upon encountering a rare case of CL-HCC, an attempt was made to seek additional such cases by the senior author (L.F.) among a group of pathologists. Ten such cases were identified and compiled from 4 different centers between 2000 and 2009. Approval was obtained from the individual institutions’ review boards. The following data was collected: (1) age and sex of patient and cause of liver disease; (2) pre-OLT clinical knowledge

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or detection of HCC; (3) serum AFP values; (4) pre-OLT imaging results; (5) gross photograph and/or gross description of the explanted liver, specifically the size ranges and distribution of cirrhotic-like abnormal pale or cholestatic nodules; (6) detailed review of the routine formalin-fixed, paraffin-embedded, and hematoxylin and eosin stained 4 $\mu$ m thick microscopic sections; (7) immunohistochemical studies on formalin-fixed and paraffin-embedded representative sections of the tumor for the following markers: CD10, CD34, HepPar-1, Ki-67, cytokeratins 7 and 19, AFP, glypican-3, and ubiquitin; and (8) available follow-up including recurrence of HCC in the graft. The demographic, clinical, pathologic, and follow-up information was collected from individual sites. All microscopic sections were reviewed by 4 participating pathologists as a panel with concurrence of findings.

Macroscopically, the livers were examined and sampled for microscopic evaluation according to the individual medical center's protocol. At all places, the livers were thinly sliced at approximately 0.5 cm intervals and random protocol sections from both lobes were taken, a minimum of 5 and a maximum of 14. In all cases, abnormal appearing cholestatic or pale nodules were documented for their size range and extent, and additional sections (5 to 10) from these abnormal nodules were taken. Formalin-fixed paraffin-embedded sections were processed, embedded, cut at 4 $\mu$ m, and stained routinely with hematoxylin and eosin. The sections were examined microscopically with emphasis on presence of HCC in random sections of cirrhotic nodules, differentiation, and additional histologic tumor characteristics. Immunohistochemical studies were performed on one representative tumor bearing section for the following markers: CD10 (Leica Microsystems, Bannockburn, IL), HepPar-1 (Cell Marque, Rocklin, CA), CD34 (Cell Marque, Rocklin, CA), Ki-67 (Dako, Carpinteria, CA), cytokeratin 19 (Cell Marque, Rocklin, CA), cytokeratin 7 (Cell Marque, Rocklin, CA), AFP (Cell Marque, Rocklin, CA), glypican-3 (Cell Marque, Rocklin, CA), and ubiquitin (Invitrogen, Carlsbad, CA). Cytokeratins 7 and 19 were performed to determine if there was admixed cholangiocarcinoma component. In patients where follow up was available, it was studied for tumor recurrence, metastases and graft and patient survival.

## RESULTS

### Clinical Features

The patient demographic data included 9 males and 1 female in the age range of 35 to 80 years with the mean age of 61 years. All 10 patients had cirrhosis from varying etiologies [3 hepatitis C virus (HCV), 3 alcoholic hepatitis, 1 hepatitis B virus (HBV), 1 autoimmune, and 2 mixed HCV/alcoholic hepatitis and hemochromatosis/HCV]. All patients met the clinical and laboratory criteria for OLT qualification and underwent OLT without pretransplant diagnosis of HCC. In particular, HCC appeared clinically silent and without stigmata such as rapid weight

loss, tumor-related ascites or hepatomegaly, palpable mass, or evidence of metastases. In all 10 cases, the first suspicion of diffuse HCC ensued after the explanted liver was examined grossly and cut surfaces showed abnormal appearing pale and/or cholestatic cirrhotic-like nodules scattered among the cirrhotic nodules.

### Serology

The AFP values were below 20 ng/mL in 7 patients and increased in only 3 patients at 144, 150, and 252 ng/mL, respectively. In these cases, HCC was clinically suspected but as imaging studies did not identify a mass, these raised values were regarded as nonspecific and related to chronic liver disease.

