RESEARCH ARTICLE

MACROTRABECULAR MASSIVE HEPATOCELLULAR CARCINOMA (MTM-HCC): A RECENTLY DESCRIBED HISTOLOGICAL SUBTYPE WITH CLINICAL IMPLICATIONS

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ABSTRACT

Aim: *Macrotrabecular Massive Hepatocellular Carcinoma (MTM-HCC) is one of the newly described aggressive morphological variants of HCC. The aim of this study was to determine the frequency of MTM-HCC and to evaluate its clinicopathological significance.*

Material & Methods: *We conducted this retrospective study in our institute. The cases were retrieved and reviewed by pathologists to look for this variant. Cases were correlated with tumor size, serum alpha fetoprotein levels, cirrhosis, lymphovascular invasion (LVI), pathological grade and stage. Data were analyzed on SPSS version 22.*

Results: *MTM-HCC pattern was identified in 16.1% of the cases. Correlation between MTM HCC and histological grade (p=0.048), Lymphovascular invasion (p=0.005) and AFP levels (p=0.015) were found to be statistically significant.*

Conclusion: *Our study showed that the MTM-HCC subtype represents an aggressive form of HCC that may require more specific therapeutic strategies.*

Keywords: *Alpha fetoprotein, Hepatocellular carcinoma (HCC), Hepatitis B virus infection, Hepatitis C virus infection, Macrotrabecular massive.*

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the sixth most common cancer and a fourth leading cause of cancer death worldwide[1]. Hepatitis B and C viral infections are the most common causes of HCC in underdeveloped countries, accounting for up to 32% of cases[2,3]. Other possible causes include smoking, alcohol and nonalcoholic fatty liver disease. HCC has a wide spectrum of histological patterns, common being solid, pseudo glandular and trabecular. Recently, in the 5th edition of the World health organization (WHO) Classification of Digestive System Tumors, certain distinctive histological patterns were described which are important to recognize due to their prognostic significance[4]. These include clear cell, lymphocyte rich, fibrolamellar, steatohepatitic, scirrhous and macrotrabecular massive (MTM-HCC). WHO has defined macrotrabecular pattern as trabeculae of hepatocytes more than or equal to 10 cells thick involving more than 50% of the entire tumor[5]. Studies have shown MTM-HCC has distinct molecular features and is associated with aggressive clinical behavior and poor prognosis. The aim of this study was to determine the frequency of MTM-HCC and to evaluate its clinicopathological significance.

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MATERIAL AND METHODS

This study was conducted after taking approval from Institutional Review Board and Ethics Committee. All resection specimens of HCC cases diagnosed at Shifa International Hospital between January 2018 to December 2019 were retrieved from the archives and reviewed for the presence of macrotrabecular massive pattern by a consultant histopathologist. All cases showing > 50% growth of macrotrabecular pattern ($\geq$ 6 - 10 cells thick) as per WHO criteria were categorized as MTM-HCC (Figures 1 & 2). Histological grade, lymphovascular invasion and pathologic stage were also evaluated and correlated. Serum alpha protein levels (AFP) of the individual cases were retrieved from each patient's electronic medical record and stratified into 3

groups. These groups were; those having normal range AFP levels (<10 ng/ml), slightly raised (10-100 ng/ml) and markedly raised (>100 ng/ml). Suboptimal core biopsies and cases in which other parameters, such as serum AFP levels, were not available were excluded from the study. Statistical analysis was performed using the SPSS version 22. Chisquare test was applied for correlation. Significance was defined as p value of < 0.05.

RESULTS

A total of 92 HCC cases were included. Out of these, 78 cases were male and 14 were female (M: F is 5.5:1). Age range was 35-76 years (mean age 54.4 years). The mean tumor size was 4.3cm. MTM-HCC pattern was identified in 15 cases (16.3%) (Figure 1). LVI (Lymphovascular invasion) was present in overall 39 cases (42.4%), out of these 20% cases were of MTM-HCC. The most common etiology of HCC was Hepatitis C (54.3%) followed by Hepatitis B infection. (Figure 2) Correlation between MTM HCC and histological grade (p=0.048), Lymphovascular invasion (p=0.005) and AFP levels (p=0.015) were found to be statistically significant. (Table 1)

HCC is one of the common cancers occurring worldwide and the commonest cause of primary liver cancers. It has a high propensity for recurrence, distant metastasis and chemoresistance. In the latest 5th edition of the World Health Organization (WHO) Classification of Digestive System Tumors, several histological subtypes have been described[5]. The significance of these subtypes is validated by their clinical relevance and genetic makeup. Among these subtypes, a novel and distinct subtype of HCC defined by the histological pattern of tumor cells is MTM-HCC.

MTM-HCC was recognized as a distinct pattern in 1983 and was suggested to represent a subtype of HCC, but due to lack of supporting studies, it was not until recently recognized as a separate subtype[7]. We followed WHO criteria of defining MTM-HCC which is the presence of macrotrabeculae of more than 10 cells thick in >50% of sampled tumor. This cutoff was similar to a study by Tan et al[9]. In contrast, studies conducted by Ziol et al and Jeon et al, MTM pattern was defined as the presence of macrotrabeculae of more than 6 cells thick in >50% of the tumor[6,9].

