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ULTRASOUND GUIDED FINE NEEDLE ASPIRATION CYTOLOGY AS TOOL FOR CYTOMORPHOLOGIC STUDY AND CLASSIFICATION OF GALLBLADDER CARCINOMA: A MUTICENTRIC CASE SERIES

Pathology

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ABSTRACT

Background: Ultrasound guided (US)fine needle aspiration (FNA) cytology serves as the first line modality for the assessment of mass lesions and mural thickening of the Gallbladder (GB). **Aim and Objective:** To assess the application of pre-operative US guided FNA cytology to study morphology of GB carcinoma cases and eventually to classify GB carcinoma . Material and methods: The present one year retrospective study was conducted on 47 patients suspected to have GB carcinoma on ultrasonography. US guided FNA from GB was done in these patients and simultaneous FNA of other organs was done in 17 patients. Histopathology was available in 5 cases. **Results:** Ultrasonography revealed mass/thickening of GB wall in 47 cases. Out of 47 cases malignancy was cytologically diagnosed in 43 (91.4%) cases while 03 (6.4%) cases were inflammatory and 1 (2%) case was labelled as inadequate. Metastatic tumour deposit in liver was noted in 15 cases, in abdominal lymph nodes in 1 case and in retroperitoneal lymph nodes in 1 case. Necrosis and haemorrhage posed as the main diagnostic pitfall. **Conclusion:** US guided FNA cytology provides a rapid and reliable tool to study the morphology and thereby classify cases of GB carcinoma.

KEYWORDS

Gallbladder; Fine Needle Aspiration Cytology; Ultrasonography; Morphology; Classification

INTRODUCTION

Carcinoma of gallbladder is the most common malignant tumour of the biliary tract [1] and is one of the five most common forms of gastrointestinal cancers worldwide [2]. It shows marked geographic variation and ethnic variation. India has a high incidence of gallbladder cancer and contributes to about 10% of the global gallbladder carcinoma burden [3]. A particularly high prevalence of gallbladder carcinoma is found in Gangetic basin of north India [1]. It is eight times more common in North India than in South India [3, 4]. The incidence in North India is 10–22/100,000 population and is similar to that of other countries with high incidence such as in South America [3].

Due to absence of any specific sign and symptom and along with aggressive biological nature, it results in silent progression and rapid spread to adjacent vital organs. In most cases either it is diagnosed incidentally during cholecystectomy or when a patient experiences symptoms due to local spread of malignancy. In either case it is usually too late to surgically resect the tumour as the tumour has already progressed to advanced stage. The ultrasound (US) guided fine needle aspiration (FNA) cytology has emerged as rapid, readily available and inexpensive method to accurately diagnose and type the gallbladder carcinoma [5,6,7,8,9.Its utility is even more for rural and suburban region of north India where general population cannot afford expensive and repeated tests.

Reports of FNA of the gallbladder lesions in the Gangetic basin of north Indian region of Kanpur and Azamgarh are limited.

In this study we have reviewed the US guided aspiration of gallbladder mass lesions and mural thickenings along with clinical and radiological correlation. The aim of this study is to assess the application of pre-operative US guided FNA to outline cytomorphologic features of GB carcinoma.

MATERIAL AND METHODS

This is a retrospective study of one year. 47 patients who showed gallbladder mass lesion or wall thickening on routine abdominal ultrasonography were selected for Fine needle aspiration cytology. Among 47 cases, FNA of another organ was simultaneously done in 17 patients as while performing ultrasonography apart from GB mass, these cases presented with mass in other organ as well. This included 15 cases of liver (as space occupying lesion) and 1 case each of abdominal and retroperitoneal lymph nodes respectively.

