# Steatohepatitic hepatocellular carcinoma: Two cases report with literature review

**Dao Thi Huyen, Le Thi Thanh Xuan, Le Duy Dung**
**Le Thi Trang, Le Minh Son, Ngo Thi Minh Hanh**

*108 Military Central Hospital*

**Summary**

Steatohepatitic hepatocellular carcinoma (SH-HCC) is one of the most common hepatocellular carcinoma (HCC) subtypes, with a frequency of 5-20%. These tumor are well-differentiated and show distinct histologic features resembling steatohepatitis: Macrovesicular steatosis, inflammation, balloon cells, Mallory-Denk bodies and pericellular fibrosis. Because of their similar characteristics, distinguishing SH-HCC from background fatty liver can be a diagnostic challenge. The histology of SH-HCC has been described in resection specimens. Unfortunately, diagnostic criteria to aid in the evaluation of biopsy specimens have not been well established; therefore, the diagnosis of SH-HCC in biopsies remains challenging. On diagnostic imaging tests, SH-HCC may be difficult to distinguish from surrounding liver parenchyma in patients with severe hepatic steatosis or other fat-containing liver lesions such as angiomyolipoma or clear cell HCC. We report two cases of SH-HCC that we documented along with diagnostic difficulties.

*Keywords:* Steatohepatitic hepatocellular carcinoma, hepatocellular carcinoma.

## 1. Background

HCC have a variety of morphological patterns, about 35% of which form distinct subtypes, representing distinct clinicopathological/molecular entities [1]. The observation that there can be fat in a hepatocellular carcinoma has been known for a very long time, but a paper by Salomao et al (2010) was the first to recognize SH-HCC as a distinct histological variant [6]. In the 2019 5$^{th}$ edition of the WHO classification, approximately 65% of all HCCs are classified as not-otherwise-specified HCC (NOS-HCC), without any distinguishing histopathologic features, whereas the remaining HCCs are classified into the following subtypes: Steatohepatitic, clear cell, macrotrabecular-massive, chromophobe, fibrolamellar, neutrophil-rich, and lymphocyte-rich HCCs. In this latest classification, SH-HCC is officially recognized as one of eight subtypes of HCC. SH-HCC shows macrovesicular steatosis, balloon cells, Mallory hyaline, inflammation and fibrosis. Analysis of the clinical correlates showed cases with a SH-HCC morphology were highly enriched for features of the metabolic syndrome and the background livers were highly enriched for metabolic associated fatty liver disease (MAFLD). The strongest molecular correlates to-date include a low frequency of *CTNNB1* mutations and possible activation of the IL6/JAK/STAT pathway [1], [2], [5], [6], [7]. Subtypes of HCC are important for 2 primary reasons: They help improve diagnostic accuracy, as different subtypes have their own diagnostic pitfalls; they are an important building block to the personalization of patient care, as subtypes are enriched for shared genetic changes and biological associations [3].

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***Correspondence to**: Dao Thi Huyen, Department of Pathology, 108 Military Central Hospital*
***Email:** daothihuyen1802@gmail.com*

## 2. Case presentation

### *2.1. Case 1*

A 63-year-old-male patient who is a known diabetic type II and had been on regular medication.

Patient presented with complaints of pain in the upper abdomen for last 2 months. Ultrasound and computed tomography (CT) scan suggested a mass of 5.5x4.5x4.5cm in the segment VI of the liver, which had a typical image of HCC. The HbsAg had a positive value while the HCV Ab had a negative value. Tumor markers, such as AFP, CA19-9, and CEA, were all negative. A diagnostic biopsy was performed on the patient before surgery. The pre-operative pathological diagnosis was steatohepatitic hepatocellular carcinoma after combining the results of Hematoxylin and eosin (HE) and immunohistochemistry stain. After that, he underwent partial hepatectomy.