### Imaging

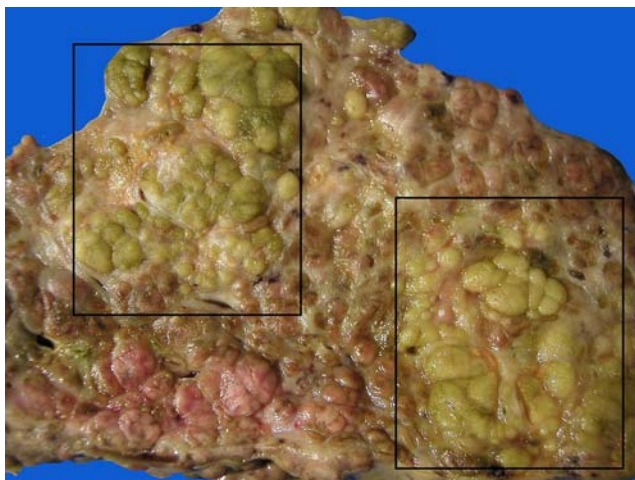
The ultrasonography performed on 6 of 10 cases showed normal hepatic echogenicity, diffuse coarseness compatible with cirrhosis, and no focal lesions. There was trace ascites or perihepatic fluid. The other 4 cases had dynamic imaging-CT of the abdomen with and without contrast and/or MR with and without gadolinium. In 2 of these 4 cases, small lesion(s), < 1 cm, were noted but these showed no vascular enhancement and hence were not regarded as HCC. All cases, however, showed heterogeneous nodular appearance of liver consistent with cirrhotic morphology. In addition, expected findings of portal hypertension such as splenomegaly, variable paraesophageal varicosity, and mild pelvic and abdominal ascites were observed.

### Gross Pathologic Features

The external surfaces of the explanted livers showed variable cirrhotic nodularity but no protruding larger masses. The cut surfaces revealed abnormally pale and/or cholestatic cirrhotic-like nodules, 0.2 to 0.6 cm in size and distinct from surrounding cirrhotic nodules, raising suspicion of HCC. In majority of the cases (8 of 10), these abnormal nodules were innumerable (>1000 in numbers) and diffusely scattered throughout the liver sometimes occupying up to 50% of the total volume (Fig. 1). Some cirrhotic nodules were partially pale suggestive of partial involvement of cirrhotic nodule by tumor (Fig. 2). In 2 of 10 cases, the nodules were fewer, about 20, and more localized within the liver (Fig. 3). Aggregate tumor sizes were estimated between 5 and 23 cm. There was no necrosis and no tumor was grossly seen to invade the vessels or the bile ducts.

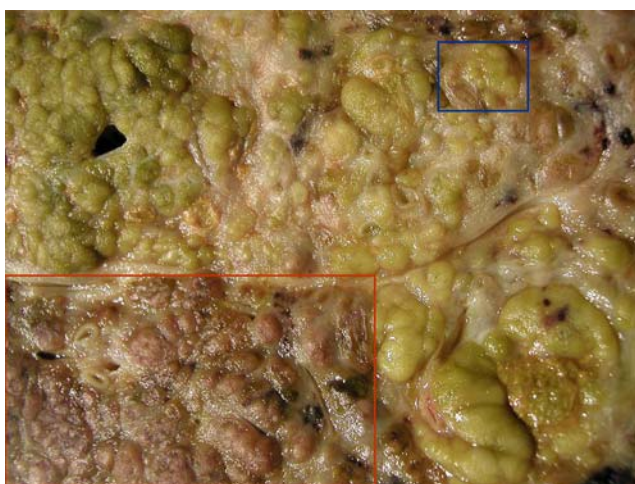
### Histologic Features

Representative sections from all cases were reviewed and the tumor nodules in each case were classified and graded according to the World Health Organization criteria.<sup>4</sup> There was general uniformity of grade among multiple nodules in each individual patient. Almost all tumor nodules were either moderately or well-differentiated carcinoma of hepatocellular origin and often showed pseudoglandular pattern (Fig. 4A). Corresponding well with the macroscopically visible pallor and/or cholestasis, the tumor cells frequently showed ballooning

