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Clinicocytological Analysis of Hepatic Neoplastic Lesions with Particular Reference to Morphological Pattern Assessment

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Abstract

Background: The liver is the site of numerous neoplastic and non-neoplastic lesions, with neoplastic lesions accounting for a prominent cause of morbidity and mortality. Being a common site for metastatic tumors, it becomes imperative to differentiate the same from hepatocellular carcinoma, owing to varied management modalities involved. Diagnosis by fine needle aspiration cytology (FNAC), is considered a prominent investigative procedure in this regard. However, it is not without its limitations and disadvantages.

Aim and Objectives: This retrospective research analyzes the cytological features of hepatic masses, with particular reference to pattern assessment, cellular and nuclear details along with background characteristics of note which could define differentiating characteristics of hepatocellular carcinoma from metastatic malignancy. Accompanying clinico-radiological and biochemical parameters that could be helpful in this regard were also studied. An attempt was also made to distinguish the features characteristic to different grades of hepatocellular carcinoma (HCC).

Method: FNAC of 114 hepatic neoplastic lesions received during a two years period in the pathology department of a tertiary care hospital were retrospectively analyzed. Clinico-radiological and biochemical parameters were correlated, and data thus retrieved was analyzed statistically for relevance. Results: Males were predominantly affected both by primary and metastatic malignancy with primary over 60 years of age. Jaundice, history of prior alcohol consumption, pre-existing liver disease, elevated LFT along with AFP levels >400 ng/ml was seen in significant cases of hepatocellular carcinoma. Radiologically, metastasis showed multiple lesions with most cases less than 5cms in diameter with invasion of adjacent structures. Analysis of three characteristic cytological features including presence of cytoplasmic bile, intranuclear inclusions and traversing blood vessel was carried out and it was observed that the highest chance of tumor being HCC was when all three were seen. After analyzing features to differentiate between the different grades of HCC it was observed that as the grades progressed the cells became undifferentiated and similarities increased. Cytohistological correlation was seen in 91.3% of cases of primary and 86.9% of metastatic malignancies.

Conclusion: Close attention to cytological features like cell clusters, intranuclear inclusions, endothelial rimming in conjunction with radiological images and biochemical markers provide valuable pointers in distinguishing between primary HCC and hepatic metastatic carcinomas thus obviating the need of invasive procedures.

Keywords: Hepatocellular carcinoma • Cytology • Intranuclear inclusions

Introduction

Liver disease is the third most common cause of death among individuals between the age of 25 and 59 years and 7th most common cause of all disease related death [1]. Hepatocellular carcinoma has become the leading cause of death in patients with liver cirrhosis [1]. It is a major cause of morbidity and mortality in certain parts of Africa and South Asia with incidence of 100/1,00,000 people per year [2]. The liver is also a common site for metastatic tumors, accounting for 25% of all metastasis to solid organs [3]. In adult oncology patients, most hepatic metastasis are adenocarcinoma followed by squamous cell carcinoma and neuroendocrine carcinoma [4].

Evaluation and appropriate management of hepatic lesions is dependent on accurate diagnosis. The liver can be considered as the most common easily accessible solid organ and hence Fine Needle Aspiration is often used as a diagnostic modality. Compared to a core biopsy, it is a more sensitive, less invasive method with a lower complication rate [5]. FNAC aided by Ultrasonography, is fast becoming an effective inexpensive first line investigative aid in the diagnosis and preoperative assessment of hepatic masses.

The normal liver parenchyma comprises of heterogenous population of cells namely-hepatocytes, Bile duct and ductular epithelium, Kupffer cells, Endothelial cells, Mesothelial cells, Inflammatory cells. There are a number of benign and malignant lesions that pose a diagnostic dilemma to the pathologist in assessment of cytological smears aspirated from liver lesions.

Diagnostic difficulties arise at the end of spectrum that is distinguishing WD-HCC from benign lesions like reactive and dysplastic hepatocytes, Cirrhotic nodule, Dysplastic nodule, Focal Nodular Hyperplasia and hepatic adenoma while malignancies mimicking HCC are primary hepatic tumors like Hepatoblastoma, intrahepatic cholangiocarcinoma and metastatic malignancies [6].

To delineate the difference between the two and assess features characteristic of different grades of HCC, this study embarks on an analysis of the clinical and cytological parameters of hepatic masses, with particular reference to cytological pattern assessment.