*Histopathological examination*

*Gross examination:* Right hepatectomy specimen measured 16x10×7cm. Outer surface was well encapsulated. Serial sections revealed a tumor mass measuring 5x5x4.5cm located 0.5cm away from the closest resected margin. The cut surface was not homogeneous, with brown mixed with bright yellow areas. *Microscopic Examination:* Sections from the tumor nodules showed normal HCC areas mixed with HCC areas with characteristics of steatohepatitis, including: Macrovesicular steatosis, many foci of lobular inflammation, balloon cells, occasional Mallory-Denk bodies and thin fibrous bands in tumor tissue. The steatohepatitic morphology involved approximately 70% of the tumor area. In view of the characteristic morphological features a diagnosis of steatohepatitic hepatocellular carcinoma was made.

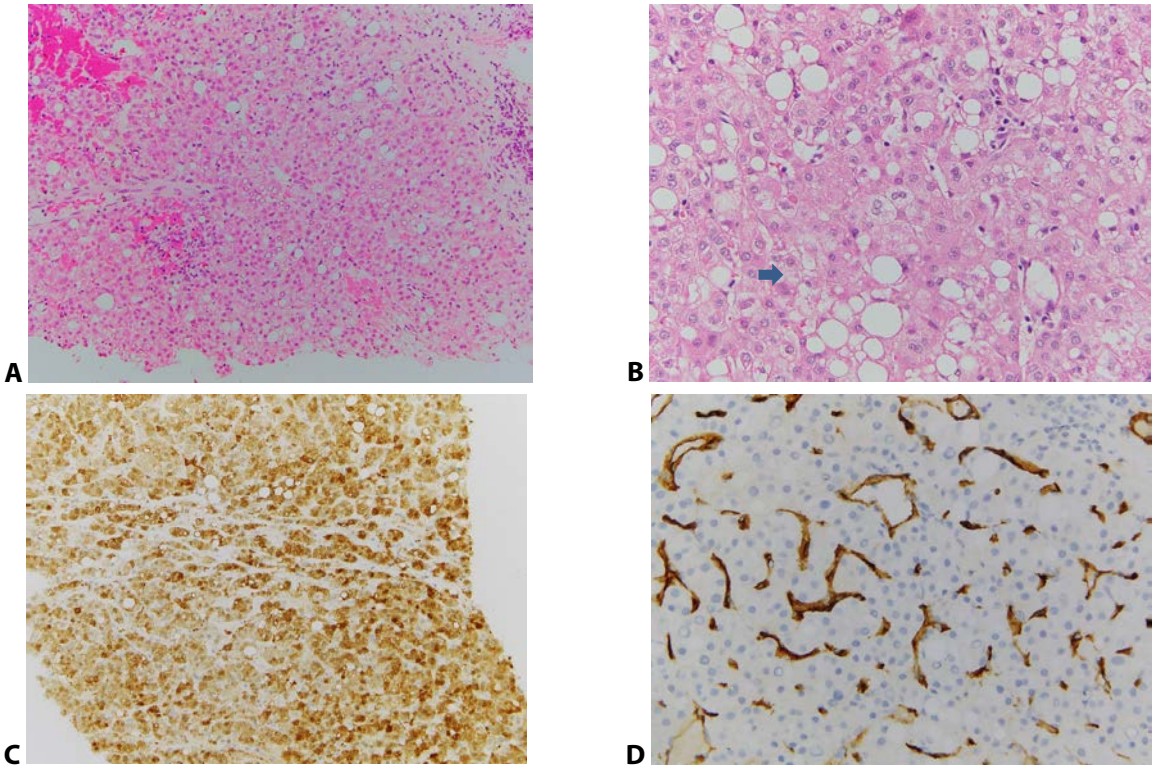


**Figure 1.** The histopathological and immunohistochemistry finding of case 1. A: (HEx200) Core biopsy sample. Sinusoidal dilatation and congestion, hepatic macrosteatosis in the tumor make it difficult to assess the number of cell rows per liver trabeculae. B: (HEx400) Mallory-dense body (blue arrow) C, D: Immunohistochemical staining images. C. Glutamine Synthetase (GS): strong cytoplasmic staining in almost tumor cells, without a map-like pattern (diffuse homogeneous pattern). D. CD34: CD34 immunostaining highlights capillarization of sinusoids (the complete CD34 staining pattern).