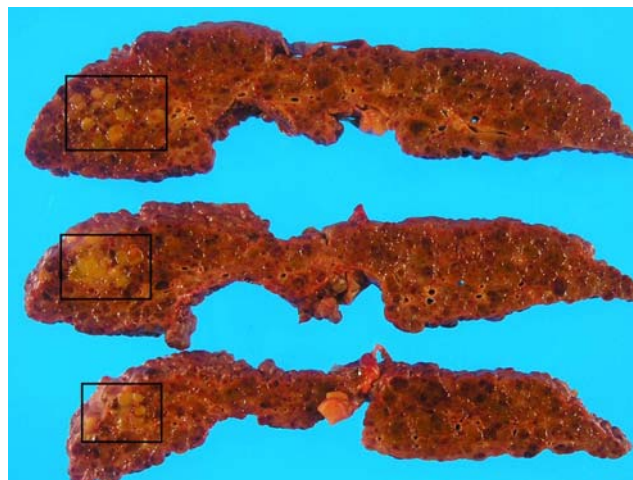


**FIGURE 1.** Cut surface of liver showing pale and cholestatic cirrhosis-like hepatocellular carcinoma nodules (highlighted with the rectangles) no bigger than darker non-neoplastic cirrhotic nodules and occupying about 50% of the liver volume.

and/or cholestasis and there were focally numerous Mallory bodies (Fig. 4B) in 8 of 10 cases. Many tumor nodules showed perinodular fibrous rims (Fig. 4C) greatly mimicking cirrhotic nodules and invasion in small intratumoral and peritumoral vessels (Fig. 4D). However, larger segmental and hilar vessels showed no invasion. Occasionally, cirrhotic nodules were partially and abruptly invaded by the tumor cells (Fig. 5A). Purported preneoplastic changes such as dysplasia (large cell and small cell change) or foci or nodules of altered hepatocytes were not noticeable in the intervening cirrhotic nodules. Although individually, none of these characteristics signify histologic uniqueness, the combined gross



**FIGURE 2.** Close-up of the liver cut surface showing darker non-neoplastic cirrhotic nodules (highlighted by the red rectangle) and partial involvement of cirrhotic nodule by paler cirrhosis-like hepatocellular carcinoma (highlighted by the blue rectangle).



**FIGURE 3.** Series of slices showing more localized and fewer pale nodules of cirrhosis-like hepatocellular carcinoma (highlighted with the rectangles).

and microscopic pattern is quite consistent and distinctive of this CL-HCC variant.

