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Steatohepatitic Variant of Hepatocellular Carcinoma-Incidental and Rare Finding on Autopsy

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Abstract **Case Report**

Hepatocellular carcinoma (HCC) constitutes 70-85% of all primary liver tumors and ranks as the fifth most common cancer and the second most common cause of cancer deaths worldwide [1, 2]. Steatohepatitic hepatocellular carcinoma (SH-HCC) is a variant of hepatocellular carcinoma (HCC) with established association with nonalcoholic steatohepatitis (NASH), while its association with alcoholic steatohepatitis (ASH) is unclear. The steatohepatitic variant of HCC (SH-HCC) typically presents in patients with metabolic risk factors and either cirrhotic or non-cirrhotic NAFLD and shares many of the histological features found in non-alcoholic steatohepatitis (NASH). It accounts for 5-20% of HCCs, and the background liver may show steatohepatitis [3, 4]. We present a case of a 53-year-old deceased male. Part of liver was received after autopsy, which appeared nodular grossly and histopathological diagnosis of Steatohepatitic variant of Hepatocellular Carcinoma was made.

Keywords: Hepatocellular carcinoma (HCC), liver tumors, cancer, alcoholic steatohepatitis (ASH).

INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes 70-85% of all primary liver tumors and ranks as the fifth most common cancer and the second most common cause of cancer deaths worldwide [1, 2]. HCCs mostly arise in a background of chronic liver disease, the most common etiologies being hepatitis B, hepatitis C, chronic alcohol abuse, non-alcoholic fatty liver disease, inherited diseases (e.g. hemochromatosis and glycogen storage disease), and exogenous substances, such as aflatoxin B1 [5, 6]. A minority of HCCs develop in a background of normal or near-normal liver, the most common setting being HCCs arising in hepatocellular adenomas [5, 7, 8].

Histologically, conventional HCCs demonstrate hepatocytic differentiation (i.e., the tumor cells resemble the appearance of hepatocytes with varying degrees of cyto-architectural atypia). The typical HCC tumor cells are cuboidal in shape, contain abundant eosinophilic cytoplasm with centrally located nuclei, and are frequently arranged in a trabecular pattern of variable thickness that at least vaguely recapitulates the trabecular architecture of the normal hepatic acinus, with very little intratumoral stroma. The steatohepatitic variant of HCC, or steatohepatitic HCC, demonstrates the histological features of steatohepatitis within the tumor, including steatosis, ballooning of tumor cells, inflammation and the typical "chicken-wire pattern" pericellular fibrosis [3, 4, 9, 10]. It accounts for 5-20% of HCCs, and the background liver may show steatohepatitis [3, 4]. Although this variant has been shown to be less often associated with vascular invasion or satellite nodules, its prognosis seems to be similar to conventional HCCs so far [9]. The key molecular features include IL-6/JAK/STAT activation, and lower frequency of *CTNNB1*, *TERT*, and *TP53* mutations compared to other HCCs [9].

CASE REPORT

Viscera of 45yr old deceased male with alleged history of drug overdose was sent to the department of the pathology.

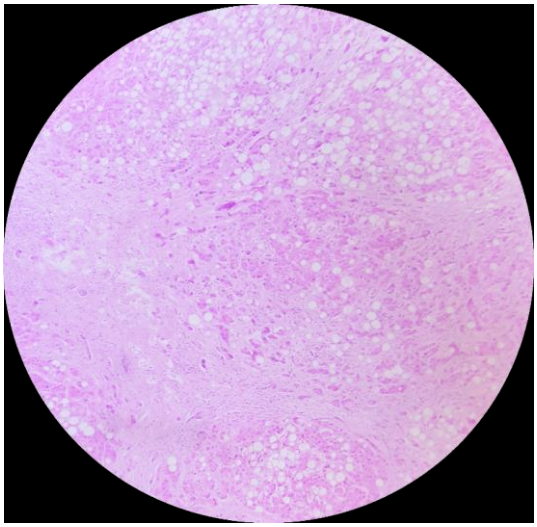
Gross Examination: Part of Liver
Gross weight: 50gms
Dimensions: 6.5x4x2.5cm.
External surface: Nodular and cut surface is yellowish.

External surface- Nodular

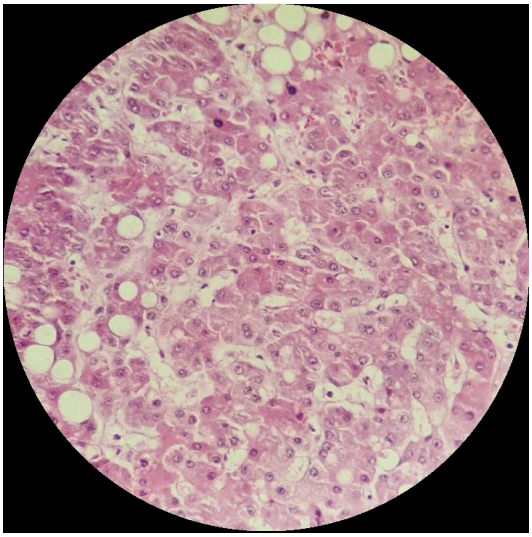
Microscopic Examination

Sections examined show extensive intratumoral steatosis, hepatocyte ballooning and Mallory-Denk bodies and perisinusoidal "chicken-wire pattern" fibrosis. Thickened hepatic cell plates, invasion of the portal tract by the tumor cells also noted.