Table 1: Gender Based Distribution Of Presenting Complain

Presenting complain	Male(N=13)	Female(N=34)
Pain in right hypochondrium	8(60%)	22(65%)
Jaundice	4(30%)	10(32%)
Nausea /vomiting	7(50%)	17(50%)
Loss of appetite	10(76%)	28(83%)
Itching	1(7%)	3(10%)
Clay coloured stool	1(7%)	2(5%)

The most common presenting complain in male as well as female patients was loss of appetite(seen in 76% males and 83 % female patients respectively) followed by chronic pain in the right hypochondrium/ abdomen, jaundice, nausea, vomiting, weight loss, itching or clay coloured stool as shown in table 1 .

After routine work up for prothrombin time, platelet count and obtaining written consent, the patients underwent a pre -operative US - guided FNA as an outpatient procedure. Prior to aspiration, the GB lesion was localized under ultrasonic guidance and an estimate of depth of lesion was noted. Accordingly access site was selected. After selecting the optimal access site, the overlying skin of the anterior abdominal wall was sterilized. Percutaneous transhepatic aspiration was done using 23-27 G needle and 10 ml disposable syringe. The aspirated material was smeared on glass slides. In all cases half of the slides were air dried and stained with Leishman Giemsa and the other half of the smears were immediately fixed with 95%alcohol and stained with Papanicolaou (Pap) stain and haematoxylin and eosin (H&E) stain. Due to inadequate material in first attempt, a repeat FNA was performed in the second attempt in 6 cases (12.5%).

For analysing smears, diagnostic criteria laid down by G. Kocjan et al [9] and Berkane et al [10] was used. The presence of five to six groups of cells deemed to represent the lesion was considered adequate for reporting. Histopathology of gallbladder was available in five cases.

RESULTS

Total 47 cases were studied. Out of this 13 were male (28.8%) and 34 (71.1%) were female. Their age ranged between 32 and 75 years (median age 57 years). Maximum numbers of cases (50%) were seen in the age group 55-75 years. Table 2 shows the correlation of FNA cytodiagnosis of GB lesions with age and sex distribution of the patients.

Table 2: Age and Sex Distribution of Cases.

Cytodiagnosis	No. of cases (N=47)	Age range (years)	M:F ratio
Malignancy	43 (93.5%)	32-75	1:4
inflammation	3 (6%)	35-62	1:2
Inadequate/inconclusive	1 (2%)	58	M

USG revealed mass/thickening of wall of GB in 47 cases. Among 47 cases aspirated, malignancy was observed in 43 (93.5%) cases and 3 (6%) cases were inflammatory and 1 (2%) case was inconclusive. The cytological smear in the inconclusive/ inadequate category was acellular.

Among malignant cases, 35(82%) cases were of adenocarcinoma, 5

(11%) cases of undifferentiated carcinoma and 3(7%) cases of neuroendocrine tumour. Table 3 shows the cytomorphologic features of different cytologic subtypes of gallbladder carcinoma. Figures 1, 2 and 3 show the cytomorphologic features of adenocarcinoma, neuroendocrine tumour and undifferentiated carcinoma respectively. Depending on the presence of papillae or mucin pool adenocarcinoma cases were further typed into papillary and mucinous subtypes respectively.

Table 3: Classification of Gallbladder Carcinoma According to Cytomorphologic Features (N=43)

Cytologic subtype	Cytomorphologic features	Number	Percentage (%)
Adenocarcinoma	Cohesive fragments, sheets, small acini, focal mucin	32	74
Papillary adenocarcinoma	Papillae with fibrovascular core	02	5
Mucinous adenocarcinoma	Single cells/ clusters in pool of extracellular mucin	01	2
Neuroendocrine tumour	Rosettes, salt and pepper chromatin, nuclear moulding, anisonucleosis	03	7
Undifferentiated carcinoma NOS	Highly pleomorphic cells, abundant necrosis	05	12

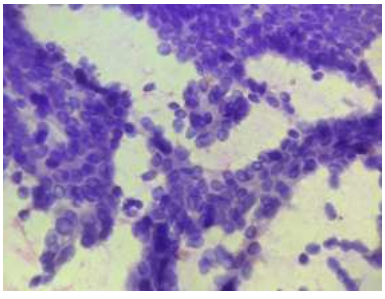

Figure 1: A cohesive sheet and micro acini of mildly pleomorphic hyperchromatic cells with high N:C ratio and scant cytoplasm in an aspirate from a case of adenocarcinoma gallbladder (H and E stain, magnification: x40).

