LUPINE PUBLISHERS

Current Trends in Gastroenterology and Hepatology

DOI: 10.32474/CTGH.2022.03.000175

ISSN: 2641-1652

Mini Review

Transmogrification and Seepage-Hepatocellular Carcinoma

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Received: August 24, 2022 **Published:** September 09, 2022

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Hepatocellular carcinoma is denominated as a primary hepatic malignancy demonstrating features of hepatocellular differentiation. Previously designated as hepatoma, hepatocellular carcinoma emerges from low grade hepatocellular dysplasia with gradual transition to high grade dysplasia, preliminary hepatocellular carcinoma, and progressive hepatocellular carcinoma. Hepatocellular carcinoma predominantly occurs within elderly subjects. Median age of disease emergence is beyond sixth decade within Caucasian population and between third decade to sixth decade within Asians. A male predominance is observed with a male to female proportion of 3:1. Accumulation of diverse molecular alterations such as telomere shortening, activation of TERT gene along with inactivation of cell cycle checkpoint inhibitor may occur. Promoter mutations within TERT gene is significant for progression of hepatocellular carcinoma. Specific categories of hepatocellular carcinoma depict diverse molecular or cytogenetic anomalies as

a) Scirrhous subtype is associated with genomic mutations of TSC1 / TSC2.

b) Steatohepatitic subtype commonly delineates activation of IL6/ JAK/ STAT pathways.

c) macro-trabecular or massive subtype exhibits TP53 mutation and genomic amplification of FGF19.

d) fibro-lamellar subtype demonstrates the occurrence of DNAJB1-PRKACA fusion gene.

Hepatocellular carcinoma preponderantly emerges within hepatic parenchyma whereas tumour metastasis is frequent within pulmonary parenchyma, portal vein, portal lymph nodes, intra-abdominal lymph nodes or bone, in decreasing order of frequency. Hepatocellular carcinoma may be engendered with distinctive conditions as hepatic cirrhosis, infections with hepatitis B virus, hepatitis C virus, chronic viral hepatitis, metabolic disorders as non-alcoholic fatty liver disease, hemochromatosis, alpha-1 antitrypsin deficiency, hyper-citrullinemia or fructosemia, environmental exposure to substances such as aflatoxins, tobacco, alcohol, anabolic steroids, thorotrast or oral contraceptives [1,2]. Additionally, congenital disorders such as Abernethy malformation, Alagille syndrome, ataxia telangiectasia, bile salt export protein deficiency or tyrosinemia type I may induce hepatocellular carcinoma. Occasionally, hepatocellular adenoma may undergo malignant metamorphosis and induce hepatocellular carcinoma.

Incriminated individuals exhibit distinctive clinical symptoms as abdominal pain, hepatomegaly, splenomegaly, conjugated hyperbilirubinemia, ascites, and loss of weight. World Health Organization categorizes hepatocellular carcinoma into distinct categories as

a. well differentiated tumefaction which is comprised of tumour cells recapitulating mature hepatocytes and demonstrate minimal to mild nuclear atypia.

b. moderately differentiated neoplasm is constituted of cells with hepatocellular differentiation delineating moderate nuclear atypia and associated features of malignancy.

c. poorly differentiated hepatocellular carcinoma is composed of frankly malignant tumour cells with significant nuclear atypia. Neoplastic cells may simulate diverse, poorly differentiated neoplasms.

Modified Edmondson-Steiner grading system classifies hepatocellular carcinoma into

a) grade I wherein tumour cells resemble hyperplastic hepatocellular elements.

b) grade II where tumour cells simulate mature hepatocytes and appear incorporated with minimally enlarged,

hyperchromatic nuclei, distinct, sharply defined cellular perimeter and frequent configuration of hepatic acini.

c) grade III where enlarged tumour cells are permeated with minimally acidophilic cytoplasm and hyperchromatic nuclei. Tumour giant cells are innumerable. Focal trabecular distortion is observed

d) grade IV is comprised of minimally cohesive tumour cells pervaded with scanty, mildly granular cytoplasm and intensely hyperchromatic nuclei. Neoplastic cells appear as spindle-shaped, compact or plump. Tumour giant cells are observed. Neoplasm demonstrates minimal hepatic acini, medullary configuration and decimated trabecular pattern.

