

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Histopathological Features of the Steatohepatitic Variant of Hepatocellular Carcinoma and Its Relationship with Fatty Liver Disease

Emine Turkmen Samdanci

Abstract

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver in adults. Steatohepatitic HCC (SH-HCC) is a recently described, rarer variant of HCC and is associated with nonalcoholic fatty liver disease (NAFLD). The relationship between fatty liver disease and/or steatohepatitis and SH-HCC is now known. This subtype can be confused with lipid-containing nodules (such as cirrhotic nodules, regenerative nodules, focal nodular hyperplasia) clinically, radiologically and histopathologically. Here, the histopathological features of SH-HCC, its relationship with fatty liver disease and briefly its clinical features will be discussed. In addition, histopathological features of this specific variant, immunohistochemical staining of the tumor and diagnostic difficulties in tru-cut biopsies will also be discussed. Actually, I think this article will raise clinicopathological awareness about this rare variant.

Keywords: Hepatocellular carcinoma, steatohepatitic HCC, steatohepatitis, NASH, alcoholic steatohepatitis, IHC

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver in adults, the fifth most common cancer in the world and also the third most common cancer of cancer-related deaths [1]. It is the malignancy of hepatocytes with varying degrees of differentiation [2]. The most common cause of death in patients with HCC is cirrhosis. Despite all the unknowns, hepatocarcinogenesis is a multistep process, and chronic inflammation plays the major role [2–6].

2. Epidemiology and etiology

HCC has a multifactorial etiology, and its incidence and prevalence varies by country [7]. Although the incidence of HCC is different in different geographies, the incidence increases with age [8]. It is more common in men than in

women (male:female ratio; ranging between 2:1 and 4:1 in various countries). Cirrhosis, viral hepatitis, alcohol, aflatoxin, metabolic diseases, metabolic syndrome characterized by fatty liver are the main causes of HCC etiology. Although the activation of the WNT/B-catenin pathway is one of the main events in HCC, the effects of viral antigens on the nucleus, mutations, and DNA instability constitute the pathogenesis of HCC [9]. There are also molecular studies showing that activation of the JAK/STAT pathway also contributes to the development of SH-HCC [1, 10].

2.1 Cirrhosis

Most patients with HCC have underlying liver cirrhosis. Cirrhosis is therefore considered a major risk factor for HCC [8, 11, 12]. Although macronodular cirrhosis is considered as a higher risk for HCC than micronodular cirrhosis, cirrhotic liver can create HCC for any reason [13]. Cirrhosis also has a geographical distribution, the etiology of cirrhosis is chronic viral hepatitis in Asian countries, and nonviral causes in European and American countries [14]. Despite this known association between cirrhosis and HCC, HCC also develops from the noncirrhotic liver [15–17].

2.2 Viral hepatitis (hepatitis B and hepatitis C)

Most HCCs develop from the background of chronic viral hepatitis, including hepatitis B and Hepatitis C [18–21]. Viral hepatitis-related HCCs are more common in countries where hepatitis B and hepatitis C are more prevalent, such as Asia and Africa. Viral-related HCC appears to be decreasing in countries where clinical follow-up increases, and whom include hepatitis B vaccine in regular vaccination programme. Integration of hepatitis B virus into the host hepatocyte genome is thought to initiate hepatocarcinogenesis. In the etiology of HCC, hepatitis C is as important as hepatitis B [22–24]. Being men and older, having coinfection (such as HBV, HIV), alcohol use, diabetes, and fatty liver constitute a high risk for HCC formation. Even the development of HCC in liver coinfecting with hepatitis C and hepatitis B viruses, is higher than in those infected with other viruses [13]. It is thought that ongoing liver damage and accompanying regeneration caused by the immune response and direct cytopathic effect in hepatitis C infection induce malignant transformation [25, 26].

2.3 Aflatoxin

Consumption of foods contaminated with aflatoxins produced by fungi can lead to the formation of HCC [8, 27, 28]. Aflatoxin B₁, one of the toxin types, is thought to be mainly responsible for HCC formation [8]. It contributes to the formation of HCC by making mutations (Guanine and Thymine mutations) in DNA via cytochrome p450. Aflatoxin exposure is thought to affect patients with chronic HCV hepatitis more [8, 29, 30].

2.4 Alcohol

The relationship between alcohol use and HCC is both by direct effect and being a cofactor in viral infections [31, 32]. Reactive oxygen radicals, that occur while alcohol is metabolized to acetaldehyde, initiate hepatocarcinogenesis by causing damage and transformation in DNA. HCC development in alcoholic cirrhosis is in the form of DNA instability caused by DNA hypomethylation [33–36].

2.5 Metabolic diseases

HCC can develop in some of the livers with metabolic diseases. However, the development of HCC is more common with hereditary hemochromatosis, tyrosinemia and α 1-antitrypsin deficiency [37–41]. In these diseases, the direct toxic effect of accumulations (such as iron), mutation (p53 mutation), immunological abnormalities and DNA damage by lipid peroxidation initiate the development of HCC [8, 42, 43].

2.6 Metabolic syndrome and fatty liver disease

Metabolic syndrome is a mortal endocrinopathy that is accompanied by systemic disorders such as abdominal obesity that begins with insulin resistance, diabetes, dyslipidemia, hypertension and coronary artery disease. This situation has led to an increase in HCC formation, which has the characteristics of metabolic syndrome [44–47]. The risk of HCC increases 2–3 times in patients with diabetes [37, 48, 49]. The increase in metabolic syndrome in developed countries also brought an increase in nonalcoholic fatty liver disease (NAFLD) [50–55].

In obese patients, the decrease in the release of fatty acids from adipose tissue, tumor necrosis factor- α and adiponectin causes insulin resistance and thus chronic hyperinsulinemia. Insulin and insulin growth factor-1 (IGF-1) contribute to hepatocarcinogenesis by preventing apoptosis and increasing cellular proliferation with the signals they send to insulin receptors and IGF-1 receptors [8].

Since steatohepatitic HCC (SH-HCC) will be mentioned here, NAFLD, steatohepatitis and their associated HCC formation mechanism are explained in a little more detail.

