ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 07 | July - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ROLE OF CD10 IMMUNOSTAINING IN DIFFERENTIATING HEPATOCELLULAR CARCINOMA FROM SECONDARY MALIGNANCIES OF LIVER

Pathology

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ABSTRACT

Introduction: Primary liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer mortality worldwide. Secondary liver cancer is a malignant tumor that metastasizes to the liver from an extrahepatic origin. Secondary liver cancer is much more common in Europe and North America, whereas primary liver cancer is more common in southeast Asia. Fine needle aspiration biopsy (FNAB) is the diagnostic procedure of choice for evaluation of liver lesions. **Material And Methods:** Our aim was to assess the role of CD10 immunostaining in differentiating the primary malignant tumors of liver from metastatic deposits and to compare the result of CD10 immunostaining of cell blocks with core needle biopsy and to compare diagnostic yield and sensitivity of ultrasound guided FNAC and cell blocks in suspected malignant liver masses. After preparing cytological smears from FNA material, any excessive material, was submitted in 50% Ethanol for cell block preparation. Formalin fixed, paraffin embedded tissue sections were first stained with routine haemtoxylin and eosin and diagnosis was made. Then CD 10 IHC staining was done and evaluated. **Results:** The present study included 50 cases of radiologically and clinically suspected hepatic malignancies, of which 14 cases were hepatocellular carcinoma and 36 cases of hepatic metastatic carcinomatous deposits. After making cytology smears, majority of cytology diagnosis were metastasis comprising of 76% (n=38) and rest were HCC about 24% (n=12). After making cell blocks from residual material, morphological features of each of case were considered resulting in 74% cases of metastasis (n=37) and 26 % cases of HCC (n=13) on cell blocks. CD10 immunomarker was done on all the cell blocks and core needle biopsies with sufficient material of which 72% cases of metastasis (n=36) and 28% cases of HCC (n=14) were reported. **Conclusion:** CD10 immunostaining on cellblock, obtained from FNAC aspirate, is useful in discriminating HCC and metastatic carcinoma of the liver with a high statistical significance.

KEYWORDS

Cell block, HCC, CD10,

INTRODUCTION

Primary liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer mortality worldwide, with an estimated 841,000 cases (9.3 cases per 100,000 person-years) and 782,000 deaths (8.5 deaths per 100,000 person-years) in 2018. It is more common in men than in women.[1] Liver cancer incidence rates vary from 5.1 per 100,000 person-years in Europe to 17.7 per 100,000 person-years in eastern Asia. Secondary liver malignancy is much more common in Europe and North America, whereas primary liver cancer is more common in south-east Asia.[2-4] Secondary liver cancer usually develops in non-cirrhotic liver parenchyma.[2] Because the liver receives a dual blood supply (systemic [arterial] and portal [venous]), the liver is one of the most common hematogenous metastatic sites. Although 75% of malignant lesions of the liver can be correctly diagnosed through cytomorphological analysis and good clinicoradiological correlation, around 25% can pose differential diagnostic problems. Application of immunohistochemistry markers can help to resolve this dilemma. CD10 immunomarker can be used on cell blocks which is highly specific marker for hepatocytic differentiation.

MATERIAL AND METHODS

The present study was conducted in 50 patients having malignant liver masses received in the Department of Pathology, Government Medical College, Amritsar, after approval from the institutional thesis and ethics committee. Informed consent of the patient was taken (if required in vernacular language). The study sample included those patients attending cytology department during the study period from September 2018 to September 2020 with clinically and radiologically suspected hepatic malignancy having normal PTI, Bleeding time and clotting time.

1. Under USG guidance, FNAC was performed using a 21-23 gauge lumbar puncture needle, depending on the depth of lesion, fitted to a 20-ml disposable syringe attached to a metallic syringe holder.
2. Direct air-dried smears were prepared for routine may-Grunwald–Giemsa (MGG) and a few smears were immediately fixed in 95% alcohol for haematoxylin and eosin stain (H&E).
3. After that, trucut biopsy was performed using core biopsy gun (22mm) and was preserved in 10% buffered formalin for tissue processing.
4. Cellblocks were prepared from the aspirate from FNAC by plasma thrombin clot method. After proper processing, paraffin sections were stained by H and E stain. Furthermore, core-needle biopsies (CNB) specimen were processed and paraffin sections were stained by H and E stain.

RESULTS

The present study included 50 cases of radiologically and clinically suspected hepatic malignancies, of which 14 cases were hepatocellular carcinoma and 36 cases of hepatic metastatic carcinomatous deposits. FNAC smears and cell blocks were reported on the basis of morphology and CD10 immunostaining was performed on both cell blocks and core needle biopsies. Subsequent results were evaluated.