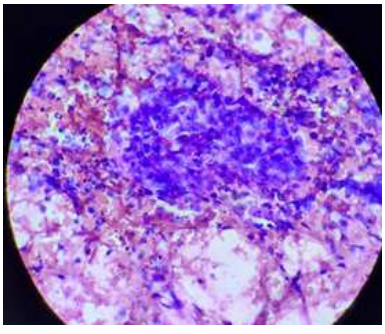

Figure 2: Dyshesive tumor cells with cytoplasmic stripping in an aspirate from case of neuroendocrine carcinoma of gallbladder. Nuclear moulding is evident (Papanicolaou stain, magnification: x40).

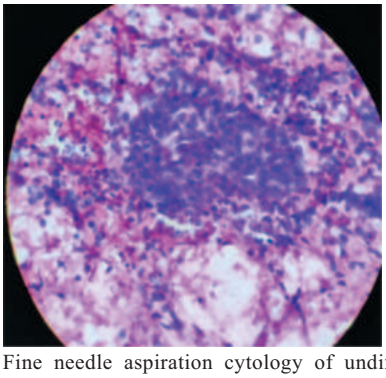

Figure 3: Fine needle aspiration cytology of undifferentiated carcinoma showing highly pleomorphic cells and necrotic background (H and E stain, magnification: x40).

Total 17 cases (36%) presented with simultaneous metastasis to other organs. The liver was noted as the major organ for tumour metastasis in all subtypes of GB carcinoma. Out of a total 17 cases, 15 cases (94%) showed space occupying lesions in the liver. Other than liver, metastatic deposits were noted in lymph nodes, one each in the abdominal and retroperitoneal lymph nodes. Figure 4 shows histopathology of liver metastasis. Table 4 shows metastases in different types of GB carcinoma.

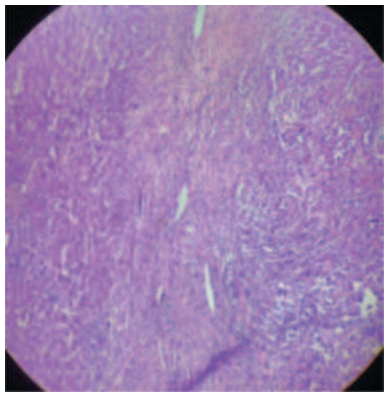

Figure 4: Histopathology slide of metastatic adenocarcinoma gallbladder shows liver tissue on left and metastatic adenocarcinoma with tubule formation and desmoplasia on right (H and E stain, magnification: x10).

Table 4: The Metastasis In Gallbladder Carcinoma.

Malignancy (N=43)	Number	Metastasis to liver (space occupying lesion)	Metastasis to abdominal lymph node	Metastasis to retro-peritoneal lymph node
Adenocarcinoma	35	12	1	
Undifferentiated carcinoma	5	3		1
Small cell neuroendocrine carcinoma	3	1		

All 3 cases cytologically diagnosed as inflammatory lesions showed thickened GB wall on ultrasonography. The pus was aspirated and showed large number of polymorphs in background of necrotic debris. In one of these cases foamy macrophages, inflammatory cells along with capillary fragments were seen, hence possibility of xanthogranulomatous cholecystitis was suggested. Histopathology was performed in 5 cases. 0f the 2 cases diagnosed cytologically as adenocarcinoma, histopathology confirmed the diagnosis. Of the 3 cases diagnosed inflammatory on cytology 2 were diagnosed as chronic cholecystitis and 1 as xanthogranulomatous cholecystitis on histopathological examination.