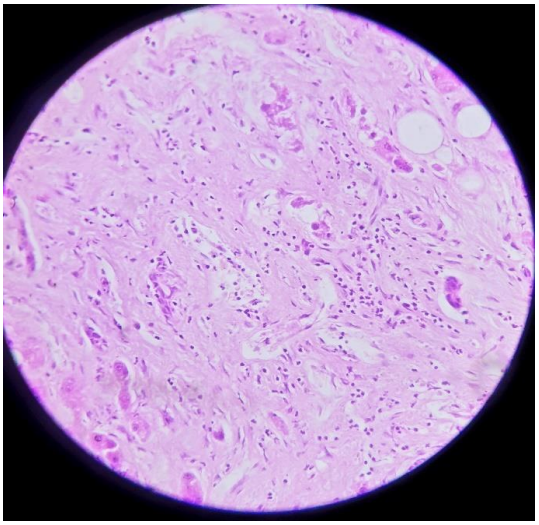
Histopathological diagnosis of Steatohepatitic variant of Hepatocellular Carcinoma was made.



Hepatic parenchyma with extensive steatosis (H&E, × 40)



Thickened hepatic cell plates (H&E, ×40)



Invasion of the portal tract by the tumor cells (H&E, ×40)

DISCUSSION

HCC has a striking variety of histological variants including fibrolamellar, scirrhous, clear cell, biphenotypic, lymphocyte-rich, sarcomatoid, cirrhotomimetic, granulocyte colony-stimulating factor (G-CSF) producing, and the most recently described, SH-HCC. In 2010, Salomao *et al*., [4] first recognized SH-HCC in explant livers with chronic HCV infection and noted that it shared many of the morphological features of steatohepatitis, such as large droplet steatosis, ballooning malignant hepatocytes, Mallory-Denk bodies and pericellular fibrosis [4]. They reported that SH-HCC was present in 35% of HCC cases in explant livers with chronic HCV infection, and of these cases, two-thirds of the patients possessed risk factors for NAFLD [4]. Furthermore, the non-neoplastic background liver in 63% of the SH-HCC cases demonstrated NAFLD-like changes superimposed on those of chronic HCV infection. From these fndings, they proposed a potential link between NAFLD in the setting of HCV infection and the subsequent development of SH-HCC [4]. SH-HCC was found more often in patients with either non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH) compared to those with other underlying chronic liver diseases. In addition, patients with SH-HCC were found to have a higher prevalence of metabolic syndrome risk factors when compared to patients with conventional HCC. These findings further supported a potential causative association between SH-HCC, metabolic syndrome and steatohepatitis [3].

Macroscopically, resected SH-HCC tends to be slightly more golden-yellow in color compared to other HCC variants due to the relatively greater degree of fbrosis and steatosis [3]. Tumors are nodular, well-demarcated and range in size from 0.5 to 11 cm [3, 4]. SH-HCC is defined by the presence of features typical of steatohepatitis including large-droplet steatosis, fibrosis, ballooning of malignant hepatocytes, Mallory-

Denk bodies and inlammation. These features may be present in varying combinations; however, they should constitute ≥ 5% of the tumor volume. SH-HCC often exhibits an infiltrative growth pattern into nearby portal tracts. Mitotic activity is minimal. The fibrosis pattern of SH-HCC can include a trabecular pattern with 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 [4]. As in other variants of HCC, the absence of portal tracts in the lesion remains a key feature.

The diagnosis of SH-HCC on biopsy material is extremely challenging because these tumors commonly occur in a background of steatohepatitis, which shares multiple overlapping features with SH-HCC, including minimal to mild pleomorphism. 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. One recently proposed explanation for the steatotic phenotype of SH-HCC and its association with fatty liver disease may lie in how cancer cells selectively evolve to survive in a lipid-rich environment as in patients with NAFLD. Selective metabolic reprogramming of cancer cells to adapt to local environmental conditions is a hallmark of carcinogenesis. Although fatty acid oxidation is often used by cancer cells to generate energy, excessive fatty acid oxidation due to high intracellular fat levels can lead to metabolic stress and eventually lipotoxic cell death, e.g. ballooning degeneration [5]. In patients with NASH, extremely high levels of fatty acids from dietary intake and lipolysis of visceral adipose tissue can lead to lipotoxic hepatocyte death. This lipotoxic effect is an important promoter of NASH-associated HCC, and thus, HCC must adapt in order to survive in such a lipid-rich environment.

CONCLUSION

SH-HCC accounts for 5-20% of HCCs and the background liver show steatohepatitis .As the incidence and prevalence of obesity and metabolic syndrome continue to rise worldwide, NAFLD has replaced viral disease and alcohol abuse as the main driver for the development of HCC.

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