Materials and Methods

A retrospective study was conducted on 114 out of 115 cases of cytologically diagnosed primary and metastatic hepatic tumors, received in the department of Pathology, Kasturba Medical College, Manipalduring a two year period. Clinical and cytological parameters of the cases thus included in the study

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were scrutinized, excluding one case of cirrhotic nodule on review of FNAC slides, thus revising the total number of cases as 114, from 115.Of these 114 cases, clinical data was available for 96 cases.

Clinical data were analysed for presenting symptoms, history of preexisting liver disease, alcohol consumption, or any other malignancy detected. Radiological (USG/CT) findings noted included number and size of lesion, invasion of adjacent structures, background cirrhosis. Biochemical parameters of LFT, HBsAg, HCV, tumor markers namely AFP, CEA, CA125 were analysed. All cases of FNAC liver diagnosed as hepatocellular carcinoma or metastatic malignancy, of all age groups and gender were included, with nonmalignant lesions being excluded.

FNAC smears of 114 cases stained by the Papanicolaou technique were assessed for various cytological features including cellularity, cell pattern(cell clusters, monolayered sheets, syncytia, acini, trabeculae, dispersed single cells, molding, rosette), cell morphology (size of cells, cytoplasmic vacuoles, cytoplasmicbile, shape of cell like spindle shaped, round, hepatocyte like, columnar), nuclear features(size, chromasia, intranuclear inclusions, anisonucleosis), presence or absence of nucleoli and mitotic figures, and background characteristics (bare nuclei, traversing blood vessels, fibrosis of stroma, necrosis, inflammation and hemorrhage). The slides of smears diagnosed cytologically as HCC, were further graded using a three tier system for differentiation (well, moderately and poorly differentiated).

IN 69 cases, histopathological sections were available for critical evaluation and correlation with the cytological findings. Data obtained was analyzed statistically using SPSS software (version 14.0 for windows; SPSS, Inc; Chicago, IL) using chi-square test. A p-value of <0.05 was considered statistically significant.

Results

Predominant cases of primary HCC were seen to be over the age of 60 years with a range of 60-65 years; poorly differentiated variant was seen in older patients, whereas metastasis was seen in younger patients. PD-HCC had the highest mean age of 65 years when compared to the other grades.

Clinically, patients presented with many symptoms, predominant among them being abdominal pain in both categories, followed by loss of weight. Jaundice was seen more in patients with primary malignancy (12.50%) and was statistically significant (P=0.048).

Of the total number of 115 cases, HCC was diagnosed in 47 cases with the most frequently found grade being WD-HCC (24.60%). 68 cases of metastatic carcinoma were seen, with adenocarcinoma forming the major group (36%). A single case of cholangiocarcinoma was also seen. One case which was diagnosed as WD-HCC on cytology was thought to be cirrhotic nodule with atypia on review and hence removed, making the total number of cases as 114. Out of 47 cases of HCC, 23 were WD-HCC, 10 MD-HCC and 4 PD-HCC.

Analysis of available medical records of 96 cases, revealed pre-existing liver disease in a higher number of primary malignancies (31.4%) and a known primary in most of the cases with secondary malignancy (90.6%), both of which were statistically significant [(P=0.039) and (P=<0.001) respectively]. HCC was associated with a marginally higher number of cases (29.4%) showing prior alcohol consumption (Table 1).

Radiological analysis of the tumour in 85 cases (Table 1), depicted significant number of metastasis with multiple lesions, which were smaller (<5 cms), ill-defined with invasion of adjacent structures. HCC showed slightly a greater number of cases with single lesion, often more than 5 cms in size, less ill-defined and seen in a background of cirrhosis (Table 2).

Liver function tests (Table 2), were noted to be elevated more often in primary malignancy and was statistically significant (P=0.037), though elevation of alkaline phosphatase was not significant in the two groups. Surprisingly, HBsAg positivity was seen in both primary and metastatic malignancies. The single case which was HCV positive was found to have HCC.

Table 1. HCC Vs Metastatic carcinoma: comparison of radiological findings (N=85).

CT/USG			
	Primary (n=35)	**Metastasis (n=50)**	**P Value**
No of lesions			
Single	19(54.3%)	4(8.0%)	<0.001; Sig
Multiple	16(45.7%)	46(92.0%)	
Size			
<5 cm	4(11.4%)	16(32.0%)	0.003; Sig
5-10 cm	12(34.3%)	10(20.0%)	
>10 cm	13(37.1%)	6(12.0%)	
Ill-defined	6(17.1%)	18(36.0%)	
Invasion of adjacent structures(n=36)	7(19.4%)	15(31.3%)	0.223; NS
Background cirrhosis	11(30.6%)	0(0%)	

Table 2. HCC Vs Metastatic carcinoma: comparison of biochemical parameters.

