International Journal of Clinical Images and Medical Reviews

ISSN 2771-6309

Case report

Steatohepatitic variant of Hepatocellular Carcinoma. "Wolf in a sheep's clothing" - A Case report and review of literature

Dr·Sunitha Ramachandra[1*], Dr·Lakshmi Rao[2], Dr·Masoud Al Kindi[1]

[1]Department of pathology, Armed Forces Hospital, Muscat, Sultanate of Oman.

[2]Senior Consultant Pathologist, Armed Forces Hospital, Muscat, Sultanate of Oman.

Abstract

We report a rare variant of HCC (hepatocellular carcinoma) called the steatohepatitic variant of HCC (SH-HCC) which is a malignant tumour of the liver with very bland morphology and histologically mimics steatohepatitis. This variant is strongly associated with metabolic syndrome (MS) and steatohepatitis . The well-known commonly associated conditions with HCC are chronic hepatitis B and C infections (HBV and HCV), alcoholic fatty liver and cirrhosis. Recently, NAFLD (non-alcoholic fatty liver disease) is identified as an important risk factor for the development of HCC. SH-HCC was identified in the explant livers for HCV. The present case is that of a patient with metabolic syndrome, diabetes and hypertension with a history of bladder cancer six years back and was lost to follow up. Presently he came with hematuria. A bladder growth was identified on cystoscopic examination. During his staging workup, CT abdomen showed an interval lesion in the liver, which was reported as metastatic carcinoma from bladder on radiology. Biopsied bladder lesion showed a recurrent urothelial carcinoma and segmental resection of the liver lesion showed SH-HCC.

The aim of this paper is to elucidate the various histopathological features of this rare variant of HCC with radiological, clinical and biochemical correlation and review of the literature.

Key words: hepatocellular carcinoma, steatohepatitic type of HCC, NAFLD and metabolic syndrome.

Introduction

HCC is the most common malignant tumour of the liver accounting for 85-90% of all primary liver cancers.1 HCC shows an increasing incidence worldwide in both the developed and developing nations.2 It is the fifth most common cancer and the second most frequent cause of cancer mortality.3 The prevalence of HCC is high in Asia and Africa when compared to rest of the world.1 Etiological association with chronic viral hepatitis (HBV and HCV) and ALD (alcoholic liver disease) are well documented.2 Recently, NAFLD and NASH (non-alcoholic steatohepatitis) have also been implicated in the development of cirrhosis and HCC.4 Several co-factors like genetic susceptibility, diet and MS interact to increase the risk of development of HCC in NAFLD.4 MS encompasses diabetes, hypertension and obesity. Recent advances show hepatic cancers with distinct histologic features and immunoprofile resulting in many variants and subtypes.5 One such variant is the SH-HCC described by Salamao et al. strongly associated with MS.1 SH-HCC show marked overlapping histological features with NASH, like steatosis (in more than 5% of tumour area), ballooning change of malignant hepatocytes, inflammation, Mallory Denk bodies and pericellular fibrosis.1,2 Most of the reports of SH-HCC were diagnosed on excised specimens and unfortunately, may be misdiagnosed on core biopsies as benign lesion. Pathologists very often receive core needle biopsies. As the histological features of this variant are very subtle and overlap with benign conditions like NASH, it is very important to elucidate the subtle histological features to differentiate and diagnose this condition on biopsy.

Case history

66 year old gentleman diagnosed with bladder cancer six years ago was lost to follow up.

Currently presented with complains of hematuria. He is a known diabetic and hypertensive on medications. Cystoscopic examination showed bladder lesion and the same was resected.

HPE (histopathological examination) showed a recurrent invasive high grade papillary urothelial carcinoma. CT abdomen was done for staging the bladder tumour. The presence of an interval heterogenous lesion was noted in the liver segment 6 measuring 4.1 x 4 x 3.4 cm. which was not identified in his previous CT. This lesion showed heterogenous density on pre contrast study with mild heterogenous arterial enhancement and continuing to enhance in the venous phase. The background liver was unremarkable.[Fig 1]. Tumour markers – like AFP, CEA and Ca 19-9 were within normal limits. LFT (liver function test) did not show any derangement. Rest of the biochemical and routine bloods were normal except for elevated CRP, which was 7.2 mg/L. With clinical and radiological diagnosis of suspicious metastatic bladder cancer and to rule out other possibilities, segmental (5&6) liver resection was done.

