

Original Article

FNAC of Hepatic Malignancy and it's Clinical Correlation.

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Abstract:

Background: Hepatic malignancy is an important clinical condition which is associated with poor outcome. Clinical assessment of a patient with hepatic malignancy is crucial to sort out the primary and secondary, and so biochemical and radiological investigations are needed. Hence fine needle aspiration cytology (FNAC) of the lesion is essential which is a minimal invasive procedure to combat a deadly disease.

Objective: The aim of this prospective cross sectional observational study was clinical assessment of primary and secondary hepatic malignancy and its co-relation with FNAC of hepatic malignancy.

Methods: Patients admitted in Medicine Department, Dhaka medical College, with hepatic malignancy from January 2013 to June 2014 and then confirmed by FNAC (USG guided) of liver mass were included in the study. A total 100 patients were enrolled in the study in a non-random convenient sampling method.

Result: In this study 42 patients were found having primary Hepatocellular Carcinoma (HCC) and 58 patients had secondary hepatic malignancy. FNAC confirmed secondary hepatic malignancy (n=58) as metastatic adenocarcinoma 43(74.1%), metastatic small cell carcinoma 9(15.5%), Gastro Intestinal Stromal Tumour (GIST) 2(3.4%), squamous cell carcinoma 2(3.4%) & Non Hodgkins lymphoma 2(3.4%). Most of the patients of primary hepatic malignancy between 20-40 years 18(42.9%) and secondary hepatic malignancy between 40-60 years 35(60.3%). Incidence in male is more in both primary 31(73.8%) and secondary 38(65.5%) hepatic malignancy. Both HCC and secondaries predominantly presents with abdominal pain, 39(92.9%) cases of HCC and 47(81.0%) of secondaries. Incidence of multiple lesion in ultrasonogram is more in both primary 30(71.4%) and secondary 47(81.0%) hepatic malignancy. Positive HBsAg, Positive Anti HBc (total), Positive Anti HCV were found in 15(35.7%), 11(26.2%) and 9(21.4%) cases of HCC respectively. Positive Alpha Feto Protein (AFP) was found insignificant in this study.

Conclusion: Fine Needle Aspiration (FNA) is a useful diagnostic test for evaluating patients with discrete hepatic masses. Correlation with clinical, radiological and cytological findings is helpful in arriving at the correct diagnosis and therefore increases overall accuracy and cost-effectiveness of the procedure.

Key words: Fine Needle Aspiration Cytology (FNAC), Hepatic malignancy.

Introduction:

Hepatocellular carcinoma is now the fifth most common cancer worldwide and the third most common cause of cancer death¹. On the other hand, Liver is one of the most common sites for metastatic disease accounting for 25% of all metastasis to solid organ². Differentiation between benign and

malignant primary or secondary tumor is extremely important from management point of view. The clinical manifestations of hepatic infiltration with secondaries are similar to their primary malignancy. Presence of metastases usually rules out surgery, whereas if HCC is diagnosed at an early stage, surgical resection is possible and may assure cure. Despite recent improvement, radiological imaging does not always allow precise characterization of the lesions. Serological markers (such as AFP) can be useful in narrowing the differential diagnosis when they are markedly elevated but a substantial number of patients unfortunately do not have high level of these markers at the time of presentation. The cytological examination of the specific lesion and the clinical profile of that patient can narrow the differentials. So, Fine needle aspiration of cellular materials under image guidance has gained increasing acceptance as the diagnostic procedure of choice for patients with focal hepatic lesions. The present study was done to observe the clinicopathological correlation between FNAC from primary and secondary neoplasm of the liver with clinical assessment of patients.

Materials and methods:

This was a cross-sectional observational study conducted at Dhaka Medical College Hospital, Dhaka since January 2013 to June 2014. A total 112 patients were enrolled in the study in

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a non random convenient sampling method with clinical features of hepatic malignancy and supported by biochemical and radiological investigation. Then USG guided FNA of hepatic lesion was done and sent for cytological study. 12 cases revealed no malignancy in cytological study though these cases were presented clinically and radiologically as hepatic malignancy. So they were excluded from study. A structured case record form was applied for clinical profile.

Statistical analysis:

Univariate analysis was used to find out the association between clinical sign and symptoms and the demographic and lab findings and student t test was done to observe the significance. Some of the baseline characteristics of the cases were expressed as means and +/- SD and others as percentages. P value ≤ 0.05 is considered as significant.