Biochemical Parameters		**Diagnosis**		**p-value**
		Primary	**Metastasis**	
LFT(n=83)	Elevated	23(62.2%)	18(39.1%)	0.037; Sig
ALP(n=79)	Elevated	21(58.3%)	20(46.5%)	0.295; NS
HBsAg(n=31)	Positive	9(50.0%)	2(15.4%)	0.52; Sig
HCV(n=16)	Positive	1(12.5%)	0(0%)	0.5; NS
AFP(n=59)	<400 ng/ml	18(48.6%)	22(100%)	<0.001; Sig
	>400 ng/ml	19(51.4%)	0(0%)	
CEA(n=25)	Elevated	2(22.2%)	10(62.5%)	0.063; NS
CA-125(n=6)	Elevated	0(0%)	4(80.0%)	0.333; NS

AFP levels were significantly elevated in primary malignancies with AFP above 400 ng/ml. CEA and CA-125 levels were both found to be elevated in metastasis (Table 3).

Biochemical parameters (Table 3) were also compared between different grades of HCC. More than 50% of cases showed raised LFT with the maximum number of cases being of MD-HCC. Serum levels of alkaline phosphatase increased exponentially to the differentiation. Viral markers were seen in all casesof poorly differentiated HCC, followed by WD-HCC. AFP level elevation was more in MD-HCC, CEA levels were seen to be normal only in PD- HCC (Table 4).

Both primary and metastatic malignancy showed smears of moderate cellularity predominantly (Table 4). Cell pattern was seen to be in the form of cell clusters highest in metastasis followed by an acinar pattern. Primary malignancies showed predominantly cell clusters followed by monolayered sheets and syncytia (P=<0.001). Hence presence of acini could be considered significant for metastatic adenocarcinoma and monolayered sheets for HCC (Figures 1-5) Dispersed cells were seen in both with fewer in metastasis. Molding when present was significantly higher in metastasis (P=0.028) (Figures 1-5, Table 5).

Intra nuclear inclusions and bare nuclei were significantly seen in HCC (P=<0.001) (Table 5). Traversing blood vessels was typical of primary malignancy especially endothelial rimming. Endothelial rimming of all cell aggregates was absent in metastasis (Figure 6 & 7).

When the different grades of HCC were analyzed (Table 5), it was noted that moderately cellular smear meant MD and WD- HCC and scant cellular smears were noted in PD-HCC. Combination of cell clusters and monolayered sheets were features of well differentiated HCC, of cell clusters, monolayered sheets and syncytia of MD-HCC, of predominantly cell clusters and syncytia

Table 3. Comparison of biochemical findings in various grades of HCC (n=47).

Biochemical parameter	WDHCC (n=23)	MDHCC(n=10)	PDHCC (n=4)
LFT(n=37) Elevation	12(52.2%)	9(90.0%)	2(50.0%)
ALP(n=36) Elevation	10(45.5%)	7(70.0%)	4(100.0%)
HBsAg(n=18) Positive	4(50.05)	5(71.4%)	0(0%)
HCV(n=8) Positive	0(0%)	1(50.0%)	0(0%)
AFP(n=37) Elevated	8(31.8%)	9(75.0%)	2(50.0%)
CEA(n=9) Elevated	1(16.7%)	1(33.3%)	0(0%)

Table 4. HCC Vs Metastasis: Analysis of cellularity and cell pattern (N=114).

	Primary HCC (n=47)	Metastasis (n=67)	p-value
Scant	3(6.4%)	9(13.4%)	0.211
Moderately cellular	30(63.8%)	46(68.7%)	
Highly cellular	14(29.8%)	12(17.9%)	
Cell clusters	41(87.2%)	63(94.0%)	0.177
Monolayered sheets	33(70.2%)	17(25.4%)	<0.001
Syncytia	21(44.7%)	23(34.3%)	0.264
Acini	9(19.1%)	35(52.2%)	<0.001
Trabeculae	27(57.4%)	7(10.4%)	<0.001
Dispersed Cells			
Few cells	16(34.0%)	41(61.2%)	0.013
Many cells	7(14.9%)	4(6.0%)	
Molding	8(17.0%)	24(35.8%)	0.028
Rosette	2(4.3%)	4(6.0%)	0.518