### Immunohistochemical Features

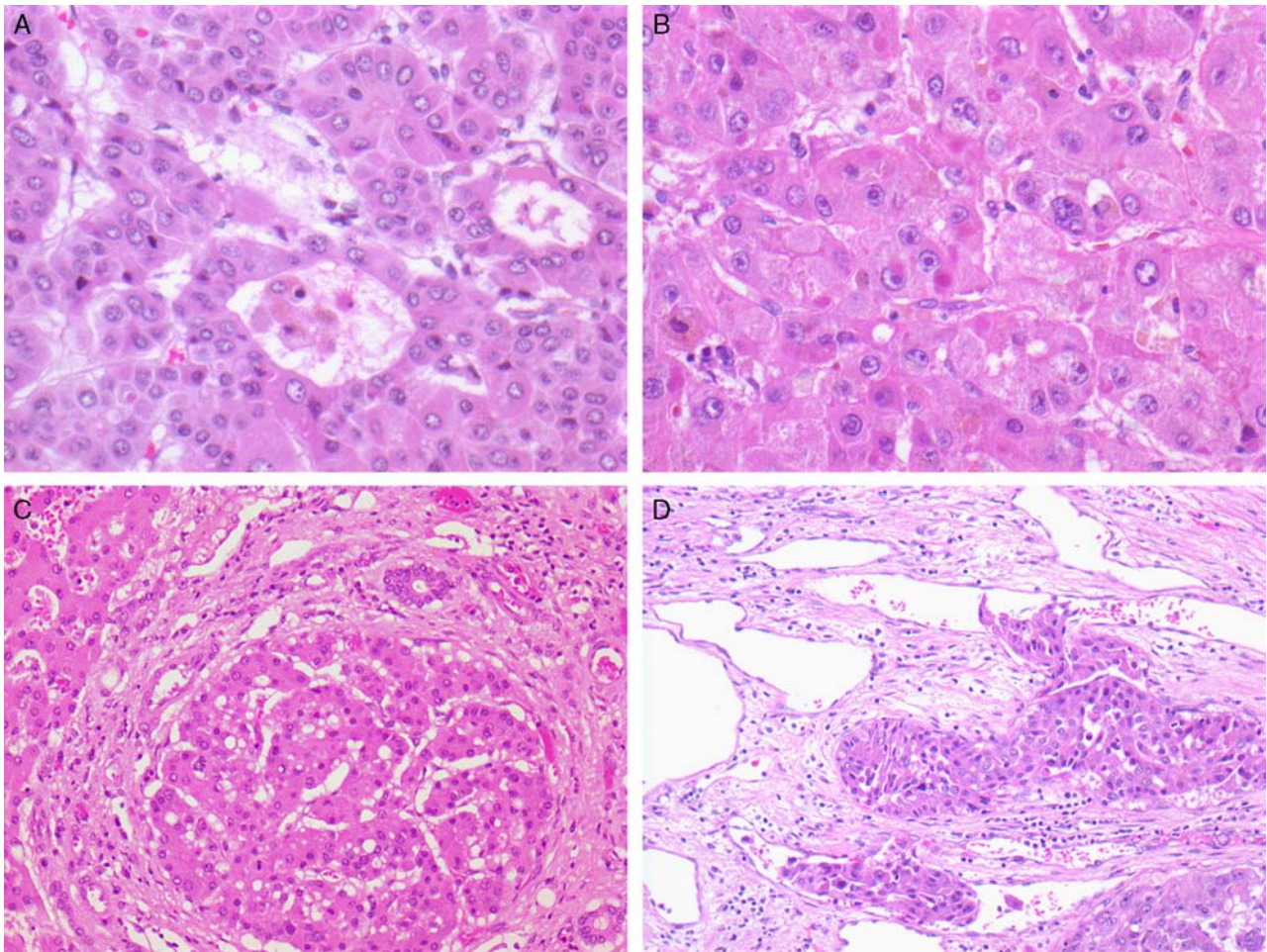
The immunophenotypic profile showed results anticipated for well and moderately differentiated HCC in most cases. All tumor cells were positive for HepPar-1 and glypican-3 (Fig. 5B), negative for AFP and cytokeratins 7 and 19 and showed strong CD34 expression by sinusoidal endothelial cells (Fig. 5C). All cases with Mallory bodies (8 of 10) showed expected ubiquitin positivity. Apart from the usual pericanalicular CD-10 expression, 6 of 10 cases showed strong membranous and cytoplasmic positivity (Fig. 5D). Ki-67 proliferative index was low (1% to 25%, mean of 14%) conforming to the better differentiation of HCC.

### Follow Up

At the time of transplant, not only was there no tumor suspected within the liver, but also no metastatic tumor was described clinically. Considering the extensiveness of the tumor, surprisingly no tumor was found in the major branches of hepatic or portal veins. Follow up was available in 5 out of 10 cases. Two of these 5 patients expired within 3 years—one from cardiac complications related to hemochromatosis but without tumor recurrence or metastasis and the second with tumor recurrence in the allograft and metastases to lungs. The remaining 3 patients are surviving for more than 3 years without known recurrence or metastases. One of these 3 surviving patients had fewer, more localized tumor nodules while the other 2 patients had diffuse involvement. The clinical data is summarized in Table 1.

### DISCUSSION

Multiplicity of primary neoplasm in the liver, especially with underlying chronic liver disease and cirrhosis is not uncommon. However, the CL-HCC variant seems to