Results:

The study was done among 100 clinically suspected cases of hepatic malignancy and confirmed through FNAC of liver Space Occupying Lesion (SOL). The cytology and clinical correlation were observed meticulously. Mean age of the patients for HCC was 47.02 ± 17.5 years and secondary malignancy was 53.32±12.93 years (Figure 1). Incidence in male was more in both primary 31(73.8%) and secondary 38(65.5%) hepatic malignancy. Female incidence in primary hepatic malignancy was 11(26.2%) and in secondary malignancy was 20(34.5%).

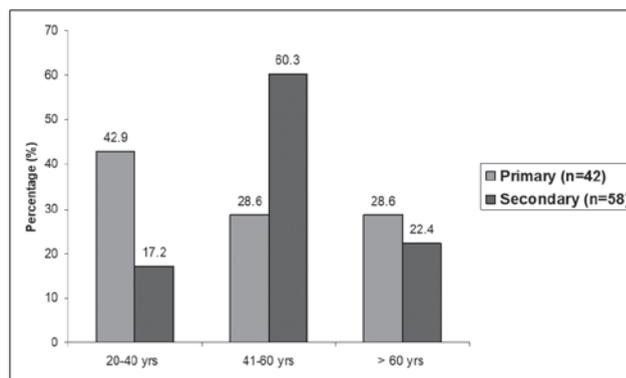


Figure 1

Hepatocellular carcinoma presents with abdominal pain (92.9%), abdominal swelling (76.2%), fever (54.8%), loss of appetite (50.0%), jaundice and weight loss (47.6%). Secondary hepatic malignancy presents with abdominal pain (81.0%), loss of appetite (72.4%), abdominal swelling (55.2%), fever (51.7%), weight loss (46.6%) & jaundice (22.4%). The jaundice was significantly observed in primary HCC and loss of appetite was observed in secondaries significantly. Abdominal swelling was predominant findings in HCC (Table 1).

Stigmata of CLD predicts the primary HCC significantly while hepatic bruit is also an important sign in suspicion of HCC. The lymph node enlargement in clinical record can

Table-1:

Clinical Symptoms and Signs	Hepatic malignancy		p value
	Primary (n=42) N (%)	Secondary (n=58) N (%)	
Abdominal pain	39(92.9%)	47(81.0%)	0.093
Weight loss	20(47.6%)	27(46.6%)	0.916
Loss of appetite	21(50.0%)	42(72.4%)	0.022
Abdominal swelling	32(76.2%)	32(55.2%)	0.031
Jaundice	20(47.6%)	13(22.4%)	0.008
Fever	23(54.8%)	30(51.7%)	0.764
Hepatic facies	18(42.9%)	17(29.3%)	0.161
Wasting	24(57.1%)	48(82.8%)	0.005
Fever	21(50.0%)	32(55.2%)	0.609
Lymph node	0(0.0%)	8(13.8%)	0.012
Edema	8(19.0%)	12(20.7%)	0.839
Hepatomegaly			
Hard	30(71.4%)	43(74.1%)	0.763
Tender	34(81.0%)	38(65.5%)	0.090
Irregular	29(69.0%)	11(19.0%)	0.166
Hepatic bruit	11(26.2%)	4(6.9%)	0.008
Splenomegaly	4(9.5%)	6(10.3%)	0.893
Ascites	12(28.6%)	9(15.5%)	0.114
Stigmata of CLD			
Spider naevi	4(9.5%)	0(0.0%)	0.016
Palmer erythema	4(9.5%)	0(0.0%)	0.016
Gynaecomastia	6(14.3%)	0(0.0%)	0.003
Breast atrophy	6(14.3%)	0(0.0%)	0.003

predict the chance of secondary malignancy as it is statistically significant and virtually rule out primary hepatic malignancy.

Positivity for hepatitis B surface antigen (HBsAg) was found in 35.7% cases and hepatitis B core antibody [Anti HBc (total)] was found in 26.2% while anti HCV antibody was detected in 21.4% in HCC. Secondary hepatic malignancy also shows positivity 3.4% for HBV and none for HCV.

Elevated Serum AFP level was detected in primary hepatocellular carcinoma. Although AFP was found to have a tool for primary HCC, in this study it is not statistically significant. The tumor markers Carcino Embryonic Antigen (CEA) and CA-19.9 can predict secondary malignancy and found to have level of significance in this observation (Table 2).