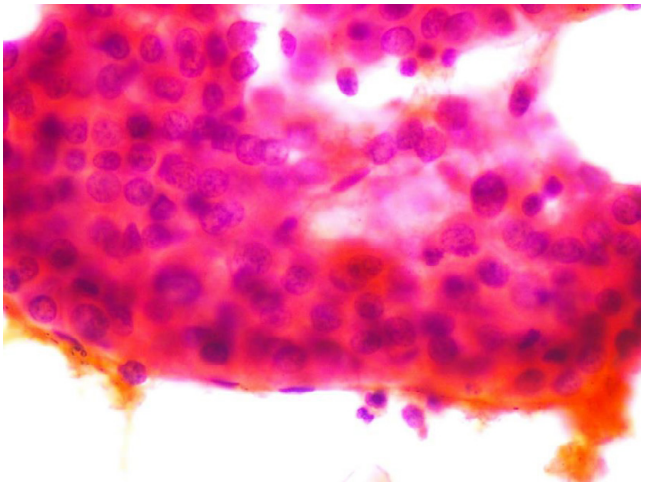

Figure 1. WD-HCC: broad trabeculae with endothelial rimming (Papx400).

of PD-HCC (Figures 8 & 9). Dispersed cells, rosette and molding were seen in very few cases across the categories. There was no difference between categories when cell shape, size, presence of cytoplasmic bile and vacuoles were analyzed.

Bare nuclei were seen more in MD-HCC and PD-HCC, whereas traversing blood vessels were seen often in WD-HCC and MD-HCC. Fibrous stroma

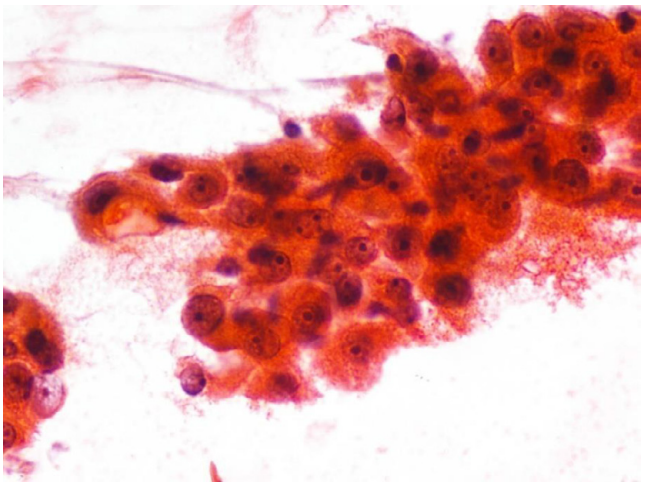

Figure 2. HCC: Targetoid nuclei (Papx400).

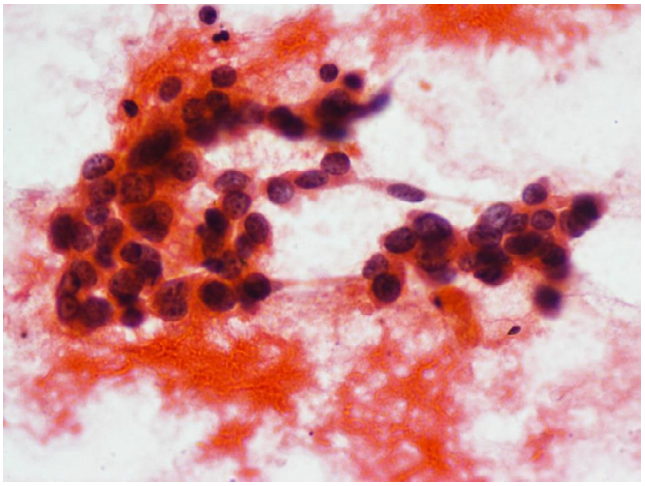

Figure 3. Small cell HCC (Pap x400).