***Corresponding Author:** Dr.Sunitha Ramachandra, Department of pathology, Armed forces Hospital, Al- khoud, PO Box 325, PC Seeb 111, Muscat, Oman.

Received: November 07, 2022 **Published:** November 21, 2022

Citation: *Dr.Sunitha Ramachandra. Steatohepatitic variant of Hepatocellular Carcinoma. "Wolf in a sheep's clothing" - A Case report and review of literature. Int Clin Img and Med Rew. 2022; 3(3): 1121.

DOI: 10.55920/IJCIMR.2022.03.001121

Grossly the liver showed an oval well circumscribed pale yellow lesion measuring 4.4 x 4.3 x 3.2 cm. No haemorrhage or necrosis was identified. Surrounding liver was unremarkable.

Microscopy showed a well differentiated steatohepatitic tumour. Loss of architecture with acinar formation, extensive macro and microvesicular fatty change, ballooning of the hepatocytes, Mallory Hyaline bodies, inflammation and intracytoplasmic bile and canalicular bile stasis were noted. Hepatocytes were separated by capillarized vessels and no portal tracts or bile ducts were identified within the lesion. A pseudocapsule with dense fibrosis was noted at the interphase between the lesion and the surrounding liver. Microvesicular fatty change and portal tract inflammation were seen in the surrounding liver.[Fig2] IHC – Tumour cells were strongly positive for glutamine synthetase (GS) cytoplasmic staining and CK7 showed absence of bile ducts within the lesion and CD 34 showed capillarization of sinusoids within the lesion.[Fig3]

With the above gross, microscopic and IHC findings, a diagnosis of a well differentiated HCC – steatohepatitic variant was rendered.

A repeat CT done six months after resection showed no new lesions in the liver. But, tiny recurrences were noted in the bladder. Tumour markers and CRP remained normal.

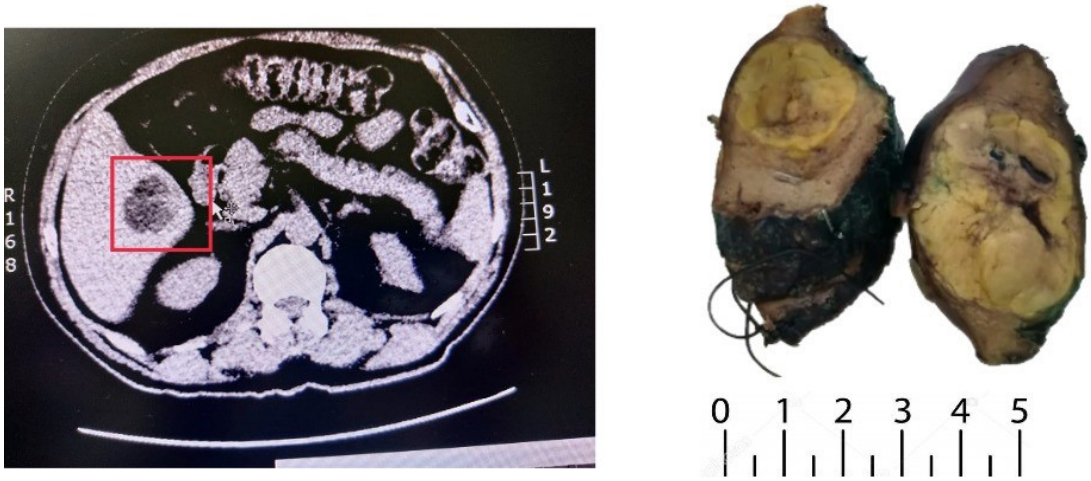

Figure 1: *An oval well circumscribed pale yellow lesion with surrounding normal liver and CT image.*