In our study, MTHCC constituted 16% of all HCCs as compared to 12% in the study by Ziol et al[3]. MTHCCs showed a male predominance similar to studies by Ziol and Jeon[6,10]. The mean age at diagnosis is 54 years. In contrast with Ziol, our study revealed slightly larger tumors in the MT-HCC subtype i.e 4.3 cm compared with Conventional HCC[6]. Similar to the findings of Ziol and Jeon, MT-HCC was more frequently observed in the context of viral hepatitis than with non-viral etiologies[6,10]. MTM-HCC exhibited a higher histological grade and tumour stage than CV-HCC.

In the review article by Calderaro et al he broadly classified HCC into proliferative and non-proliferative categories each carrying characteristic oncogenic pathway[11]. Among the proliferative types, MTM HCC is the distinct novel morphological pattern and their gene expression profiling revealed a unique gene expression related to neoangiogenesis causing over activation of angiopoietin 2 and Vascular Endothelial Growth Factor-A [VEGFA][11]. The association between negative biological and pathological criteria including high serum AFP serum levels, bigger tumour growth, vascular invasion and satellite nodules are most likely caused by underlying genetic disorders. Ziol and colleagues also demonstrated this connection[6].

In our study p-value was found to be statistically significant for tumor stage, vascular invasion and AFP levels. One important point to emphasize is that hepatocellular carcinomas are usually diagnosed on radiology and liver biopsy are not routinely done in every case. But now considering the importance of this pattern in this era of developing personalized medicine question on biopsy of every case arises so as to predict the natural course of the disease and to separate the potentially aggressive variant[12].

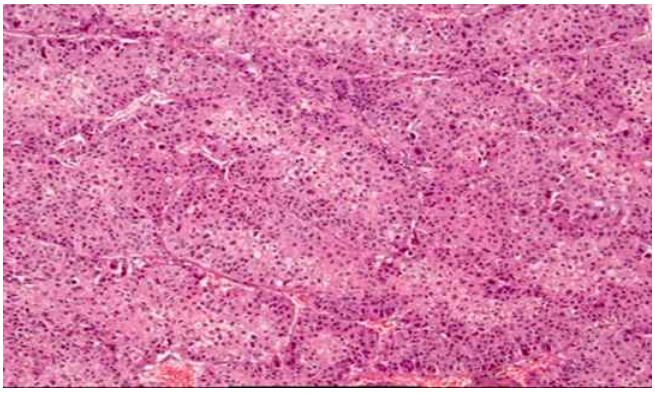

Figure 1: Macrotrabecular pattern of Hepatocellular Carcinoma showing thick trabeculae with more than 6-10 cell thick Hepatic plate (Hematoxylin & eosin stain, 10x magnification).

Table 1: Clinicopathological characteristics of MTM-HCC vs Conventional HCC (non MTM pattern)

	MTM-pattern	Non MTM-pattern	p-value
Sex	M:F 6.5:1	M:F 5.4:1	-
Age (y) mean	55	50	-
Size (cm) [%]	Upto 5cm (60) ➢5cm (40)	Upto 5cm (74) ➢5cm (26)	0.2
AFP levels (>100ng/ml) (%)	46	14	***0.015***
Stage (%)	pT1 (40) pT2 (33) pT3 (27) pT4 (0)	pT1 (39) pT2 (39) pT3 (13) pT4 (9)	*0.5*
Histologic Grade (%)	G1 (0) G2 (60) G3 (40)	G1 (7) G2 (79) G3 (14)	***0.04***
Lymphovascular invasion (%)	80	67	***0.005***

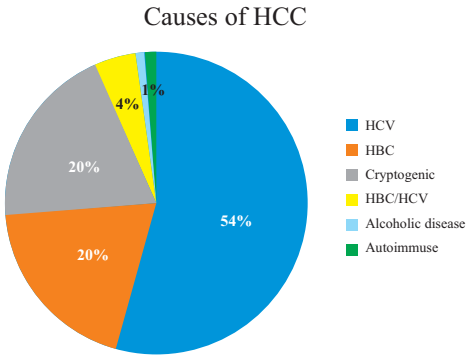

Figure 2: Different causes of Hepatocellular Carcinoma in our population. Hepatitis C viral infection being the most common cause, followed by Hepatitis B viral infections and cryptogenic causes.

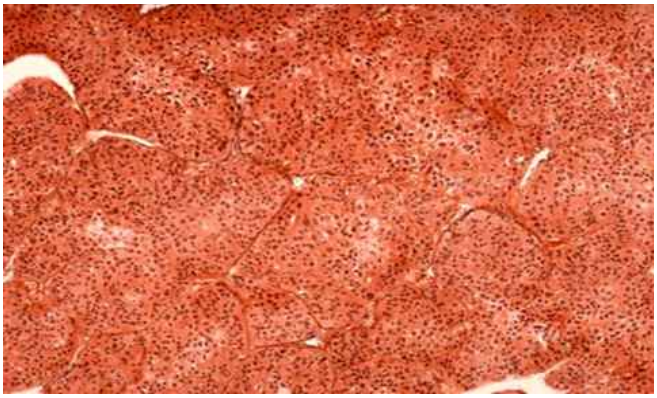

Figure 3: Special stain Reticulin highlighting thickened hepatic plate. These thickened plates contain more than 10 cells thick tumor cells which is consistent with Macrotrabecular pattern (Reticulin stain, 10x magnification).

CONCLUSION

Our results suggest that MTM-HCC is an aggressive version of HCC and therefore may require more intensive therapy.

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