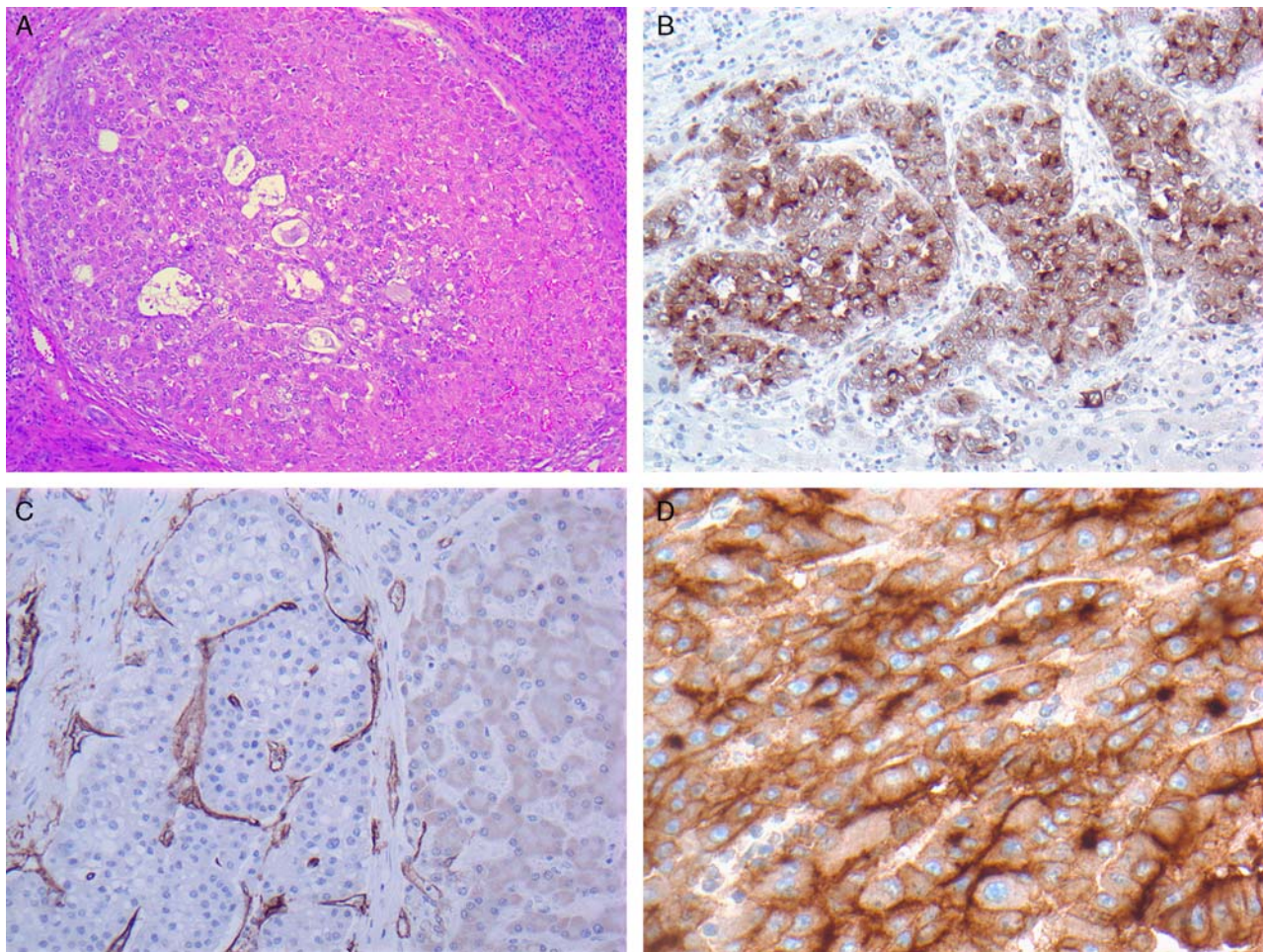


**FIGURE 4.** Well-differentiated hepatocellular carcinoma showing pseudoglandular pattern (A) and moderately differentiated hepatocellular carcinoma showing ballooning, cholestasis, and several Mallory bodies (B) (hematoxylin and eosin, magnification  $\times 400$ ). Cirrhosis-like hepatocellular carcinoma nodule showing perinodular sclerotic rim (C) and foci showing small vessel invasion (D) (hematoxylin and eosin, magnification  $\times 200$ ).

be a unique neoplastic process that necessitates understanding of phenomena such as macroscopic small nodular growth pattern extensively through the liver, microscopic and immunophenotypical preference for certain uncommon findings, multiclonal tumor growth versus intrahepatic metastases from a single primary neoplasm, ability to evade clinical detection, and implications of recurrence in the graft from such unforeseen pretransplant tumor mass. Our collection of only 10 cases over 9 years of assessment and from multiple medical centers are likely reflective of the rarity of this variant. And although statistical determinations are not possible with this relatively minute population, some insight may be gained from their unifying characteristics.