In present study, comparing the age groups, 41-70 yrs age group showed all HCC cases whereas Metastatic group show maximum cases between 51-60 yrs (36%) followed by 61-70 yrs (16%).

However, male predominance was seen in both HCC and Metastatic groups. Male to female ratio for HCC is 1.8:1 whereas in metastasis, it is 1.25:1.

After making cytology smears, majority of cytology diagnosis were metastasis comprising of 76% (n=38) and rest were HCC about 24% (n=12). After making cell blocks from residual material, morphological features of each of case were considered resulting in 74% cases of metastasis (n=37) and 26 % cases of HCC (n=13) on cell blocks.

CD10 immunomarker was done on all the cell blocks and core needle biopsies with sufficient material of which 72% cases of metastasis (n=36) and 28% cases of HCC (n=14) were reported.

CD10 IMMUNOMARKER

Two patterns of CD10 immunohistochemistry were noted; canalicular and cytoplasmic. 12 out 14 cases (86%) of HCC show positivity for

CD10 immunomarker in canalicular staining pattern on cell blocks and core needle biopsies which is specific pattern for hepatocytes. 5 out of 31 cases (13%) of metastasis show positivity for CD10 immunomarker in cytoplasmic staining pattern on cell blocks and biopsies.

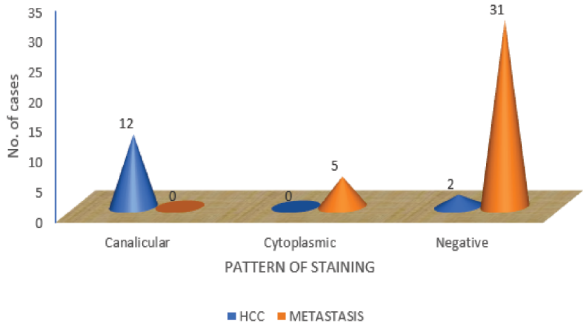

Figure 1 : Showing Cd10 Staining Patterns In Hcc And Metastasis Cases On Core Needle Biopsy.

DISCUSSION

Liver is one of the most common sites for metastatic disease accounting for 25% of all metastases to solid organs[8] and hepatocellular carcinoma is the most common primary malignancy of the liver in adults. The most common primaries producing hepatic metastasis are those of the breast, lung and colon, although any cancer in any site of the body may spread to the liver.[9]

Clinical manifestations of HCC as well as metastatic tumours are seldom characteristic. Laboratory studies may be helpful but are rarely conclusive.[9] Fine needle aspiration cytology (FNAC) of the liver under ultrasound guidance (USG) or computed tomography guidance has become a popular procedure to establish a diagnosis for liver masses.[8]

However sometimes distinction of poorly moderately to differentiated HCC from metastatic carcinoma is a major diagnostic problem encountered by the cytopathologist. The treatment and prognosis of HCC and metastatic carcinoma are significantly different and hence the ability to distinguish primary from metastatic malignancy is clinically important.[10]

Despite many advantages, at times FNA does not yield enough information for precise diagnosis and the risk of false negative or intermediate diagnoses always exists. This may be due to poor spreading, air drying artifact, and presence of thick tissue fragments despite aspiration of adequate material.[11]

Large amount of material remains in the needle hub after preparation of smears and this is generally discarded. The material that remains in the needle hub can be used in CB preparation, thus, increasing the sensitivity of diagnosis. It offers many advantages over other cytological preparations. Architectural features, particularly of small tissue fragments, are best appreciated in a CB.[12]

Various Immunohistochemical markers are used to resolve the diagnostic difficulties in this scenario such as polyclonal CEA (pCEA), HepPAR1, CD34 and cytokeratins. CD10 is newly discovered marker in this regard which has shown varying results in past literature.

Our study observed 28% (14 cases) diagnosed as HCC whereas remaining 72% (36 cases) diagnosed as metastatic deposits after considering morphological and immunohistochemical findings. Metastatic tumors were the most common (72%).

Results are comparable with other studies such as, Dhameja et al.[13], Rasania et al.[14] and Ali SR et al.[15] which showed 77.7%, 70.4% and 58% of metastatic tumors respectively among the total liver malignancies. However, study by Swamy et al.[16] found primary malignancies more common than metastatic lesions.