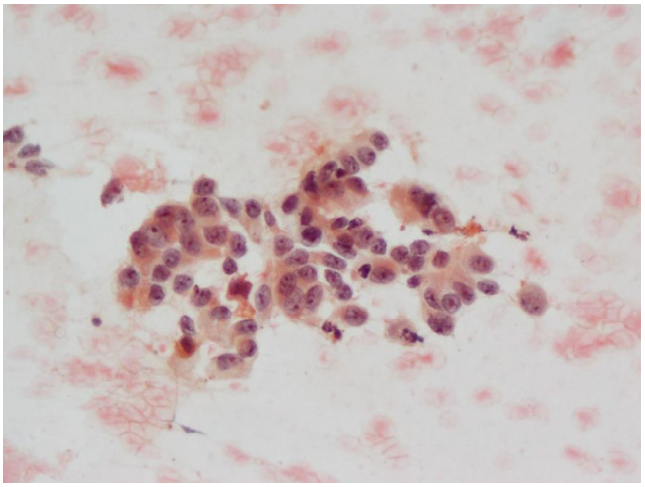

Figure 4. Adenocarcinoma: columnar cells (Pap x100).

was absent in PD- HCC and seen most often in MD-HCC. Necrosis was more often noted in MD-HCC while inflammation was grade 1 and prominent in WD-HCC (Figures 8 & 9, Table 6).

To distinguish features distinct to metastatic malignancy as compared to primary HCC, an analysis of three characteristic cytological features including "presence of cytoplasmic bile, intranuclear inclusions and traversing blood vessels", was carried out (Table 6). It was observed that the highest chance of the tumor being HCC was when all three were seen,

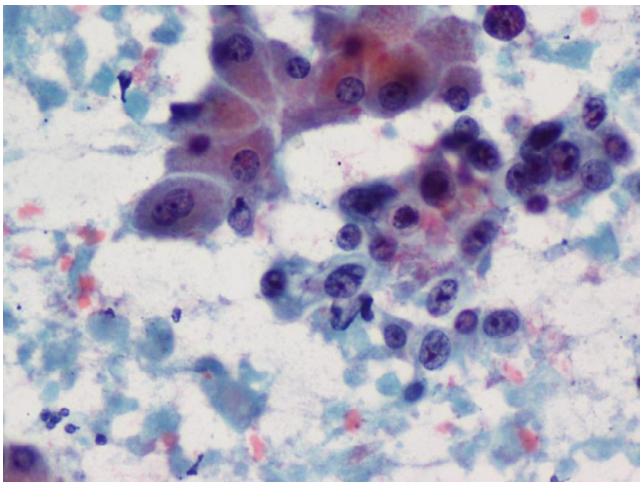

Figure 5. Metastatic adenocarcinoma: malignant cell cluster with adjacent benign hepatocytes (Pap x400).

Table 5. HCC Vs Metastasis: Analysis of cellular features & background (N=114).

Cellular features	Primary HCC (n=47)	Metastasis (n=67)	p-value
Cell Size			
Cell size :			
Small	2(4.3%)	4(6.2%)	0.594
Intermediate	37(78.7%)	56(83.1%)	
Large	8(17.0%)	7(10.8%)	
Cytoplasmic Vacuoles	15(31.9%)	20(29.9%)	0.814
Cytoplasmic bile	7(14.9%)	5(7.5%)	0.168
Intranuclear inclusions	30(63.8%)	17(25.4%)	<0.001
Anisonucleosis	39(83.0%)	53(79.1%)	0.606
Bare nuclei	28(59.6%)	14(20.9%)	<0.001
Traversing blood vessels	38(80.9%)	14(20.9%)	<0.001
Fibrous stroma	16(34.0%)	22(32.8%)	0.893

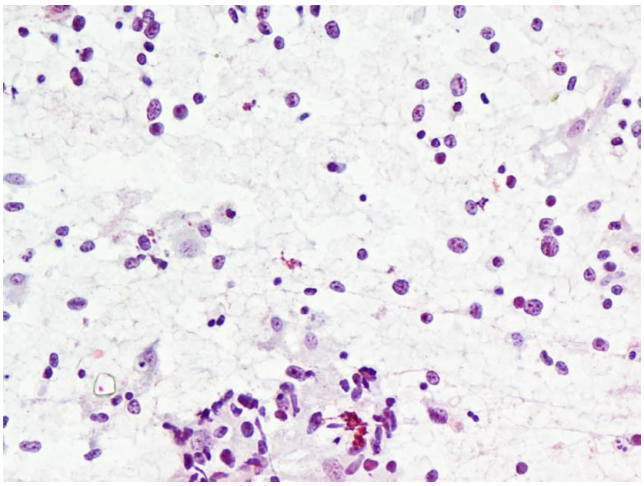

Figure 6. HCC: Bare nuclei (Pap x 100).

followed by a combination of intranuclear inclusions and traversing blood vessels. The possibility of a smear being that of HCC was least when only bile was present, or all three features were absent.