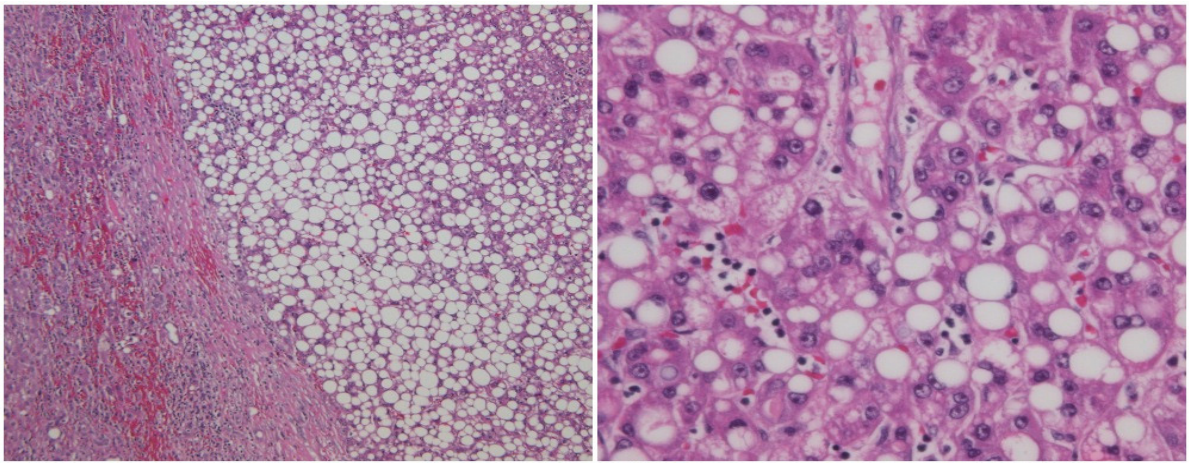

Figure 2: *Lesion with pseudocapsule, scanner view. (Haematoxylin and Eosin stain, x 4) High power view. (Haemotoxylin and Eosin stain, x 40)*

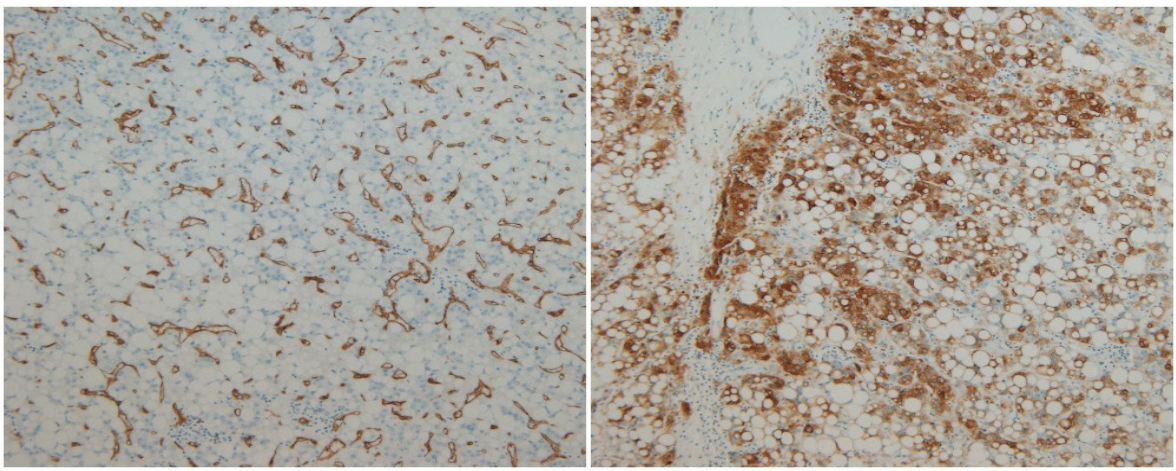

Figure 3: *IHC CD34 positive sinusoids, GS positive tumour cells.*

Discussion

HCC is the most common primary liver cancer.2 The carcinogenesis is a multistep process.

HBV, HCV, ALD, toxins and hemochromatosis are well established causes associated with HCC. Recently, NAFLD / NASH has been identified as an important risk factor for the development of SH-HCC. Association with a cofactor like MS risk factors was higher in SH-HCC than with conventional HCC.3 This new histologic subtype SH-HCC was first described by Salamao et al in explant liver with HCV.3 After its initial description, it was observed that many cases of SH-HCC described often showed association with NAFLD / NASH and ALD.3 It is important to note that HCV itself induces insulin resistance that may lead to the development of type 2 diabetes and thus contributing to MS.1 Obesity, hyperlipidaemia, diabetes and hypertension are the MS risk cofactors in the carcinogenesis of SH-HCC. In conclusion, a definite causative association can be linked between SH-HCC, MS and steatohepatitis.3 In contrary to this, the study by Yeh et al in 2015 showed SH-HCC in the absence of MS or fatty liver disease thereby suggesting a tumour-specific genetic alteration identified to loss of 9q12-q31.1.6 Conventional HCC which shows frequent mutations in the beta-catenin pathway is comparatively less in SH-HCC.5 It is also found that serum amyloid A and CRP (c reactive protein) which are the classification markers of inflammatory HCA (hepatocellular adenoma) were significantly high in SH-HCC raising the possibility of HCC developing in a pre-existing adenoma.7 Another possible promoter of hepatocarcinogenesis is a double hit theory with increase in inflammatory cytokines (TNF-alpha, IL-6 and resistin) and decrease in anti-inflammatory cytokine (adiponectin) in NASH.4 Our patient had some of the risk factors of MS – diabetes and hypertension and mild elevation of CRP (7.2 mg/L). He was negative for viral hepatitis.