Results on age distribution show most common age group having malignant hepatic lesions between 51-60 years comprising about 46% (n=23), followed by 61-70 years comprising 26% (n=13) of the total cases. Hashem B. El-Serag, studied the epidemiology of HCC worldwide and concluded that in low risk population the incidence is >70 years and in high risk groups it is between 50 to 60 years.[17] However in our study, most involved age group was 51-60 years without considering risk involvement. Subrat K. Acharya studied the epidemiology of Hepatocellular carcinoma in India and concluded that the age ranges between 40 to 70 years at the time of presentation.[18] Similar results were seen in the earlier study conducted by Gatphoh *et al*.[19] and Nggada *et al.*[20]

Our results on gender distribution show male predominance in both groups. Subrat K. Acharya studied the epidemiology of Hepatocellular carcinoma in India and concluded that the male to female ratio is 4:1 in India.[18] Hashem B. El-Serag, studied the epidemiology of HCC world wide and concluded that men are at increased risk for HCC partly because they have a greater incidence of viral hepatitis and alcoholic cirrhosis.[17]

Cytology results revealed 12 cases of HCC and 38 cases of metastasis. However, on correlating with morphological and CD10 immuno histochemical marker findings in cell block and core needle biopsy, total 14 cases were categorised in HCC group and 36 as metastasis. With these findings, USG guided FNAC proved to be beneficial in our results showing sensitivity of 85.71%, specificity of 84.44%, positive predictive value 85.71%, negative predictive value 84.44% and diagnostic accuracy of 92%.

Table 1 Showing Sensitivity And Specificity Of Cytology In Malignant Hepatic Lesions

True positive	True negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Diagnostic accuracy (%)
12	34	85.71	84.44	85.71	84.44	92.00

Our results were in accordance with 90% in the study by Rasania *et al*.[14] Kuo *et al*.,[21] (86.1%), Tsai *et al*.,[22] (88.7%), Cochand-Priollet *et al*.,[23] (82.6%) and Franca *et al*.,[24] (78%).

Our results in cell block preparation show 13 cases of HCC and 37 cases of secondaries. Cell block proved to be beneficial in our scenario as one case previously considered to be metastasis on cytological picture was later reported as HCC on cell block, thus played an important role in recognizing the architectural pattern and aided in arriving at a diagnosis. In our study, sensitivity of cell block came out as 92.86%, specificity 97.22%, positive predictive value is 92.86% and negative predictive value of 97.22 % with diagnostic accuracy of 96%.

Table 2 : Showing Sensitivity And Specificity Of Cell Block In Malignant Hepatic Lesions

True positive	True negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Diagnostic accuracy (%)
13	35	92.86	97.22	92.86	97.22	96.00

Our results were similar with Basnet and Talwar study,[32] Shivakumarswamy et al. [33], Keyhani-Rofaga et al.[34] and Khan N et al.[36] CD10 was originally identified in acute leukemia as a common acute lymphoblastic leukemia antigen[46] as a cell surface enzyme with neutral endopeptidase activity and the ability to degrade a variety of biologically active compounds, CD10 is widely expressed in normal tissues and tumors, most notably hematologic malignancies and renal cell carcinomas.[78-79]

In the gastrointestinal tract, CD10 expression is limited to microvilli of the small intestinal and biliary epithelium, where it regulates the concentration of bradykinin, cholecystokinin, and other bioactive substances in the postsecretory modification of bile. Whereas in hepatocytes CD10 expression is discontinuous, with patchy apical labeling with a canalicular distribution.[80-82]

In our study, 12 out of total 14 HCC cases (85%) showed positivity in canalicular pattern whereas 5 out of total 13 metastasis cases (13%) showed cytoplasmic positivity for CD10 in cell block and core needle biopsy. One case reported as metastasis on cytology and cell block revealed as HCC after observing positivity in canalicular staining pattern on CD10 IHC.Both cell blocks and core needle biopsies showed identical results on IHC in all cases. Our study was in accordance with Borscheri et al, Lin et al, Saad et al, Ahuja et al,

Joydeb Singha, Xiao et al. and Mandal et al.

CONCLUSION

This study describes the diagnostic utility of ultrasound guided FNAC and cell blocks along with study of utility of CD10 immunomarker to differentiate between hepatocellular carcinoma from metastatic hepatic lesions. The present study recommends the simultaneous evaluation of cell blocks along with USG guided FNAC as this increases diagnostic accuracy of cytology. Furthermore, no comprehensive data about CD10 expression in HCC on cellblocks were available in the published literature as far as the this study is concerned. The present study recommends that the commonly available CD10 immunostain may be valuable if included in a panel of IHC markers for the distinction of HCC from metastatic carcinoma in cell-block specimens. As results of both cell blocks and core needle biopsies were similar, cell blocks can used for immunostaining. Finally, CD10 immunostaining on cellblock, obtained from FNAC aspirate, is useful in discriminating HCC and metastatic carcinoma of the liver with a high statistical significance.

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