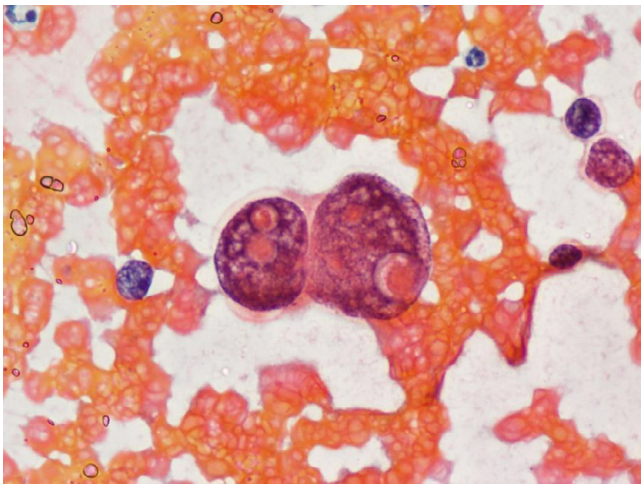

Figure 7. HCC: Intranuclear inclusions(Pap x400).

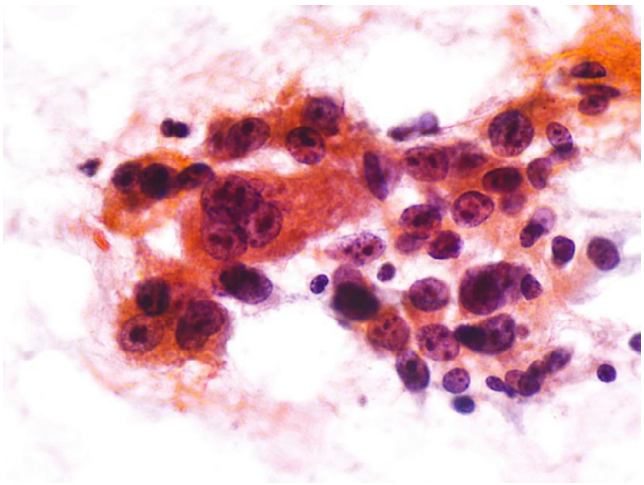

Figure 8. MD-HCC (Pap x400).

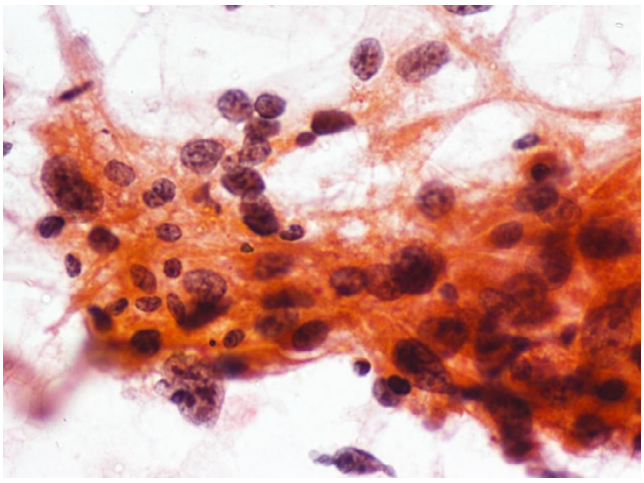

Figure 9. PD-HCC : marked anisonucleosis(Papx400).

Histopathological correlation was available in 69 cases. 21 out of 23 cases of HCC and 40 out of 46 cases of metastasis were correlating (Figures 10 &11).

Discussion

Liver is a frequent seat of metastasis, detection of which and distinguishing from HCC being important in management of the malignancy. FNAC being one of the primary modalities of evaluation in hepatic masses, cytology plays

Table 6. HCC Vs Metastasis with analysis of three cytological features.

Cytological features			No of patients		
Bile	Intranuclear inclusions	Traversing blood vessels	HCC (n=47)	Metastasis (n=67)	Probability % of HCC
P	P	P	4	0	100.0%
P	P	A	1	1	50.0%
P	A	P	2	3	40.0%
P	A	A	0	1	.0%
A	P	P	21	3	87.5%
A	P	A	4	13	23.5%
A	A	P	11	9	55.0%
A	A	A	4	38	9.5%