### *2.2. Case 2*

A 62-year-old male patient had episodes of yellow eyes, jaundice, and pain in the right upper quadrant two years ago. The patient underwent a medical examination and was discovered to have liver tumors/hepatitis B. After that he received symptomatic treatment and disease management at the provincial hospital. A follow-up examination revealed that the liver tumor had grown in size this time. Therefore, patient was transferred to the 108 Military Central Hospital for intensive treatment. The CT scan showed a tumor of 5cm in lower segments V-VIII of the liver, suspected of angiomyolipoma. Meanwhile, the magnetic resonance imaging (MRI) scan suggested a slow progression of Fibromellar HCC. Pathological examination of a small biopsy revealed that the entire biopsy piece was tumor necrosis. The patient underwent partial hepatectomy and postoperative pathological examination.

*Histopathological examination*

*Gross examination:* Right hepatectomy specimen measured 17.5x16x8cm. Outer surface was well encapsulated. Serial sections revealed a tumor mass measuring 6x5x5 cm located 1 cm away from the closest resected margin. The cut surface was not homogeneous, with a necrotic area (about 30%) mixed with a focal areas of hemorrhage, and yellow areas. The tumor was divided into lobes by the thick fibrous bands. Microscopic Examination: On HE-stained slides, large areas within the neoplasm show prominent macrovesicular steatosis, ballooning cell and foci of inflammation seen occupying > 50% of the tumor area. The tumor tissue has extensive necrosis, with approximately 30%. Masson's Trichrome stain highlight thick, irregular bands of fibrous tissue with a haphazard distribution or a pericellular "chicken-wire" pattern with thin, delicate fibrous bands interweaving between tumor cells. Finally, the postoperative pathological diagnosis was steatohepatitic hepatocellular carcinoma.

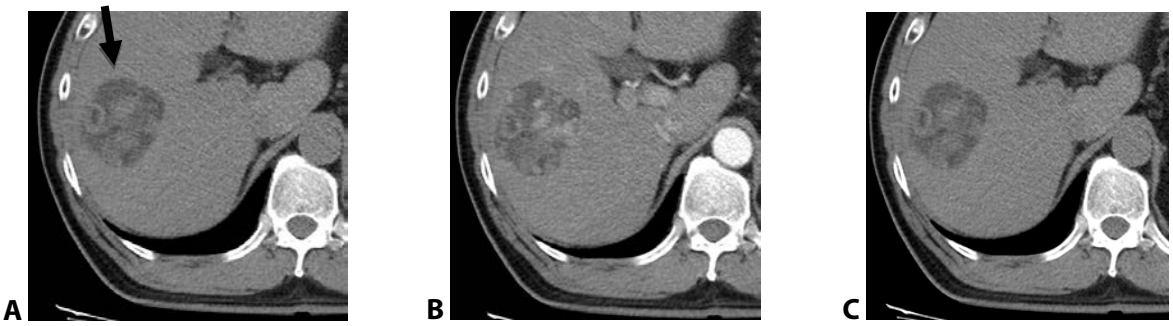


**Figure 2.** CT scan finding of case 2. A. Non-enhanced CT. A tumor (arrow) of 52x56x52mm was discovered in subsegments V, VIII, and a small portion VI. The tumor has clear boundaries, multi-arc margins, decreased density before injection, and some areas have fat density. B, C. Arterial phase and portal phase: It showed heterogeneous enhancement after contrast administration.