References have been made in the literature to macroscopic confluent multinodular growth pattern (sometimes called “cirrhotomimetic”) of HCC<sup>3,5,14,16</sup> but without emphasis on clinical undetectability, microscopic or immunophenotypical features, or incidental eligibility for OLT. Grossly, most HCCs may display 1

of 3 of the following described patterns in the decreasing order of frequency: expanding, generally solitary nodule (“massive” type) with discrete margins and apparent encapsulation, multiple discrete nodules which may or may not be satellite nodules associated a solitary large nodule (“extranodular” or “nodular” type) with margins and generally apparent encapsulation, and small “spreading” nodules (“infiltrative” or “diffuse” type) without apparent margins and a “replacing” rather than “expanding” growth pattern. Previous studies with such gross descriptions and classifications have been based upon autopsy or surgical resections rather than native explanted livers at transplantation. CL-HCC matches closely with the diffuse or infiltrative growth pattern. However, most CL-HCC nodules do have a well-defined peritumoral fibrous border unlike the original description of small nodular diffuse HCC. Having fibrous encapsulation actually enhances the chances of tumor visibility on dynamic imaging but the small size rather than fibrous encapsulation may be the primary reason for radiographic nondetection.<sup>6</sup>



**FIGURE 5.** Partial involvement of a cirrhotic nodule by CL-HCC (A) (hematoxylin and eosin, magnification  $\times 100$ ). Immunohistochemically, CL-HCC cells showing glypican-3 positivity (B), CD34 reactivity in endothelial cells contrasting with the adjacent non-neoplastic cirrhotic nodule (C), and CD10 showing the pericanalicular reactivity seen in HCC but additional strong membranous and cytoplasmic positivity (D) (magnifications  $\times 200$  for B and C, and  $\times 400$  for D). CL-HCC indicates cirrhosis-like hepatocellular carcinoma.

In addition, CL-HCC nodules on gross examination appear consistently pale and/or cholestatic corresponding with the microscopic findings of ballooning and/or cholestasis. In

fact, this gross finding may be the principal way of discriminating potential tumor nodules from adjacent non-neoplastic cirrhotic nodules as their sizes are identical.

**TABLE 1.** Summary of Clinical Data

No.	Age (y) and Sex	Cause of Cirrhosis	AFP >20 ng/mL	Pre-OLT >1 cm Mass on Imaging	Follow-up of >3 y
1	62, Male	HCV	No	No	Living, tumor free
2	60, Male	EtOH	No	No	NA
3	80, Male	HCV	144	No	NA
4	73, Male	EtOH	150	No	NA
5	65, Male	HCV	No	No	Living, tumor free
6	59, Male	EtOH	No	No	Living, tumor free
7	35, Male	HBV	No	No	NA
8	60, Male	HCV/HH	No	No	Expired, cardiac HH complications
9	61, Female	AIH	No	No	Expired, tumor recurrence in graft
10	59, Male	HCV/EtOH	252	No	NA

AFP indicates  $\alpha$ -fetoprotein; AIH, autoimmune hepatitis; EtOH, alcoholic hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HH, hereditary hemochromatosis; NA, not available; OLT, orthotopic liver transplantation.

As opposed to ambiguous neoplastic nodularity on gross examination, microscopically, CL-HCC cases demonstrate unequivocal hepatocytic malignancy with easy discrimination from intervening non-neoplastic cirrhotic nodules. Almost all cases show well to moderate differentiation (mostly moderate differentiation or grade 2) with distinctly higher nuclear/cytoplasmic ratios, stratified neoplastic cell layers, and mixed trabecular and pseudoglandular architecture with frequent cholestasis. Most tumor nodules show thin perinodular sclerotic rims. The tumor cells also show rather frequent ballooning and Mallory body formation and small vessel invasion. Although individually each microscopic finding is not uncommon in HCC, their collective frequency in CL-HCC seems noteworthy. An epiphenomenon of injury such as Mallory body, usually seen in a minority of HCC (about 16% cases),<sup>18</sup> appears quite common (80% cases) in CL-HCC.

Immunophenotypically, CL-HCC matches conventional HCC for several markers such as positivity for HepPar-1 and glypican-3 and sinusoidal endothelial CD34 reactivity and negative staining for cytokeratins 7 and 19. There is expected Mallory body-associated ubiquitin reactivity, general lack of AFP immunostaining, and low MIB-1 proliferative index common for better differentiated hepatocellular tumors.<sup>10</sup> CD10 shows distinctive cytoplasmic and cell membrane staining apart from usual pericanalicular pattern in majority of CL-HCC. This pattern has been previously correlated with poorly differentiated HCC and shorter survival compared with usual pericanalicular and noncytoplasmic CD10.<sup>8</sup> However, in CL-HCC, this pattern is associated with better differentiation and survival yet to be determined, but probably not dismal.