P = Present, A= Absent

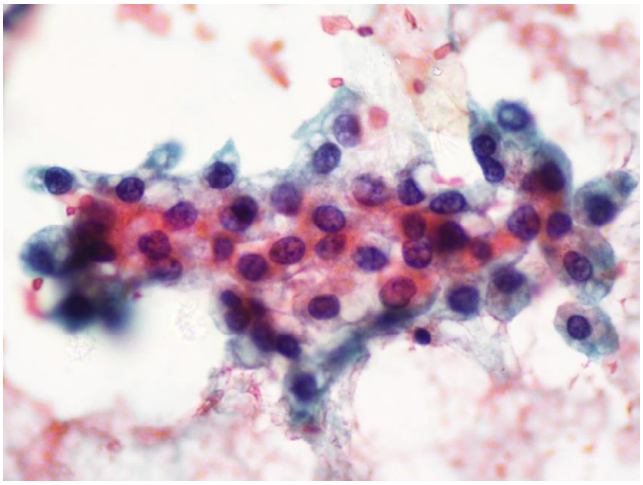

Figure 10. WD-HCC: cytoplasmic clearing (Pap x400).

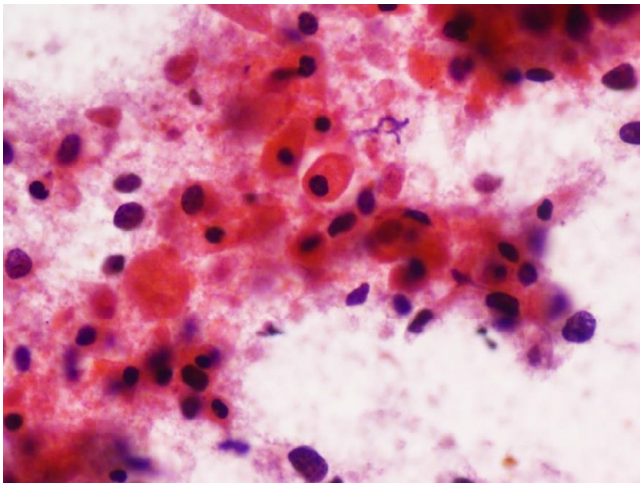

Figure 11. Hepatocyte like cells in adenocarcinoma (Pap x 400).

a big role in making this distinction. This study was carried out at a tertiary care centre as a retrospective analysis of FNAC diagnosed malignancies occurring in the liver.

Cytological features of tumors metastasing to liver: Most common tumors are Adenocarcinomas. Cytological features in favour of adenocarcinoma include hypercellularity with malignant columnar to cuboidal cells arranged in monolayered sheets, acinar pattern, palisade forms, and lying singly with granular, eosinophilic, vacuolated cytoplasm with intra or extra cytoplasmic mucin. The cells show increased N/C ratio, anisonucleosis, with central to eccentrically placed nucleus and fine to coarse dispersed chromatin in a background of benign hepatocytes, inflammation, necrosis and fibrosis [6,7].

Architectural features favoring HCC: Broad trabeculae, endothelial rimming/transgression of vessels in cell clusters, bare atypical nuclei, intracytoplasmic vacuoles, intranuclear inclusions and intracytoplasmic bile are classical cytological features favoring hepatocellular carcinoma[8,9]. Monotony and nuclear crowding are other features that suggest WD-HCC while tumor cells resembling non neoplastic hepatocytes, endothelial rimming or transgressing of cell clusters, moderately high N/C ratio, eccentric pleomorphic nuclei, multinucleation, multiple and enlarged nucleoli, few mitoses favour MD-HCC [6,10]. Anaplastic cells bearing no resemblance to hepatocytes, lack of trabecular and bile formation, increased mitoses, less prominent peripheral endothelial rimming and transgressing endothelium, anisocytosis and anisokaryosis are more frequently seen in moderately to PD-HCC [8,10]. Multinucleated giant cells with three or more atypical nuclei are seen in all grades of HCC and their presence does not increase the grade of tumor[6].Nuclear contour irregularities, enlarged nucleoli, increased chromatin density and irregular distribution of chromatin are features favoring poor differentiation in HCC [8,10].

Relationship to other studies: Similar to other studies, most of the patients in this study belonged to the age group above 40 years with metastatic malignancies seen in patients younger than those with HCC. The mean age of primary tumors was 62 years and for metastasis was 57 years, with males being predominantly affected, irrespective of primary [3,5] and secondary hepatic tumours [11-14]. Clinically in this study, the presenting symptom was most commonly pain abdomen whether it was primary or secondary followed by loss of weight, with jaundice being more often in HCC, concurring with studies by Ahuja et al. and Bottle et al. [3,15]. In our study metastatic carcinomas were more frequent than HCC with WD-HCC being the most frequent tumor [2,6], similar to other studies [13,16]. In the present study, alcohol consumption and preexisting liver disease was noted in slightly higher percentage of primary malignancies. Bottle et al. [15] quotes a study conducted in North America citing that 50% of HCC cases are seen in cirrhotic patients.