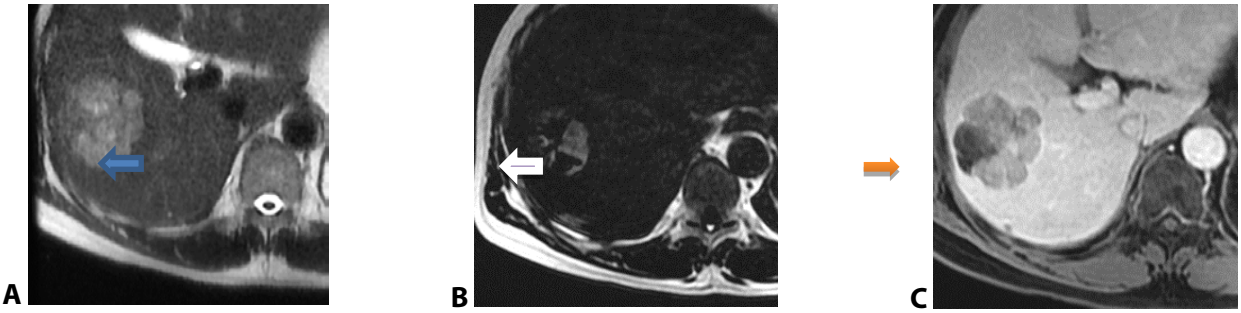


**Figure 3.** MRI scan finding of case 2. A. The tumor structure is clearly bordered and lobulated on T2W (arrow). B. Fatty components in tumor on FAT T1W 3D (arrow). C. Necrotic components do not enhance after injection magnetic resonance imaging contrast agent primovist (arrow).