Several studies have addressed the technically challenging question of molecular relationships between multiple HCC nodules; whether these are intrahepatic metastases from a single original primary neoplasm or multiclonal separate tumor foci. This has been analyzed in the literature by varied methods such as comparing genetic information of loss of heterozygosity, microsatellite instability, hypermethylation of multiple genes, comparative genomic hybridization, and HBV integration patterns as indicators of clonality in two or more separate HCC tumor nodules. Conditions best suited for such clonality studies include oligonuclear nodules where each nodule can be individually studied, recurrent tumor in the graft which is presumed to belong to the original clone and HBV-related cirrhosis where integrated HBV DNA can be compared. As these opportune conditions are lacking in our cases, such clonality studies are not attempted. Synchronous multiclonal carcinogenesis appears overall more common (36% to 75%, mean of 60%) than intrahepatic metastases.<sup>7,9,11,12,20</sup> The majority of cases with intrahepatic metastases tend to be large discrete tumors whereas multiclonal tumors tend to be small diffuse nodules. Based upon these trends, the likelihood of CL-HCC being multiclonal is greater given the lack of a dominant massive nodule. And although not planned preoperatively, OLT is an optimal therapeutic

choice as it removes not only just the tumor but also the entire cirrhotic liver seemingly predisposed to extensive preneoplastic changes.

The ability to evade clinical and radiographic detection seems to be the defining characteristic of this variant. Most HCC patients manifest some of the clinical signs and symptoms related to hepatic malignancy such as weight loss, abdominal distension, hepatomegaly, hepatic decompensation, ascites, or metastasis. CL-HCC patients do not seem to evoke such clinical suspicion. However, if the pretransplant needle biopsies show incidental HCC foci in liver needle cores when there is no radiologic tumor mass and the biopsies are random and not image guided, diagnosis of CL-HCC should be suspected (unpublished observation). Additionally, a CL growth pattern may also be associated with a more conventional HCC with a dominant large mass (unpublished observation). Most CL-HCC cases show either normal AFP or mild elevation that is not considered to signify high positive predictive value for HCC (below 200 ng/mL).<sup>2</sup> Radiographically, on ultrasound as well as dynamic imaging (CT or MR), CL-HCC shows cirrhosis but fails to demonstrate a discrete mass or focally enhancing lesion in the arterial or venous phase. Although perinodular fibrous rim increases the probability of radiographic detection, the relatively small sizes of the nodules are below the radar for visibility on imaging. This nondetectability is in fact the very basis for eligibility for OLT as awareness of such massive tumor would disqualify patients under any of the multiple criteria.<sup>1</sup>

The demographics of the patient population of this variant does not suggest any age bias (mean age 61 y). And although 9 of 10 patients are males, the population is too small to hypothesize sex predisposition at this time particularly as there is overall male predominance in HCC of 2.4 to 3.7:1.0.<sup>15</sup> The causes of cirrhosis in CL-HCC are varied and there seems to be no single etiologic predilection.

Given this unanticipated tumor burden in the explanted liver, there is a natural suspicion for poor outcome and potential recurrence of HCC in the graft. Overall, recurrence rates in HCC exceed 70% at 5 years and more likely to appear during the first 3 years of follow-up.<sup>1</sup> Some studies have shown that preoperatively undetected foci of HCC are unlikely to affect prognosis<sup>17,19</sup> and survival and tumor-free survival in HCC may be better with lower histologic grade regardless of the size of the tumor.<sup>13,22,23</sup> Three years of follow-up is available in only 5 of our 10 cases and 3 of these are living without tumor recurrence. Given the extensiveness of the original tumor this appears an encouraging sign.

CL-HCC variant is a cryptic and extensive tumor that masquerades as cirrhotic nodules and evades pre-OLT detection. It appears that such patients inadvertently qualify and probably should qualify for OLT regardless of the tumor mass as they seem to have some favorable features such as better histologic differentiation, low proliferative tumor activity, and lack of metastases at the time of OLT. Further studies are required to understand carcinogenesis of this variant and its peculiar clinicopathologic manifestations.

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