There are many studies on the incidence and prevalence of HCC in NAFLD cases, with rates varying between 3 and 35% [51, 56, 57]. Steatohepatitis varies between 3 and 5%. In some cohort studies, the rate of development of HCC (1-year cumulative incidence) was reported as 2–5% in patients with NAFLD compared to hepatitis C cases. The 5-year incidence was reported as 11% [51, 58]. In another study, the annual cumulative rate was 2–6%. In a retrospective study, NAFLD was detected in 21.2% of HCC cases. In fact, 23% of NAFLD patients without histopathologically and radiologically significant cirrhosis developed HCC [59]. In a different study, HCC develops in 5% of patients with cirrhosis secondary to NAFLD [53]. In cohort studies with large case series, both steatosis and steatohepatitis in nontumoral liver were found to be statistically significant with HCC. Moreover, a close relationship between the steatohepatitic variant of HCC (SH-HCC), which has been recently defined, and NAFLD has been described and demonstrated [22, 53, 58, 60]. Although its relationship with fatty liver diseases has been clarified, there are studies showing that SH-HCC can also develop in viral hepatitis [16, 61].

3. Clinical features

The clinical manifestations of HCC are quite ambiguous and are related to the tumor and underlying chronic liver disease [1]. Usually, patients show signs in advanced stages and even miss the chance of treatment. Patients may present with upper abdominal pain, hepatomegaly, splenomegaly, weight loss, jaundice or decompensated liver finding such as ascites [1, 8]. HCC most commonly spreads intrahepatically via the portal vein [1]. While HCC spreads with intrahepatic portal vein branches, the main portal vein and hepatic vein involvement can also be seen.

Invasion of the bile duct causes liver decompensation, resulting in rapid ascites accumulation, obstructive jaundice, variceal hemorrhages, and hepatic encephalopathy [8]. Although extrahepatic dissemination is rare, it can metastasize to the lung, lymph nodes, bone, and adrenal gland in advanced disease [1]. Paraneoplastic syndrome findings such as hypoglycemia, hypercholesterolemia, hyperkalemia, gynecomastia, carcinoid syndrome, hypertrophic pulmonary osteoarthropathy, osteopetrosis, hypertension, hyperthyroidism, porphyria cutanea tarda can be seen [8]. Median survival in patients with clinical findings who have the chance for curative treatment is around 1–3 months, and survival over 1 year is also unusual. Today, thanks to definitive treatments and advanced surgeries, patients at risk of developing HCC are followed more closely and the tumor is diagnosed at an early stage [8, 28]. Radiologic imaging methods (ultrasound, computed tomography, magnetic resonance imaging, angiography) are used for the diagnosis of liver masses and HCC [8, 17, 62, 63].

4. Pathological features

HCC is a highly heterogeneous tumor. Heterogeneity is both molecular and morphological [64, 65]. Understanding the heterogeneity is important for the diagnosis, treatment and follow-up of the disease [64].

HCCs below 2 cm are called small HCC (s-HCC) and early HCC (e-HCC) [1, 64, 66]. These tumors are divided into two as prominent nodular or indistinct nodules [64]. Early-HCC is in the form of nodules with indistinct borders and usually develops from a dysplastic nodule background. They are well differentiated, develop from the background of fibrosis-cirrhosis, and are radiologically hypovascular and rarely vascular invasion (5%) [1, 64]. Small-HCC has a prominent pseudocapsule, is well-moderately differentiated, radiologically hypervascular, and invades more frequently (40%) [1, 64]. Pedunculated HCC has a growth pattern protruding from the capsular surface [67]. Diffuse HCC is in the form of proliferation of small tumor nodules and resembles cirrhotic nodules (cirrhotomimetic) [64]. SH-HCC is more solid than other HCC subtypes and has more golden-yellow color due to the lipid contains. When the macroscopic specimen is carefully examined, fibrotic bands that divide the tumor into lobules can be seen. The tumor usually tends to be well-circumscribed or nodular and may range in diameter from 0.5 cm to 11 cm [68]. The prognosis of SH-HCC is similar to that of classical HCC [40, 57, 69, 70]. Although nontumoral liver can be cirrhotic or noncirrhotic, it is usually yellowish-brown in color suggestive of fatty liver (**Figure 1**).

After these macroscopic definitions and macroscopic heterogeneity, it is necessary to mention microscopic heterogeneity. This heterogeneity is also reflected in the histopathological subtyping of HCC [71]. In the 5th edition of WHO classification of the tumors of the digestive system (2019), the subtypes of HCC are as follows; fibrolamellar, scirrhous, clear cell type, steatohepatitic, macrotrabecular massive, chromophobe, neutrophil-rich, lymphocyte-rich [1]. More on SH-HCC will be mentioned here. SH-HCC is a newly identified subtype of HCC. It accounts for approximately 5–20% of all HCCs [1]. It is characterized by steatohepatitic features such as steatosis in tumor cells, balloon degeneration, inflammation, Mallory-Denk bodies and pericellular fibrosis [58, 72]. Tumor is usually related to MetS and steatohepatitis is detected in the background [22, 39, 57, 61, 69, 72]. Some studies have shown that steatosis and interstitial fibrosis are the main findings for SH-HCC [22, 40]. However, the minimum amount of steatosis in the steatohepatitic area in some tumors