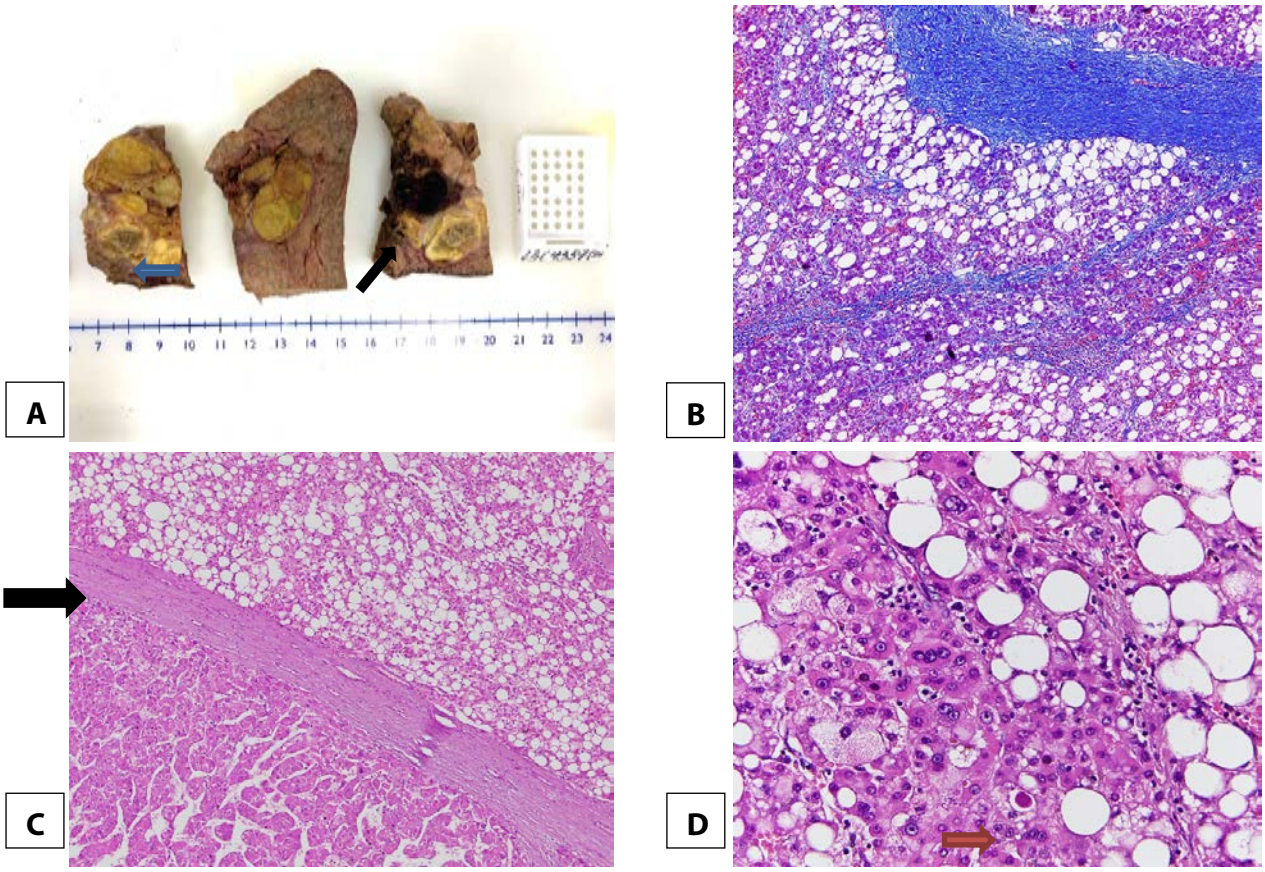


**Figure 4.** Macroscopic and microscopic findings of the tumor. A. Gross appearance of the tumor. The cut surface was not homogeneous, with a necrotic area about 30% (blue arrow) mixed with a focal areas of hemorrhage, and yellow areas. The thick fibrous bands (black arrow) separated the tumor into lobes. B. A photomicrograph of Masson's trichrome-stained sections of typical SH-HCC. trichrome stain highlights thick, irregular bands of fibrous tissue with a haphazard distribution or a pericellular "chicken-wire" pattern with thin, delicate fibrous bands interweaving between tumor cells C, D. Histopathological features in HE images. The NOS- HCC area and SH-HCC are separated by a thick fibrous band (black arrow) in the same tumor (C, HEx100). Tumor cells have feature of macrovesicular steatosis, Mallory-Denk bodies (orange arrow), balloon cell (D, HEx400).

## 3. Discussion

The 2019, 5th edition of the WHO classification of digestive system tumors estimates that up to 35% of HCC can be classified as one of eight subtypes, including: Steatohepatitic, clear cell, macrotrabecular-massive, scirrhous, chromophobe, fibrolamellar, neutrophil-rich, and lymphocyte-rich HCCs. This is the first time SH-HCC has been officially recognized by WHO as a distinct subtype of HCC [1]. The observation that there can be fat in a HCC has been known for a very long time, but in 2010, Salomao et al were the first to describe SH-HCC as a distinct histological variant [6]. SH-HCC was originally defined as having the ordinary features of steatohepatitis, including: Macrovesicular steatosis, inflammation (neutrophils and lymphocytes), balloon cells, Mallory-Denk bodies, and fibrosis. The pattern of fibrosis was reported as trabecular (thick bundles of fibrous tissue within the tumor) or pericellular (thin strands of fibrosis with a "chicken-wire" appearance) [6]. The percentage of the tumor with these findings that was needed to qualify for SH-HCC was originally defined as ≥ 5% [6], but the cut-off was later moved to ≥ 50% by the same group of authors, in which at least 3 (usually all) SH features mentioned above (no specific

minimal amount of each feature was required for diagnosis) were present [7]. Currently, WHO has not defined the best "cut-off" point to confirm the diagnosis but a higher cut off, such as 50% seems more likely to capture a biologically/molecularly cohesive set of cases [1], [6], [7], [8]. When tumor has multiple nodules, cases were classified as “SH-HCC” if at least one nodule met the above criteria [7]. Almost all studies to date have identified the association between SH-HCC and the metabolic syndrome (obesity, hypertension, diabetes, and hyperlipidemia). On the other hand, alcoholic liver disease was identified as a likely risk factor early on, but subsequent data were inconsistent, with some studies showing an association, and others showing the opposite. Studies have consistently shown that there is no difference in overall survival and disease-free survival for SH-HCC after resection compared to conventional HCC [8]. Several large studies show that SH-HCC tends to be smaller than regular HCC, although other studies find no association with size or even larger size. Other tentative associations found in larger studies include earlier tumor stage, lower serum AFP levels, and a higher frequency of bile duct invasion while vascular invasion is less common. The key molecular features include IL-6/JAK/STAT activation, and lower frequency of *CTNNB1*, *TERT*, and *TP53* mutations compared to other HCCs [1], [2], [3], [4], [8].