Radiological findings in this study were similar to Ahuja et al. [3] and included multiple lesions in metastasis as compared to primary which could present as single or multiple nodules with almost equal incidence. Comparison of biochemical parameters in the present series showed elevated LFT and AFP characterizing HCC where as elevated CEA and CA-125 was noted in metastasis. Alkaline phosphatase was almost equivocal in both. This was similar to the study by Soyuer et al. [11] Ahuja et al. [3] however differed in their study where AFP>500 ng/ ml was detected in only 11.7% of cases of HCC. In our study, serum HBs Ag positivity was seen in 50% of cases; Ahuja et al. [3] also mentions 33.3% positivity for HBsAg in cases of HCC.

Cell pattern was a distinguishing feature in this study between primary and secondary malignancies with clusters and monolayered sheets being the most prominent features followed by trabeculae in HCC. Metastasis was characterized by cell clusters followed by acini. Trabeculae were a rarity. This pattern of cellular arrangement in HCC in our study corroborates with that of Ahuja et al. [3], Soyuer et al. [11]. Dispersed cells and molding were characteristically seen in metastatic carcinoma as compared to HCC in our study. Dissociated cells in association with other patterns was noted by Ahuja et al. [3] to be seen predominantly in metastatic carcinomas. A study of nuclear characteristics of HCC and metastatic carcinomas in our cases showed intranuclear inclusions being more in primary HCC. The prominence of 'stripped' naked atypical nuclei of tumor cells in the background in smears from HCC patients has been stressed upon by several researchers [2-9] and was found to be a significant feature to differentiate from metastasis in the present study [11,17,18].

Traversing blood vessels seen within and rimming trabeculae and cell nests, were a prominent and significant feature noted by us in our cases of HCC, concurrent with Ahuja et al. [3], Swamy and colleagues [6]. Metastasis meanwhile showed blood vessels as a component of stroma.

An attempt was made to identify features that could help to differentiate between the various grades of HCC. It was observed by us that as the grade progressed and the cells became undifferentiated, the cellularity increased.

The cell pattern found to be similar between the different grades, was a mixture of clusters, monolayered and syncytial fragments, acini and trabeculae with a predominance of cell clusters in our series. However, dyscohesiveness was more a feature of PD –HCC. Aileen Wee [8] in her extensive analysis of smears from HCC has noted a similar finding that an increase in tumor grade was associated with corresponding increase in dissociation.

Tau et al. [19] suggest that prominent nucleoli, increase in number with a higher grade. This is in concurrence with findings by Takenaka et al. [14], Swamy et al. [6] and the present study. We however differ with respect to other nuclear features since irrespective of the grade; the size, the chromatin, anisonucleosis, intranuclear inclusions etc were found to be similar. Bare nuclei in all studies including ours were found to be higher in MD and PD-HCC whereas traversing blood vessels reduced as the grades got higher.

One case of HCC was called as adenocarcinoma on cytology which on review showed moderately cellular smear with columnar cells, acinar pattern and all the cytologic features of adenocarcinoma, thus giving a mistaken impression of non-hepatic malignancy. This difficulty has also been faced by other researchers [1,6,12,20] in the past especially when the smears show acini and HCC is either moderately or poorly differentiated, wherein classical features like cytoplasmic bile may be absent. Another case of HCC diagnosed as adenocarcinoma cytologically was probably influenced by a prior history of adenocarcinoma in the lung occuring a few years back in the same patient. One case which was diagnosed as adenocarcinoma on cytology based on earlier history of carcinoma lung, was found to be non-representative on biopsy.

Conclusion

Cytological features in conjunction with radiological images provide valuable pointers in distinguishing between primary HCC and hepatic metastatic carcinomas. Close attention to a combination of major cytological criteria like intranuclear inclusions, endothelial rimming of cell clusters and background stripped atypical nuclei could help identify HCC. Amongst HCC, differentiation could be assessed by degree of nuclear atypical and dyscohesiveness. Cytological diagnosis thus made could help in early detection in the case of hepatic masses, thereby obviating the need for more invasive techniques like core biopsies.

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