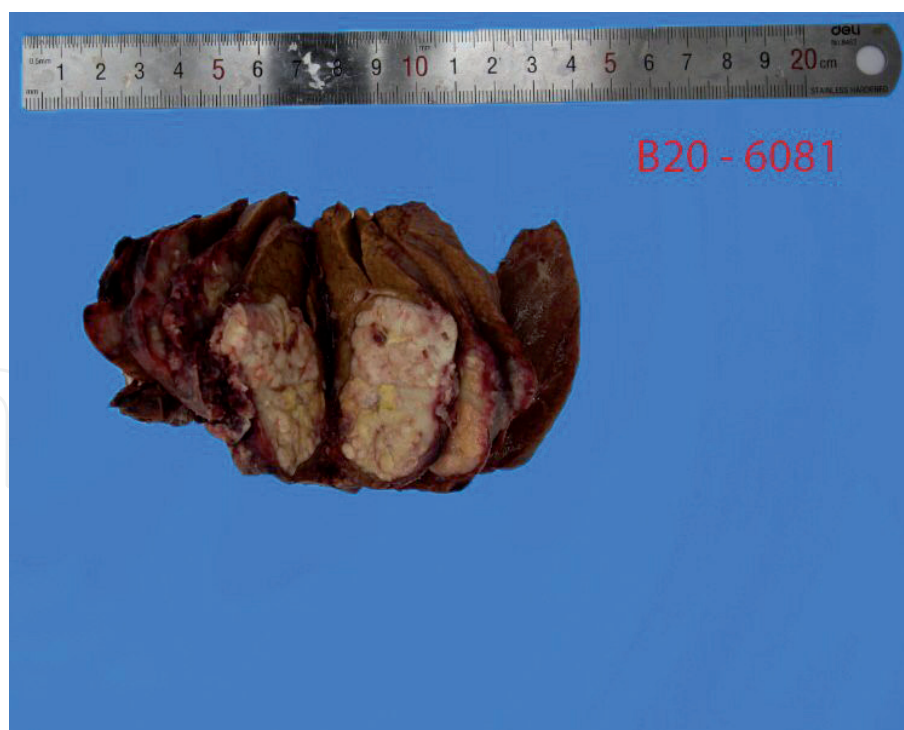


Figure 1.
Tumor with nodular border is seen in the brown-yellow noncirrhotic liver. The tumor is lobulated by fibrotic bands and has yellow areas.

that are histomorphologically SH-HCC, the presence of only steatosis in some cases, the presence of steatotic areas or cells in HCC are confusing points in the diagnosis of SH-HCC. Despite all this confusion, the steatohepatic area in HCC is diagnostic for SH-HCC. For the histopathological diagnosis of SH-HCC, the cut-off for steatohepatic features was described more than 5% of the tumor before but later moved to 50% [10, 39, 64, 72]. Hepatocellular carcinoma morphologically has 4 histological growth patterns: trabecular, solid (compact), pseudoaglandular (pseudoacinar), and macrotrabecular (trabecular thickness consisting of more than 10 cells) [1]. When SH-HCC is examined microscopically, a steatotic tumor is seen, separated from the generally steatotic liver (cirrhotic or non-cirrhotic) by a nodular or infiltrative margin. Large fat droplets are detected in tumor cells. Mallory-Denk bodies are detected in most tumors. Thin connective tissue growth (pericellular fibrosis), trabecular fibrosis, and randomly distributed collagen bundles surrounding tumor cells can be easily selected. Trabecular fibrosis, including randomly distributed collagen bundles in the tumor, and fibrosis surrounding tumor cells (pericellular) can be easily distinguished. Inflammation in the tumor is also remarkable. The inflammation is lymphocyte predominant with sparse plasma cells. More prominent neutrophil and lymphocyte infiltrations can be detected around tumor cells which contains Mallory-Denk bodies. The nuclei of tumor cells have atypia. This atypia is mild in well-differentiated tumors and quite pronounced in poorly differentiated tumors. They may even have bizarre nuclei suggested of sarcomas or pleomorphic carcinomas. However, mitotic activity is very low. Again, as in classical HCC and other subtypes, the tumor does not contain portal tracts and unpaired arteries can be seen (**Figures 2–4**) [1, 10, 45, 68, 72, 73]. The differentiation of SH-HCC is the same as that of classical HCC and is graded as well differentiated (Grade1: Tumor cells resemble mature hepatocytes with minimal to mild atypia), moderately differentiated (Grade 2: Distinctly malignant and histomorphology strongly suggests hepatocellular differentiation) and poorly differentiated (Grade 3: Clearly malignant, but histomorphology strongly suggests spectrum of

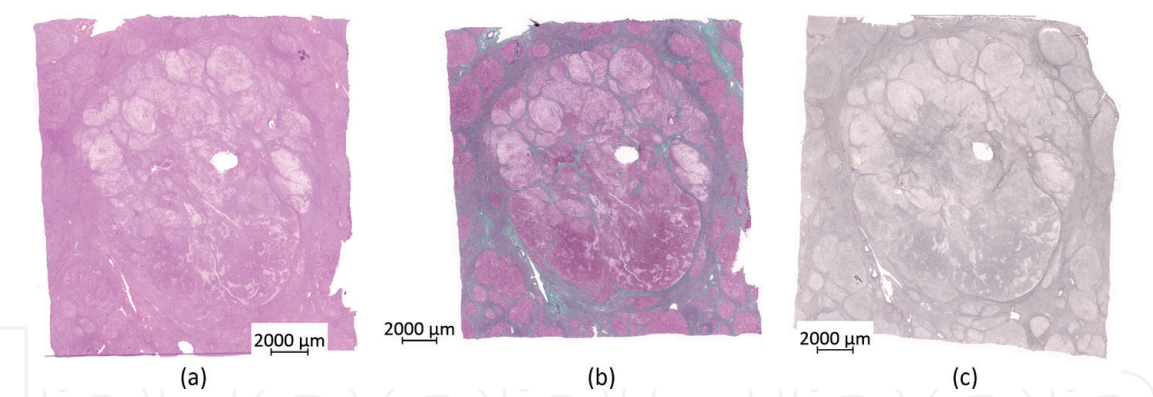


Figure 2. The tumor (pale area) is located in the center of the figure, surrounded by cirrhotic nodules (a, Hematoxylin and Eosin-H&E). Masson's trichrome (b) and reticulin (c) stains, both the tumor and its surrounding micronodular cirrhotic background are more prominent.