The two cases we report here have the typical characteristics of SH-HCC mentioned above, and were diagnosed directly by HE-stained slides of post-operative specimens. The WHO has recognized this subtype since 2019 and with limited published data, we face certain challenges when diagnosing, especially on small biopsy samples. Diagnosis of SH-HCC on biopsy may be made based on a combination of features such as absence of portal tracts, isolated arterioles, widened trabecular plates and capillarization of sinusoids [5]. In additon, invasion into nearby portal tracts by SH-HCC is a useful histological feature on resection specimens; however, this feature may not be present on limited biopsy specimens. Although isolated arterioles are often used as histological clues for the diagnosis of hepatocellular neoplasms, morphologically similar central arterialization can be seen in steatohepatitis [5]. The first case had a typical CT image of HCC, but the entire small biopsy sample was taken into tumor tissue with macrosteatotic cell, sinusoidal dilatation and congestion which make it difficult to assess the number of cell rows per liver trabeculae and overlap features of steatohepatitis. In this setting, a reticulin stain is not particularly helpful in distinguishing benign fatty liver parenchyma from SH-HCC due to the presence of intratumor pericellular fibrosis which can complicate the assessment of liver plate thickness, and the loss of reticulin staining that can occur in benign fatty liver tissue [5]. To support diagnosis, we used markers CD34, GP3, GS (HSP70 was not available at the time). The results show that GS expresses moderate to stronger cytoplasmic staining in more than 90% of lesional cells, without a maplike pattern and CD34 highlights capillarization of sinusoids, with the complete CD34 staining pattern; Glupican 3 is negative. Although immunohistochemical studies to characterize SH-HCC are relatively limited [8] and these markers may not be sensitive, the GPC-3/GS/HSP-70 panel should be obtained if there is any question regarding the benign or malignant status of “steatohepatitic” regions [6]. Careful review of histomorphology and stringent application of cytomorphologic criteria of malignancy, and clinical and imaging correlation is essential to establish a firm diagnosis of well-differentiated HCC [2]. In this case, immunohistochemical results helped confirm the diagnosis of “Steatohepatitic hepatocellular carcinoma”.

In the second case, we had no difficulty in pathologic diagnosis, however, on imaging diagnosis, we encountered a bit of difficulty and could not completely confirm the diagnosis. Radiologists considered Fibrolamellar HCC on the MRI scan as the tumor proliferated thick, irregular bands of fibrous tissue with a haphazard distribution. However, the CT scan suggested that this was a tumor of angiomyolipoma due to the presence of fat in the tumor. Intratumoral fibrosis has not been a

requirement for the diagnosis of SH-HCC in most studies, but most SH-HCC have at least mild pericellular fibrosis, that ranges from 75% to 100%. It has 2 distinct patterns of intratumoral fibrosis in SH-HCC: Pericellular fibrosis, equivalent to the classic fibrosis pattern seen with steatohepatitis in the non-neoplastic liver and thick bundles of fibrosis more typical of the scirrhous pattern of HCC. Unfortunately, the pattern of fibrosis may be occur in some other tumors of the liver. So, SH-HCC may be confused with FNH, Fibrolamellar HCC or Scirrhous HCC [4], [5]. On the other hand, SH-HCCC may also be difficult to differentiate from other fat-containing liver lesions such as angiomyolipoma or clear cell HCC due to the fat content in the tumor. Fat in mass is not a specific sign of steatohepatitic HCCs, and the noninvasive diagnosis of steatohepatitic HCCs should be considered in the appropriate clinical context only (e.g, HCC showing fat in mass in patients with steatosis) [4]. In these cases, a biopsy for preoperative pathology testing is very necessary.

## 4. Conclusion

Steatohepatitic hepatocellular carcinoma is the most common subtype of HCC, recognized by WHO 2019. It has a unique morphology, characterized by varying degrees of steatohepatitic features: Macrovesicular steatosis, balloon cells, Mallory hyaline, inflammation, and fibrosis. Understanding the histopathological characteristics of SH-HCC are essential for pathologists to avoid pitfalls in diagnosis. In this paper, we present two case reports with diagnostic difficulties that contribute to enriching the total number of SH-HCC cases in Viet Nam and the world while providing additional clinical and histopathological data for this subtype.

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