Grossly the lesions are pale yellow, nodular and single or multiple. SH-HCC are more intensely yellow than conventional HCC.3 Microscopy shows typical features of steatohepatitis – large droplet steatosis, ballooning of malignant hepatocytes, Mallory Denk bodies, inflammation and pericellular fibrosis.2,3 More than 5% of the tumour area should show these features in various combinations.1,3 Presence of portal tracts, bile ducts with portal inflammation, fibrosis and absence of capillarization of the sinusoids, distinguish NASH from SH –HCC. The present case showed all the features of steatohepatitis involving almost the entire tumour with absence of bile ducts and capillarization of sinusoids. IHC stains such as glutamine synthetase (GS), glypican-3 (GPC-3), CD34 and HSP-70 (heat shock protein) are useful for the diagnosis. The important differentials to be ruled out are clear cell type HCC, steatohepatitis and steatohepatitic-like changes in the FNH (focal nodular hyperplasia).2,3 Clear cell type HCC shows polygonal cells with clear cytoplasm.2 SH-HCC shows capillarization of sinusoids and absence of ductular reaction whereas, FNH shows ductular reaction and absence of capillarization of sinusoids along with negative IHC stains for GS, GPS-3 and CD34.3 SH-HCC shows diffuse sinusoidal CD34 staining (capillarization of sinusoids), GPC-3 is variable (cytoplasmic and canalicular) and GS is variable (cytoplasmic staining with perinuclear accentuation).3 Our case showed tumour cells positive for GS (cytoplasmic) and diffuse CD34 staining of sinusoidal endothelial cells . Tumour cells were negative for GPC-3.

SH-HCC being relatively the new entity and only few cases reported in the literature, clear prognostic details and the course of the disease are not available.

Conclusion

Present case is that of our patient previously diagnosed with bladder cancer, who subsequently develops an interval new lesion in the liver after 6 years of initial diagnosis of bladder cancer. Excision was done as the liver lesion was thought to be metastatic bladder cancer in the liver. The HPE of the liver lesion showed a less commonly known newly described variant of primary HCC, SH-HCC. This variant has a well-established association with HCV, MS and NAFLD. Few cases have been reported in a non-fatty liver in the absence of MS suggestive of multiple mechanisms involved in the carcinogenesis. As most of the cases described in the literature were diagnosed on excised lesions, diagnosis on core biopsy specimen is very challenging as these tumours mimic benign liver disease and compounded by subtle differences. No well-established diagnostic criteria are available. One needs to be aware and vigilant of this new entity as many of them may be underreported as steatohepatitis. However, it is very important to correlate radiology and clinical information to correctly diagnose this variant of HCC. Even when a mass lesion is present, core biopsy may be misinterpreted as NASH adjacent to HCC if one is not aware of this variant and its histomorphology.

Reference

1. 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;137(7):961–966. doi: 10.5858/arpa.2012-0048-OA DOI: http://dx.doi.org/10.7869/tg.165
2. Olofson AM, Gonzalo DH, Chang M, Liu X. Steatohepatitic variant of hepatocellular carcinoma: a focused review. Gastroenterology Res 2018;11:391-396.
3. Oda, K., Uto, H., Mawatari, S. et al. Clinical features of hepatocellular carcinoma associated with nonalcoholic fatty liver disease: a review of human studies. Clin J Gastroenterol 8, 1–9 (2015). https://doi.org/10.1007/s12328-014-0548-5
4. El Jabbour T, Lagana SM, Lee H. Update on hepatocellular carcinoma: Pathologists' review. World J Gastroenterol. 2019; 25(14): 1653– 1665.
5. 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. PMID: 26410018.
6. Tobari M, Hashimoto E, Taniai M, Nishino T, Tokushige K. Clinicopathological investigation of steatohepatitic hepatocellular carcinoma: A multicenter study using immunohistochemical analysis of adenoma-related markers. Clinical Journal of Gastroenterology, 10.1007/s12328-020-01215-3, (2020). https://doi.org/10.1111/hepr.13203