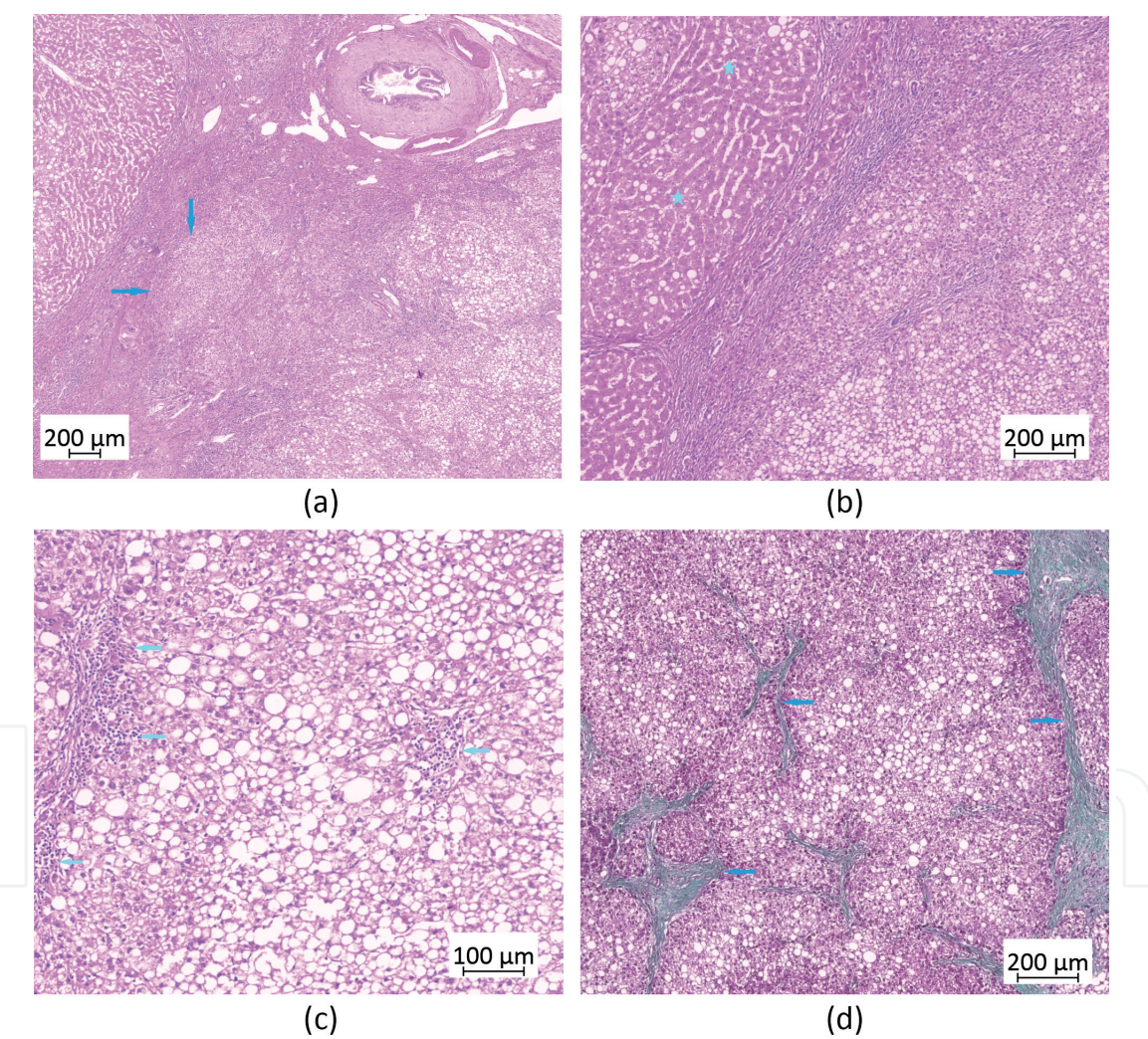


Figure 3. The parenchymal invasion area of steatohepatitic HCC is seen (arrows) (a), the tumor is seen adjacent to the fatty cirrhotic nodule (stars) (b), presence of large lipid droplets and chronic inflammation (arrows) (c), Masson's trichrome stain shows thick fibrous septa (arrows) (d).

poorly differentiated carcinomas) [1]. Most SH-HCCs are moderately differentiated and have a trabecular pattern and a pseudoglandular pattern [52].

Immunohistochemical antibodies are helpful and supportive in the diagnosis of HCC [74]. Although heppar-1, glypican-3, glutamine synthetase, arginase, heat shock protein-70 (HSP-70), β -catenin and sinusoidal staining with CD34,

canalicular staining pattern with polyclonal carcinoma embryogenic antigen (pCEA) and CD10 antibodies are used in the diagnosis of HCC, immune studies for SH-HCC are limited (**Figure 5**) [22, 68, 72, 75].