Table-2:

Tumor markers	Hepatic malignancy		p value
	Primary (n=42)	Secondary (n=58)	
	Mean±SD	Mean±SD	
AFP	88802.8±145515.3	26670.2±70371.7	0.125
CEA	23.30±21.39	297.8±330.6	0.025
CA-19.9	25.25±8.66	1153.5±498.08	0.001

The Cytomorphological analysis encompassed study of cellularity, pattern of arrangement, cytoplasmic and nuclear details and many additional features. Based on these observations, the HCC was detected in 42 cases and secondaries were detected in 58 cases. Secondary malignancy were metastatic adenocarcinoma (74.1%), metastatic small cell carcinoma (15.5%), GIST (3.4%), squamous cell carcinoma (3.4%), Non Hodgkin's Lymphoma (NHL) or Hepatoblastoma (3.4%) (Table 3).

Table-3:

Diagnosis by FNAC	Hepatic malignancy		p value
	Primary (n=42)	Secondary (n=58)	
	Mean±SD	Mean±SD	
Hepatocellular carcinoma	42(100.0%)	0(0.0%)	<0.001
Metastatic adenocarcinoma	0(0.0%)	43(74.1%)	
Metastatic small cell carcinoma	0(0.0%)	9(15.5%)	
GIST	0(0.0%)	2(3.4%)	
Squamous cell carcinoma	0(0.0%)	2(3.4%)	
NHL/ Hepatoblastoma	0(0.0%)	2(3.4%)	
Total	42(100.0%)	58(100.0%)	

Discussion:

Tissue diagnosis of hepatic masses is very important for management. Focal hepatic lesions range from cysts and inflammatory processes to neoplasm, which may be benign or malignant, primary or metastatic. Clinical, radiological and serological findings cannot reliably distinguish a benign from a malignant lesion, but they can help to narrow the differential diagnosis. In such instances, FNAC under image guidance has gained increasing acceptance as the diagnostic procedure of choice. Ultrasound guidance is usually preferred for its simplicity, real-time monitoring and flexible needle placement. Assistance of a cytopathologist during the procedure increases overall accuracy³.

This study clearly documents that the clinical manifestation of HCC and secondary hepatic malignancy are correlated with the characteristic cytology of hepatic lesion in respect to diagnosis of hepatic lesion. In this theory abdominal pain is the commonest clinical presentation for both HCC (92.9%) and secondary hepatic malignancy (81.0%). When abdominal pain is associated with abdominal swelling (76.2%), fever (54.8%), loss of appetite (50.0%), jaundice and weight loss (47.6%), it arouses suspicion of HCC. It will be noted that a vast majority of people in primary HCC use indigenous medicine (9.5%) for remedy. In secondary hepatic malignancy, abdominal pain is followed by loss of appetite (72.4%), abdominal swelling (55.2%), fever (51.7%), weight loss (46.6%) and jaundice (22.4%). In practical experience, these have proved to be a differential diagnostic feature of considerable importance and value. These clinical findings are consistent with other study report. Kew et al. reviewed 75 cases of liver cancer in England and he shows the most common presenting complaints were abdominal pain and weight loss and the most frequent findings were hepatomegaly and ascites. Less than one-half of the patients were icteric and when present, it was usually mild⁴.

From the result of the present study, it may be suspected that some features can strongly advocate the specific features of hepatic malignancy though there is significant overlap in the clinical features of hepatic malignancy. This suspicion is based on the finding that hepatocellular carcinoma cases may present with stigmata of chronic liver disease (CLD) like spider naevi, gynaecomastia, breast atrophy, palmar erythema, testicular atrophy or complications like ascites, encephalopathy, variceal bleeding or hepatic bruit. In this study we found hepatic bruit in 26.2% of HCC and this is consistent with Kew MC study which shows an arterial bruit was heard over the liver in 25% of the patients of HCC⁴.

One surveillance research in USA for HCC shows men are affected 2.1 to 5.7 times more frequently than women (mean 3.7:1). The ratio decreases to a mean of 2.4:1 in intermediate-incidence areas, and is lower in low-incidence regions⁵. This study clearly shows that men are more likely than women to develop carcinoma both primary and secondary malignancy. And this result is consistent in all parts of the world, the disparity is more pronounced in high-incidence regions. Although not fully understood, the differences in sex distribution are thought to be due to

variations in hepatitis carrier states, exposure to environmental toxins and the trophic effect of androgens ⁶.