Grossly, a well circumscribed, tan, yellow or green tumefaction with focal hemorrhage and necrosis is enunciated. Tumefaction may display a solitary or dominant nodule with multiple satellite nodules, multiple, discrete nodules or multiple, distinct nodules. Adjoining liver parenchyma appears cirrhotic. Exceptionally, hepatocellular carcinoma may demonstrate an exophytic pattern of tumour evolution, designated as 'pedunculated' hepatocellular carcinoma. Cytological evaluation exhibits a hyper-cellular tumefaction composed of broad fascicles and aggregates of malignant hepatocytes circumscribed with peripherally disseminated endothelial cells. Well and moderately differentiated hepatocellular carcinoma simulates normal hepatocytes and exhibits polygonal, monotonous cells imbued with granular or ground glass cytoplasm, enlarged nuclei with prominent macro-nucleoli, nuclear pseudo-inclusions, elevated nuclear/cytoplasmic ratio, irregular nuclear membrane, coarse chromatin and intracytoplasmic bile. Cytoplasmic inclusions such as Mallory-Denk bodies and hyaline inclusions may be observed. Poorly differentiated neoplasms demonstrate spindle-shaped or multi-nucleated tumour cells with significant nuclear pleomorphism, atypical mitotic figures and focal necrosis. Innumerable singular, isolated cells and enlarged naked nuclei can be observed. Cellular overlapping and nuclear crowding is frequent. Thickened cellular cords or neoplastic trabeculae enunciate peripheral encasement with endothelial cells. Pseudo-glandular configuration or pseudo-acinar pattern is delineated. Tumour parenchyma may be transgressed with vascular articulations. Upon microscopy, hepatocellular carcinoma exhibits distinct architectural patterns as trabecular, pseudo-glandular, solid or macro-trabecular. Mixed tumour configuration may occur with an admixture of aforesaid patterns. Tumefaction is composed of polygonal cells imbued with clear to eosinophilic cytoplasm, prominent nuclei with significant nuclear atypia, enhanced nuclear/cytoplasmic ratio, irregular nuclear membrane, and multinucleated cells. Cytoplasmic alterations such as Mallory-Denk bodies, hyaline bodies or pale bodies may be discerned. Extracellular secretion of bile may occur. Additionally, an absence of portal triad within tumour nodules, decimated hepatic reticulin framework, expansion of hepatocyte plates and enhanced arterialization along with unpaired arterioles or vascular articulations may be discerned (Figures 1 &,2), (Table 1).

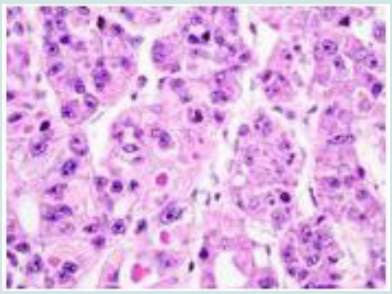

Figure 1: Hepatocellular carcinoma depicting polygonal cells with granular, eosinophilic cytoplasm, enlarged nuclei with irregular membrane, prominent macro-nucleoli, and minimal vascular congestion.

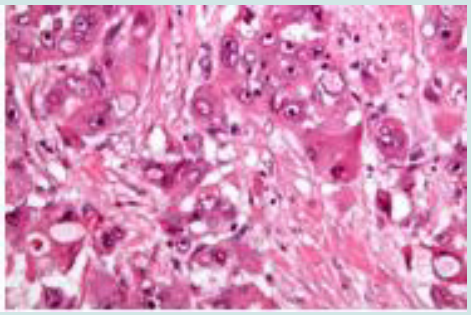

Figure 2: Hepatocellular carcinoma-fibro-lamellar variant delineating enlarged, neoplastic cells with granular, oncocytic cytoplasm, enlarged nuclei with prominent nucleoli and circumscribing, dense, parallel fascicles of collagen fibrous connective tissue.

Table 1: TNM classification of Hepatocellular Carcinoma.