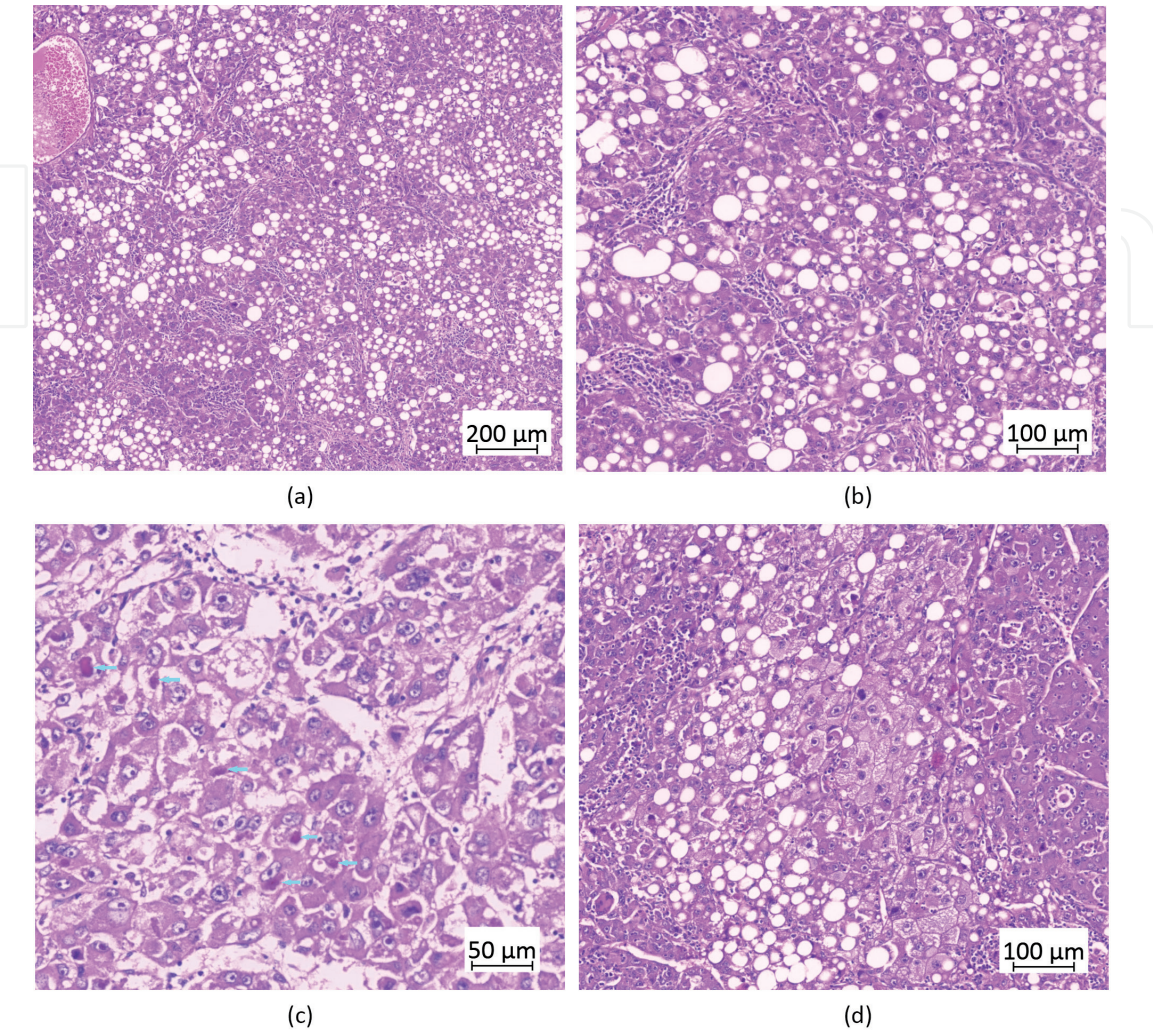


Figure 4.
Dense inflammation and fibrosis (a), pleomorphism (b), Mallory-Denk bodies (arrows) (c), and ballooning (cells with pale cytoplasm) (d) are seen in different areas of the tumor.

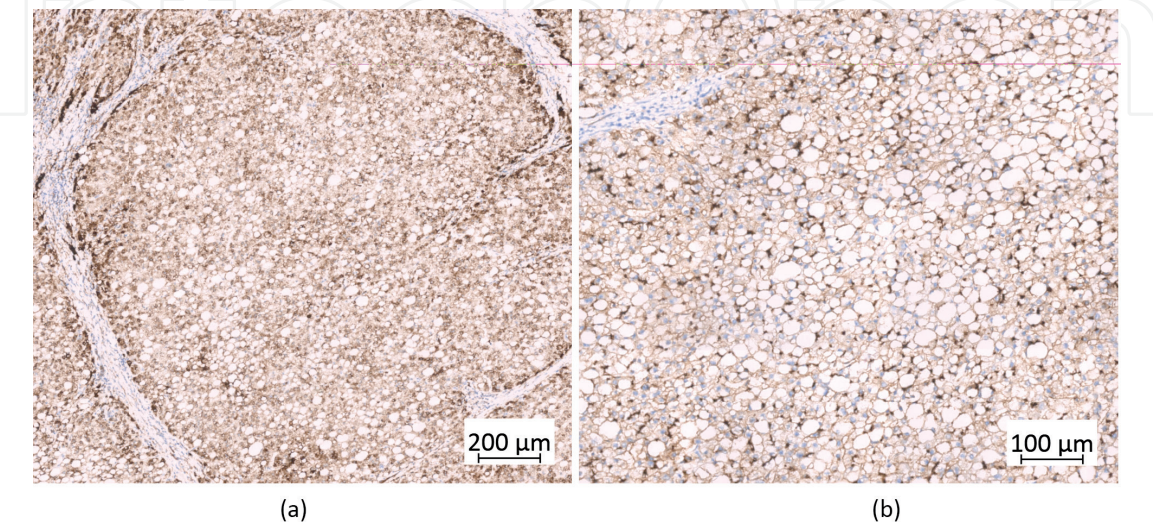


Figure 5.
Glutamine synthetase shows positive cytoplasmic staining (a), CD10 antibody shows positive canalicular staining (b).

The histopathological diagnosis of SH-HCC is usually easy in cases with explant and resection. However, tru-cut biopsies, which represent a small part of the tumor, may have diagnostic difficulties. These diagnostic difficulties are due to both the heterogeneity of the tumor and its similar morphological appearance to NAFLD with advanced fibrosis. A tru-cut biopsy from focal nodular hyperplasia (FNH) with fatty changes sometimes can be confused with a diagnosis of nodular and well differentiated SH-HCC. This difference between the diagnosis in the tru-cut biopsy and the resection material should not be interpreted as a misdiagnosis. Before interpreting it as an erroneous diagnosis, it should be remembered that this diagnostic difference is due to the heterogeneous and fat-containing nature of the tumor. Pathologists should remember that bile duct proliferation, presence of central scar (histologically and radiologically), and thick-walled abnormal vascular structures in the fibrous septa are more common in FNH when examining this tru-cut biopsy. Since fibrosis can be seen in both SH-HCC and FNH, it may not clarify the differential diagnosis. Non-invasive border and immunohistochemical staining (sinusoidal CD34 staining, glypican-3 positivity and diffuse glutamine synthetase staining) may be helpful in the differential diagnosis of steatohepatitis [8, 11, 68, 72]. Differentiation from classical HCC can be made by evaluating morphological and immune markers together [68]. In spite of all this, it would be appropriate to consult a pathologist experienced in liver pathology in cases where tumor specification could not be made.

The relationship between NAFLD, NASH, and HCC (especially SH-HCC) is now known. Adequate tumor sampling should be performed in resection materials, explants, particularly when identifying subtypes of large-diameter HCCs. It should be noted that classical HCC and other subtypes, including SH-HCC, have a heterogeneous histomorphology. While patients with metabolic syndrome, insulin resistance, obesity, fatty liver and steatohepatitis are followed up, careful radiological examination should be performed for SH-HCC that may develop from this background. In other words, the terminology of “neoplastic steatogenesis” should be kept in mind.