On radiological examination, HCC and metastatic carcinoma to liver may show overlapping features. HCC can be small and focal, solitary and large, multifocal or diffuse, and infiltrating, thereby, mimicking benign lesions on one hand and metastases on the other. In our study, 28.6% cases of HCC and 19% metastatic cases shows solitary lesion and 71.4% cases of HCC and 81% metastatic cases shows multiple lesion on ultrasound examination. Associated cirrhosis was documented in 70% HCC cases. So number and size of lesion can't distinguish primary or secondary but presence of cirrhosis lead to hepatocellular carcinoma. One study in New York shows metastatic liver tumors are variable. Though they recommend as a general rule metastases from adenocarcinoma are multiple and hypoechoic in comparison with the surrounding liver parenchyma on ultrasonogram ⁷.

Positivity for hepatitis B surface antigen (HBsAg) was found in 35.7% cases and hepatitis B core antibody i.e. Anti HBc (total) was found in 26.2% cases while anti HCV antibody was detected in 21.4% cases in HCC. Secondary hepatic malignancy also shows positivity 3.4% for HBV and none for HCV. So one has to realize that patient infected with hepatotropic virus has more chance of hepatocellular carcinoma. This findings are consistent with other representative sample of published reports. One study was done taking representative sample form 11-WHO based regions which shows globally 57% of cirrhosis was attributable to either HBV (30%) or HCV (27%) and 78% of HCC was attributable to HBV (53%) or HCV (25%). Regionally, these Infection usually accounted for >50% of HCC and cirrhosis ⁸.

One unexpected finding in this study is serum AFP level. Usually tumor markers narrow the differentials of hepatic malignancy. Serum AFP is fairly specific for HCC in contrast with secondaries, can't distinguish HCC from secondaries reliably in this theory. This result seems to be consistent with one study which shows serum AFP level is frequently normal (in 35% cases), and thus determination of serum AFP levels only is not a reliable indicator in the early detection of human HCC⁹. In contrast of this, there are some other studies which conclude that AFP is useful not only for diagnosis, but also as a prognostic indicator in patients with HCC. Here 309 pathologically proven HCC cases divided into three groups: group 1 with normal AFP (<20 IU/mL), group 2 with moderately elevated AFP (20-399 IU/mL) and group 3 with markedly elevated AFP (>or = 400 IU/mL). Of these, there were 76 (24.6%), 78 (25.2%), and 155 patients (50.2%) in groups 1, 2, and 3, respectively ¹⁰. On the other hand CEA and CA-19.9 show marked elevation in secondary hepatic malignancy.

Here we found 42 cases are HCC and 58 cases are secondaries. Further cytomorphological analysis differentiate the secondaries into metastatic adenocarcinoma (74.1%), metastatic small cell carcinoma (15.5%), GIST (3.4%), squamous cell carcinoma (3.4%), NHL/Hepatoblastoma (3.4%).

From the overall result of the present study we may conclude that a patient with hepatic SOL either single or multiple on the cirrhotic background and infection with hepatotropic virus like HBV and HCV strongly raise the suspicion of HCC. On the other hand hepatic SOL without cirrhotic background and hepatotropic virus infection presenting with hard liver, wasting and lymphadenopathy raise the suspicion of secondaries in the liver.

The most important requirement for cytodiagnosis is to obtain a representative sample. An aspirate that obtains material only from the surrounding tissue of the tumor may show reactive and proliferative changes, whereas an aspirate from the center of a large tumor may show only degenerative and necrotic material. Therefore, for aspiration to be representative, the needle should pass through the entire mass. Moreover we have to remember the distinction of moderately to poorly differentiated HCC from metastatic carcinoma can pose a major problem to cytologists and this distinction is clinically important¹¹.

Conclusion:

In this study we observe that HCC commonly presents at middle age and secondaries usually in the old age. Male sex is predominant in both primary and secondary hepatic malignancy. Abdominal pain is a common presentation for both malignancy. Stigmata of CLD is almost invariably present in all cases of primary HCC. Co-morbidities are commonly seen in secondary hepatic malignancy. Multiple hepatic SOL is common in both primary and secondary malignancies. Infection with hepatotropic virus like HBV and HCV is a high risk factor for primary HCC. AFP can give us a clue for HCC but in it doesn't help us for diagnosis. It is expected that this study will shorten the period of hospital stay in diagnosis of hepatic SOL. To obtain maximum diagnostic information with reduction of indeterminate reports, a combined approach of FNAC with clinical findings, tumor markers and ancillary techniques should be used.

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