Tumour		Node	Metastasis
TX: Primary tumour cannot be assessed		NX: Regional lymph nodes cannot be assessed	
T0: No evidence of primary tumour		N0: No regional lymph node metastasis	M0: Distant metastasis absent
T1: Solitary tumour ≤ 2 cm or > 2 cm with absent vascular invasion		N1: Regional lymph node metastasis present	M1: Distant metastasis present
T1a: Solitary tumour ≤ 2 cm with or devoid of vascular invasion	T1b: Solitary tumour > 2 cm devoid of vascular invasion		
T2: Solitary tumour > 2 cm with vascular invasion or multiple tumours < 5 cm			
T3: Multiple tumour nodules with a single nodule >5cm			
T4: Tumour infiltrates major branches of portal or hepatic vein, adjacent organs except gallbladder or perforates visceral peritoneum			

Regional lymph nodes are comprised of hilar, para-caval or inferior phrenic lymph nodes and lymph nodes distributed along hepatoduodenal ligament. Hepatocellular carcinoma is immune reactive arginase1, HepPar1, glypican 3, AFP, albumin ISH, pan-cytokeratin, MNF116, CAM5.2, CK8/CK18 or reticulin. Hepatocellular carcinoma is immune non-reactive to AE1/AE3, CK7, CK13, CK19, CK20, CDX2, monoclonal CEA, mucicarmine, MOC31, BerEP4 or reticulin (3,4). Hepatocellular carcinoma requires segregation from neoplasms such as hepatocellular adenoma, intrahepatic cholangiocarcinoma, primary hepatic lymphoma, dysplastic or regenerative liver nodules arising in hepatic cirrhosis, liver metastasis emerging from diverse neuroendocrine neoplasms, hepatic carcinomatous metastasis as from clear cell renal cell carcinoma, fibrous nodular hyperplasia or hepatic cirrhosis. Liver function tests and serum AFP appear elevated. Hepatocellular carcinoma can be appropriately discerned with imaging techniques as ultrasonography, computerized tomography with contrast enhancement or magnetic resonance imaging. Cogent tissue sampling is diagnostic although may be superfluous.

Hepatic nodules discerned in liver cirrhosis necessitate evaluation as

a) below< 1-centimeter, cirrhotic liver nodules can be subjected to ultrasonography in ~ 4 months.

b) exceeding> 1-centimeter, cirrhotic nodules can be evaluated with computerized tomography with contrast enhancement or magnetic resonance imaging. Hepatocellular carcinoma exhibits pertinent diagnostic criterion as image hyper-enhancement during arterial phase and washout during venous or delayed phase on account of altered vascular perfusion, as malignant hepatocytes are perfused with hepatic artery. Liver Imaging Reporting and Data System (LI-RADS) describes distinctive neoplastic categories as

a. LR-1: definitely benign nodule

b. LR-2: probably benign nodule

c. LR-3: intermediate probability of malignant hepatic nodule

d. LR-4: probable hepatocellular carcinoma

e. LR-5: definitely hepatocellular carcinoma

Instances challenging to ascertain upon imaging can be subjected to liver biopsy for cogent histological evaluation. Surgical intervention of hepatocellular carcinoma is optimal wherein neoplastic excision is appropriate for singular neoplasms or tumefaction associated with preserved liver function. Liver transplantation can be employed for treating solitary tumefaction < 5 centimeters or up to three neoplasms < 3 centimeters. Ablation therapy can be adopted with radiofrequency, microwave, cryo-ablation or injectable ethanol. Additionally, trans-arterial embolization (TEA) or trans-arterial chemoembolization (TACE) can be utilized. Hepatocellular carcinoma is amenable to systemic therapy with Sorafenib with consequently enhanced median survival. Prognostic outcomes of hepatocellular carcinoma are contingent to TNM tumour classification. Factors such as lymphoid or vascular invasion and poorly differentiated, solitary tumefaction >2 centimeters demonstrate inferior outcomes. Occurrence of hepatic cirrhosis, injury to hepatic parenchyma, multifocal lesions, hepatocellular carcinoma > 2 centimeters, and portal vein thrombosis exhibit unfavorable prognosis. Neoplastic immune reactivity to CK19, CD90, EpCAM and CD133 is associated with inferior therapeutic outcomes. Apart from conventional hepatocellular carcinoma, tumour subtypes demonstrating inferior prognosis are comprised of cirrhoto-mimetic, sarcomatoid, carcino-sarcoma, macro-trabecular massive or neutrophil- rich hepatocellular carcinoma. Categories depicting

favourable outcomes are steatohepatitic, clear cell, chromophobe, fibro-lamellar and lymphocyte-rich hepatocellular carcinoma. Subcategories with debatable prognostic outcomes are constituted of scirrhous hepatocellular carcinoma [3,4].

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DOI: 10.32474/CTGH.2022.03.000175