Author details

Emine Turkmen Samdanci

Pathology Department, School of Medicine, Inonu University, Malatya, Turkey

*Address all correspondence to: esamdanci@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] WHO Classification of Tumours Editorial Board. Digestive System Tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.;vol.1).
- [2] Calderaro J, Couchy G, Imbeaud S, Amaddeo G, Letouzé E, Blanc JF, Laurent C, Hajji Y, Azoulay D, Bioulac-Sage P, Nault JC, Zucman-Rossi JJ Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification. *Hepatol.* 2017 Oct;67(4):727-738.
- [3] Schirmacher P, Rogler CE, Dienes HP. Current pathogenetic and molecular concepts in viral liver carcinogenesis. *Virchows Arch B Cell Pathol Incl Mol Pathol.* 1993;63(2):71-89.
- [4] Popper H, Thung SN, McMahon BJ, Lanier AP, Hawkins I, Alberts SR. Evolution of hepatocellular carcinoma associated with chronic hepatitis B virus infection in Alaskan Eskimos *Arch Pathol Lab Med.* 1988 May;112(5):498-504.
- [5] El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011;365:1118-1127.
- [6] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;379:1245-1255.
- [7] Di Bisceglie AM, Carithers RL Jr, Gores GJ. Hepatocellular carcinoma. *Hepatology.* 1998 Oct;28(4):1161-5. doi: 10.1002/hep.510280436.
- [8] Goodman ZD, Terracciano LM, Wee A. Tumours and tumour-like lesions of the liver. In: MacSween's Pathology of the Liver 6th Edition, Churchill Livinstone, 2012. 761-851.
- [9] Van Treeck BJ, Mounajjed T, Moreira RK, Orujov M, Allende DS, Bellizzi AM, Lagana SM, Davila JI, Jessen E, Graham RP. Transcriptomic and Proteomic Analysis of Steatohepatitic Hepatocellular Carcinoma Reveals Novel Distinct Biologic Features. *Am J Clin Pathol.* 2021 Jan 4;155(1):87-96. doi: 10.1093/ajcp/aqaa114.
- [10] Vij M, Calderaro J. Pathologic and molecular features of hepatocellular carcinoma: An update *World J Hepatol.* 2021 Apr 27;13(4):393-410. doi: 10.4254/wjh.v13.i4.393.
- [11] Lefkowitz JH. In: Scheuer's Liver Biopsy Interpretation. 9th Edition. Elsevier. 2016.193-250
- [12] Calderaro J, Ziol M, Paradis V, Zucman-Rossi J. Molecular and histological correlations in liver cancer. *J Hepatol.* 2019 Sep;71(3):616-630. doi: 10.1016/j.jhep.2019.06.001. Epub 2019 Jun 10.
- [13] Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology.* 2004 Nov;127(5 Suppl 1):S35-50. doi: 10.1053/j.gastro.2004.09.014.
- [14] Nzeako UC, Goodman ZD, Ishak KG. Hepatocellular carcinoma in cirrhotic and noncirrhotic livers. A clinico-histopathologic study of 804 North American patients. *Am J Clin Pathol.* 1996 Jan;105(1):65-75. doi: 10.1093/ajcp/105.1.65.
- [15] Leung C, Yeoh SW, Patrick D, et al. Characteristics of hepatocellular carcinoma in cirrhotic and non-cirrhotic non-alcoholic fatty liver disease. *World J Gastroenterol.* 2015;21:1189-1196.
- [16] Aykutlu U, Argon A, Orman M, Ulukaya S, Zeytunlu M, Karasu Z,

- Günşar F, Nart D, Akarca U, Yilmaz F. Steatotic and Steatohepatic Hepatocellular Carcinomas: Features in a Series With Predominantly Viral Etiology. *Am J Surg Pathol*. 2021 Apr 8. doi: 10.1097/PAS.0000000000001714. Online ahead of print.
- [17] Gupta N, Rastogi A, Bihari C. Steatohepatic hepatocellular carcinoma-a case report with literature review. *Indian J Surg Oncol*. 2014 Jun;5(2):161-3. doi: 10.1007/s13193-014-0297-4. Epub 2014 Feb 27.
- [18] Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006 Oct;45(4):529-38. doi: 10.1016/j.jhep.2006.05.013. Epub 2006 Jun 23.
- [19] Hayashi PH, Di Bisceglie AM. The progression of hepatitis B- and C-infections to chronic liver disease and hepatocellular carcinoma: epidemiology and pathogenesis. *Med Clin North Am*. 2005 Mar;89(2):371-89. doi: 10.1016/j.mcna.2004.08.014.
- [20] Sun CA, Wu DM, Lin CC, Lu SN, You SL, Wang LY, Wu MH, Chen CJ. Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. *Am J Epidemiol*. 2003 Apr 15;157(8):674-82. doi: 10.1093/aje/kwg041.
- [21] Tan A, Yeh SH, Liu CH, Claudia C, Chen PJ. Viral hepatocarcinogenesis: from infection to cancer *Liver Int* . 2008 Feb;28(2):175-88. doi: 10.1111/j.1478-3231.2007.01652.x.
- [22] Ando S, Shibahara J, Hayashi A, Fukayama M. β -catenin alteration is rare in hepatocellular carcinoma with steatohepatic features: immunohistochemical and mutational study. *Virchows Arch*. 2015 Nov;467(5):535-42. doi: 10.1007/s00428-015-1836-2. Epub 2015 Aug 27.
- [23] Tornillo L, Carafa V, Richter J, Sauter G, Moch H, Minola E, Gambacorta M, Bianchi L, Vecchione R, Terracciano LM. Marked genetic similarities between hepatitis B virus-positive and hepatitis C virus-positive hepatocellular carcinomas. *J Pathol* . 2000 Nov;192(3):307-12. doi: 10.1002/1096-9896(2000)9999:9999<::AID-PATH706>3.0.CO;2-O.
- [24] Di Bisceglie AM, Lyra AC, Schwartz M, Reddy RK, Martin P, Gores G, Lok AS, Hussain KB, Gish R, Van Thiel DH, Younossi Z, Tong M, Hassanein T, Balart L, Fleckenstein J, Flamm S, Blei A, Befeler AS; Hepatitis C-related hepatocellular carcinoma in the United States: influence of ethnic status. *Liver Cancer Network. Am J Gastroenterol*. 2003 Sep;98(9):2060-3. doi: 10.1111/j.1572-0241.2003.t01-1-07641.x.
- [25] Liang TJ, Heller T. Pathogenesis of hepatitis C-associated hepatocellular carcinoma. *Gastroenterology*. 2004 Nov;127(5 Suppl 1):S62-71. doi: 10.1053/j.gastro.2004.09.017.
- [26] Block TM, Mehta AS, Fimmel CJ, Jordan R. Molecular viral oncology of hepatocellular carcinoma. *Oncogene*. 2003 Aug 11;22(33):5093-107. doi: 10.1038/sj.onc.1206557.
- [27] Qian GS, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, Wogan GN, Groopman JD. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. *Cancer Epidemiol Biomarkers Prev*. 1994 Jan-Feb;3(1):3-10.
- [28] Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, Gores G. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2016

Apr 14;2:16018. doi: 10.1038/nrdp.2016.18.