DISCUSSION

Few Indian studies have reported that carcinoma GB is more common in northern and eastern India compared to southern and western India [3]. Carcinoma of the GB occurs more commonly in elderly age groups however can affect ages between 4th and 5th decade and has female preponderance [10]. This has been documented in present study also as the male to female ratio was 1:2.5 and median age was 57 years. Various epidemiological factors like old age, female sex, multiparity, men with diabetes, intake of unsafe drinking water and heavy metal poisoning has been outlined for high prevalence of gallbladder disease in rural gangetic basin of north India [11].

Majority of carcinoma of GB develop insidiously and are detected in late stage when the growth is well established and has spread to adjacent liver and bile ducts and surgical resection is not possible. And tend to have bad prognosis [12]. On ultrasonography GB carcinomas may present as mass lesions replacing the GB, focal or diffuse thickening of the GB wall, and intraluminal mass in the GB [13]. The survival rate in GB carcinoma (GBC) can be improved if it is diagnosed at an early stage, especially when the tumour is confined to the wall[14]. US guided FNAC being a safe, rapid, cost effective and non-surgical day care investigation procedure is a useful tool for preoperative diagnosis and staging of carcinoma as is noted in the present study. A systematic review by Koimtzis et al have found a high diagnostic performance of FNAC in the assessment of gallbladder

masses and have suggested that every suspicious GB mass should be evaluated further with FNAC to facilitate the most appropriate early management [15].

In a study of 150 cases by Handa et al [16], 105 (76.7%) were considered malignant on cytology. In the present study out of 47 cases that were detected as GB mass/ thickening of wall of GB, 43 (91%) revealed malignancy on cytology.

Yadav et al [17] observed adenocarcinoma in 72.8% of their cases, neuroendocrine tumour in 0.7% cases and undifferentiated carcinoma in 5 % cases. In the present study out of the 43 cases of GB malignancy 35 (81.3%) were adenocarcinoma, 3 (6.9%) were neuroendocrine tumour and 5(11.6%) were undifferentiated carcinoma.

Precise radiological localization, multiple passes and well defined cytological criteria increase the sensitivity of the test to arrive at a final diagnosis. Repeat aspirations performed by experienced hands and better angle at imaging after initial report of inconclusive aspiration increases the sensitivity of the test [18]. In the present study repeat aspiration was performed in 6 cases to obtain adequate material. The overall adequacy rate was 86% and no major complication was reported in any of the 47 cases which is comparable to other studies [19].

In present study 3 out of 47 cases were inflammatory. Although in majority of cases USG helps in diagnosis of GB carcinoma yet inflammatory changes present in it can mimic or mask the features of malignancy. The pattern of wall thickening in GBC is often confused with benign diseases, especially chronic cholecystitis, xantho-granulomatous cholecystitis, and adenomyomatosis. Early recognition and differentiation of these conditions can improve the prognosis [20]. Hence in such cases wider sampling from multiple sites is advised. The diagnostic pitfalls included necrotic material, haemorrhage and inadequate epithelial cells [21,22]

Limitations of Study

As we studied 47 cases retrospectively during period of one year, a longer study with larger number of cases will help in better understanding the diagnostic utility of ultrasonography guided fine needle aspiration cytology in gallbladder carcinoma.

CONCLUSION

US guided fine needle aspiration is a safe and rapid procedure to study the cytomorphology of GB carcinoma and based on cytological features we can also classify the gallbladder carcinoma. USG is helpful in guiding the needle tip to the site of altered echogenicity and yields better results. However negative or inconclusive results should be interpreted with caution when there is high clinical suspicion and repeat US guided aspiration should be done in order to increase the sensitivity and diagnostic accuracy of the test.

Conflicts of Interest

Authors declare no conflicts of interest.

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