[29] Chen CH, Wang MH, Wang JH, Hung CH, Hu TH, Lee SC, Tung HD, Lee CM, Changchien CS, Chen PF, Hsu MC, Lu SN. Aflatoxin exposure and hepatitis C virus in advanced liver disease in a hepatitis C virus endemic area in Taiwan. *Am J Trop Med Hyg.* 2007 Oct;77(4):747-52.

[30] Zhang W, He H, Zang M, Wu Q, Zhao H, Lu LL, Ma P, Zheng H, Wang N, Zhang Y, He S, Chen X, Wu Z, Wang X, Cai J, Liu Z, Sun Z, Zeng YX, Qu C, Jiao Y. Genetic Features of Aflatoxin-Associated Hepatocellular Carcinoma. *Gastroenterology.* 2017 Jul;153(1):249-262.e2. doi: 10.1053/j.gastro.2017.03.024. Epub 2017 Mar 29

[31] Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. *Gastroenterology.* 2004 Nov;127(5):1372-80. doi: 10.1053/j.gastro.2004.07.020.

[32] Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. *J Hepatol.* 2019 Feb;70(2):284-293. doi: 10.1016/j.jhep.2018.10.008.

[33] Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology.* 2004 Nov;127(5 Suppl 1):S87-96. doi: 10.1053/j.gastro.2004.09.020.

[34] Stickel F, Schuppan D, Hahn EG, Seitz HK. Cocarcinogenic effects of alcohol in hepatocarcinogenesis. *Gut.* 2002 Jul;51(1):132-9. doi: 10.1136/gut.51.1.132.

[35] Lieber CS. Alcohol and the liver: 1994 update. *Gastroenterology.* 1994 Apr;106(4):1085-105. doi: 10.1016/0016-5085(94)90772-2.

[36] Ceni E, Mello T, Galli A. Pathogenesis of alcoholic liver disease: role of oxidative metabolism. *World J Gastroenterol.* 2014 Dec 21;20(47):17756-72. doi: 10.3748/wjg.v20.i47.17756.

[37] Nair S, Mason A, Eason J, Loss G, Perrillo RP. Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? *Hepatology.* 2002 Jul;36(1):150-5. doi: 10.1053/jhep.2002.33713.

[38] Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. *Gastroenterology.* 2004 Nov;127(5 Suppl 1):S79-86. doi: 10.1016/j.gastro.2004.09.019.

[39] Salomao M, Remotti H, Vaughan R, Siegel AB, Lefkowitz JH, Moreira RK. The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis. *Hum Pathol.* 2012; 43(5):737±46. Epub 2011/10/25. doi: 10.1016/j.humpath.2011.07.005 PMID: 22018903

[40] Jafri W, Kamran M. Hepatocellular Carcinoma in Asia: A Challenging Situation. *Euroasian J Hepatogastroenterol.* 2019 Jan-Jun;9(1):27-33. doi: 10.5005/jp-journals-10018-1292.

[41] Sotiropoulos GC, Molmenti EP, Lang H, Beckebaum S, Kaiser GM, Brokalaki EI, Frilling A, Malagó M, Neuhauser M, Broelsch CE. Surgery for hepatocellular carcinoma arising in hereditary hemochromatosis. *Eur Surg Res.* 2006;38(4):371-6. doi: 10.1159/000094532. Epub 2006 Jul 11

[42] Vautier G, Bomford AB, Portmann BC, Metivier E, Williams R, Ryder SD. p53 mutations in british patients with hepatocellular carcinoma: clustering in genetic hemochromatosis. *Gastroenterology.* 1999 Jul;117(1):154-60. doi: 10.1016/s0016-5085(99)70562-7.

- [43] Dragani TA. Risk of HCC: genetic heterogeneity and complex genetics. *J Hepatol.* 2010 Feb;52(2):252-7. doi: 10.1016/j.jhep.2009.11.015. Epub 2009 Nov 24.
- [44] Siegel AB, Zhu AX. Metabolic syndrome and hepatocellular carcinoma: two growing epidemics with a potential link. *Cancer.* 2009 Dec 15;115(24):5651-61. doi: 10.1002/cncr.24687.
- [45] Takahashi Y, Fukusato T. . Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol.* 2014 Nov 14;20(42):15539-48. doi: 10.3748/wjg.v20.i42.15539.
- [46] Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. *Nat Rev Gastroenterol Hepatol.* 2019 Jul;16(7):411-428. doi: 10.1038/s41575-019-0145-7.
- [47] McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. *Hepatology.* 2021 Jan;73 Suppl 1(Suppl 1):4-13. doi: 10.1002/hep.31288. Epub 2020 Nov 24.
- [48] Caldwell SH, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. *Gastroenterology.* 2004 Nov;127(5 Suppl 1):S97-103. doi: 10.1053/j.gastro.2004.09.021.
- [49] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003 Apr 24;348(17):1625-38. doi: 10.1056/NEJMoa021423.
- [50] Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73e84.
- [51] Degasperi E, Colombo M. Distinctive features of hepatocellular carcinoma in non-alcoholic fatty liver disease. *Lancet Gastroenterol Hepatol* 2016;1:156e64.
- [52] Jain D, Nayak NC, Kumaran V, Saigal S. Steatohepatitic hepatocellular carcinoma, a morphologic indicator of associated metabolic risk factors: a study from India. *Arch Pathol Lab Med.* 2013 Jul;137(7):961-6. doi: 10.5858/arpa.2012-0048-OA.
- [53] Alexander J, Torbenson M, Wu TT, Yeh MM. Non-alcoholic fatty liver disease contributes to hepatocarcinogenesis in non-cirrhotic liver: a clinical and pathological study. *J Gastroenterol Hepatol.* 2013 May;28(5):848-54. doi: 10.1111/jgh.12116.
- [54] Zhang X. NAFLD Related-HCC: The Relationship with Metabolic Disorders. *Adv Exp Med Biol.* 2018;1061:55-62. doi: 10.1007/978-981-10-8684-7_5.
- [55] Michelotti GA, Machado MV, Diehl AM. *Nat Rev NAFLD, NASH and liver cancer.* *Gastroenterol Hepatol.* 2013 Nov;10(11):656-65. doi: 10.1038/nrgastro.2013.183. Epub 2013 Oct 1.
- [56] Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; 34: 274-85.
- [57] Shibahara J, Ando S, Sakamoto Y, Kokudo N, Fukayama M. Hepatocellular carcinoma with steatohepatitic features: a clinicopathological study of Japanese patients. *Histopathology.* 2014 Jun;64(7):951-62. doi: 10.1111/his.12343. Epub 2014 Feb 5.
- [58] Yeh MM, Liu Y, Torbenson M. Steatohepatitic variant of hepatocellular carcinoma in the absence of metabolic

- syndrome or background steatosis: a clinical, pathological, and genetic study. *Hum Pathol.* 2015 Nov;46(11):1769-75. doi: 10.1016/j.humpath.2015.07.018. Epub 2015 Aug 4
- [59] Dyson J, Jacques B, Chattopadhyay D, et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. *J Hepatol* 2014; 60: 110-17.
- [60] Baffy G, Brunt EM, Caldwell SH (2012) Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol* 56:1384-1391. doi:10.1016/j.jhep.2011.10.027
- [61] Lee JS, Yoo JE, Kim H, Rhee H, Koh MJ, Nahm JH, Choi JS, Lee KH, Park YN. Tumor stroma with senescence-associated secretory phenotype in steatohepatitic hepatocellular carcinoma. *PLoS One.* 2017 Mar 8;12(3):e0171922. doi: 10.1371/journal.pone.0171922. eCollection 2017.
- [62] Ikeda K, Saitoh S, Koida I, Tsubota A, Arase Y, Chayama K, Kumada H. Imaging diagnosis of small hepatocellular carcinoma. *Hepatology.* 1994 Jul;20(1 Pt 1):82-7. doi: 10.1016/0270-9139(94)90137-6.
- [63] Inui S, Kondo H, Tanahashi Y, Fukukura Y, Sano K, Morisaka H, Saito K, Kondo F, Fukusato T, Furui S, Oba H. Steatohepatitic hepatocellular carcinoma: imaging findings with clinicopathological correlation. *Clin Radiol.* 2021 Feb;76(2):160.e15-160.e25. doi: 10.1016/j.crad.2020.09.011. Epub 2020 Oct 10.
- [64] Torbenson MS. Hepatocellular carcinoma: making sense of morphological heterogeneity, growth patterns, and subtypes. *Hum Pathol.* 2020 Dec 30:S0046-8177(20)30262-8. doi: 10.1016/j.humpath.2020.12.009. Online ahead of print.
- [65] Torbenson M, Washington K. Pathology of liver disease: advances in the last 50 years. *Hum Pathol* 2020 Jan;95:78e98.
- [66] Kojiro M. Pathology of hepatocellular carcinoma. India: Replika Press Pvt. Ltd.; 2006. p. 174.
- [67] Yeh CN, Lee WC, Jeng LB, Chen MF. Pedunculated hepatocellular carcinoma: clinicopathologic study of 18 surgically resected cases. *World J Surg* 2002;26:1133e8.
- [68] Olofson AM, Gonzalo DH, Chang M, Liu X. Steatohepatitic Variant of Hepatocellular Carcinoma: A Focused Review. *Gastroenterology Res.* 2018 Dec;11(6):391-396. doi: 10.14740/gr1110. Epub 2018 Dec 17.
- [69] Qin J, Higashi T, Nakagawa S, Fujiwara N, Yamashita YI, Beppu T, Baba H, Kobayashi M, Kumada H, Gunasekaran G, Schiano TD, Thung SN, Fiel MI, Hoshida Y, Ward SC. Steatohepatitic Variant of Hepatocellular Carcinoma Is Associated With Both Alcoholic Steatohepatitis and Nonalcoholic Steatohepatitis: A Study of 2 Cohorts With Molecular Insights. *Am J Surg Pathol.* 2020 Oct;44(10):1406-1412. doi: 10.1097/PAS.0000000000001533
- [70] Hoshida Y, Nijman SM, Kobayashi M, et al. Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. *Cancer Res.* 2009;69:7385-7392.
- [71] Samdanci ET, Akatli AN, Soyulu NK. Clinicopathological Features of Two Extremely Rare Hepatocellular Carcinoma Variants: a Brief Review of Fibrolamellar and Scirrhous Hepatocellular Carcinoma. *J Gastrointest Cancer.* 2020 Dec;51(4):1187-1192. doi: 10.1007/s12029-020-00500-1.
- [72] Salomao M, Yu WM, Brown Jr RS, Emond JC, Lefkowitz JH.

Steatohepatic hepatocellular carcinoma (SH-HCC): a distinctive histological variant of HCC in hepatitis C virus-related cirrhosis with associated NAFLD/NASH. *Am J Surg Pathol* 2010;34:1630-6.

[73] Jabbour TE, Lagana SM, Lee H. Update on hepatocellular carcinoma: Pathologists' review *World J Gastroenterol*, 2019 Apr 14;25(14):1653-1665.

[74] Yasir S, Chen ZE, Said S, Wu TT, Torbenson M. Biopsies of hepatocellular carcinoma with no reticulin loss: an important diagnostic pitfall. *Hum Pathol*. 2021 Jan;107:20-28. doi: 10.1016/j.humpath.2020.09.015. Epub 2020 Oct 8.

[75] Taniai M, Hashimoto E, Tobari M, Kodama K, Tokushige K, Yamamoto M, Takayama T, Sugitani M, Sano K, Kondo F, Fukusato T. Clinicopathological investigation of steatohepatic hepatocellular carcinoma: A multicenter study using immunohistochemical analysis of adenoma-related markers. *Hepatol Res*. 2018 Nov;48(12):947-955. doi: 10.1111/hepr.13203. Epub 2018 Oct 15.