DIAGNOSTIC ACCURACY OF FINE NEEDLE ASPIRATION CYTOLOGY IN BENIGN AND MALIGNANT LESIONS OF THE BREAST

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ABSTRACT: **BACKGROUND AND OBJECTIVES:** Fine needle aspiration cytology is a simple, inexpensive and an accurate procedure for the diagnosis of palpable breast masses. The present study aims to correlate the cytologic findings in palpable breast masses with the corresponding histologic diagnosis and to evaluate the diagnostic accuracy of FNAC in distinguishing benign from malignant diseases of the breast in order to reiterate its usefulness in centres like ours where core needle biopsy is not yet established and practised.

METHODS: Fifty patients with palpable breast lumps were subjected to fine needle aspiration cytology of the breast and a post-lumpectomy or mastectomy histologic correlation was obtained in all the cases except one. The accuracy of FNAC in diagnosing benign and malignant lesions of the breast was calculated.

RESULTS: Benign diseases of the breast accounted for 38 (76%) of the 50 cases while the malignant lesions comprised of 12 cases (24%). The cyto-histologic concordance was 89.2% for benign lesions and 90.9% for malignant lesions of the breast. In distinguishing benign breast lesions from malignant lesions, the sensitivity of FNAC was 91.6%, the specificity 100%, positive predictive value 100%, negative predictive value 97.4%, false positive fraction was zero and the false negative fraction was 8.4%.

INTERPRETATION AND CONCLUSION: The simplicity and accuracy of FNAC justifies its continued use either alone or in combination with core needle biopsy for preoperative diagnosis of palpable breast masses.

KEYWORDS: Fine needle aspiration cytology, FNAC, Core needle biopsy, Carcinoma breast.

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INTRODUCTION: Cancer of the breast is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. Breast cancer is now also the leading cause of cancer death among females in developing countries, a shift from the previous decade during which the most common cause of cancer death was cervical cancer.[1] In India, as per the National Cancer registry programme, all the urban cancer registries except Ahmedabad i.e. Bangalore, Chennai, Mumbai, Nagpur, Pune and Delhi recorded an increase in the incidence of cancer breast over the last decade.[2] Most diseases of the breast present as palpable masses or nipple discharge. Although most breast lesions are benign, in view of the high prevalence of carcinoma breast, the investigation of palpable breast lumps utilizes a multidisciplinary approach that centres around the 'triple test', analyzing clinical and radiologic findings in conjunction with the pathologic features to diagnose the lesion and determine the best treatment plan for the patient.[3]

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Fine needle aspiration cytology (FNAC) is an established procedure and has been used for more than four decades for the diagnosis of palpable breast masses.[4,5] The advantages of FNAC include simplicity, accuracy, low morbidity, minimal patient discomfort, relatively low cost and immediate availability as an office procedure without anaesthesia. Prompt diagnosis relieves patient's anxiety and allows time to plan definitive treatment. Many benign conditions can be diagnosed accurately and surgery avoided, also the need for frozen section diagnosis is reduced.[6] The reported sensitivities of FNAC range from 43.8% to 95%, specificities from 89.8% to 100%, positive predictive values from76.2% to 100% and negative predictive values from 46.3% to 98.8%.[6] If skilled cytopathologists are provided with adequate material, the diagnostic accuracy of FNAC is high. Although FNAC (preceded by mammography/ultrasonography) continues to be the first line investigation of breast lesions especially in screening and symptomatic populations, the use of core needle biopsy (CNB) is increasing.[3] Core needle biopsy (especially with vacuum assisted larger bore needle of 8 to 11-gauge) has better sensitivity and specificity for most breast lesions and can confirm invasion in malignant lesions.[7] In many centres of the country and abroad CNB is increasingly being used now as the only diagnostic method for breast lesions.[3] However studies have shown FNAC to be more accurate in diagnosing malignancy in palpable breast lesions.[8] In our institution core needle biopsy is yet to be established as a routine procedure and FNAC is

routinely used as the first line investigation of palpable breast lesions. The present study aims to correlate the cytologic findings in palpable breast masses with the corresponding histologic diagnosis and to evaluate the diagnostic accuracy of FNAC in distinguishing benign from malignant diseases of the breast in order to reiterate its relevance and utility in centres like ours where core needle biopsy is not yet established and practised.

MATERIALS AND METHODS: The study was conducted on fifty patients (49 females and one male) who reported to the cytology section of the Department of Pathology, Government Medical College Jammu for fine needle aspiration of palpable breast lumps. FNA was done by the standard Jack-Hammer technique using a 20cc disposable syringe fitted in Franzen handle and a 21 or 22 gauge needle. Adequate sampling was ensured and a minimum of five smears were made in each case, two of these were immediately fixed in 95% ethanol for Papanicolaou (Pap)[9] staining and the remaining were kept air-dried for May Grunwald Giemsa (MGG)[9] and other special stains as and when required. A detailed microscopic examination of the smears was carried out to arrive at a provisional cytologic diagnosis. Histopathologic correlation with post-operative lumpectomy or mastectomy was done in each case except one. Formalin fixed and routinely processed tissue sections were stained with the Haematoxylin and eosin stain[10] and a condition was labelled as benign or malignant on the basis of the definitive histological diagnosis. Only one case that was reported as squamous cell carcinoma on cytology was included in the study without the availability of the respective tissue sections, since the patient expired a few days after FNAC was done. However, this case had sufficiently distinctive cytological features to merit inclusion in the study. But for this case of squamous cell carcinoma, only those cases were included in the study for which both the cytologic smears and the corresponding tissue sections were available. Finally, the initial cytologic findings were matched with the confirmatory histologic diagnosis.

RESULTS: Of the 50 cases studied, 38 i.e. 76% were diagnosed as having a benign breast disease where as 12 i.e. 24% had a malignant lesion (Table-1). On cytology the benign lesions were characterized by a bimodal population of ductular and myoepithelial cells in cohesive clusters with numerous bare bipolar nuclei in the background. Malignant lesions, on the other hand, were marked by high cellularity comprising of loose aggregates of atypical cells and absence of bare nuclei. Within this template each specific lesion had its own characteristic cytologic pattern permitting a provisional cytologic diagnosis that was subsequently confirmed on histology.

Benign breast diseases and their cyto-histologic concordance (Table-2):

1. Fibroadenoma (Fig.1,2) was observed to be the commonest benign lesion of the breast after histologic confirmation, accounting for 16 of the 38 cases (42%). Both intra- and peri-canalicular patterns were seen in 11 cases while a predominantly intracanalicular pattern was seen in 5 cases. On FNAC, 15 of these were reported as fibroadenoma while one case was labelled fibroadenosis (cyto-histologic concordance of 15/16 i.e.93.75%). On cytology fibroadenoma was characterized by the presence of branching, stag-horn shaped monolayered sheets of bi-modal epithelial cells, numerous single bare nuclei and fragments of fibromyxoid stroma.
2. Fibroadenomatosis, with 7 cases (18.4%), combined the features of both fibroadenoma and fibrocystic disease. Of these, 3 cases were reported as fibroadenoma, 3 as fibroadenosis and one erroneously as benign Phyllodes tumour on FNAC. Considering both fibroadenoma and fibroadenosis to be consistent with the histologic diagnosis of fibroadenomatosis, a cyto-histologic concordance of (6/7) 85.7% was achieved.
3. Fibrocystic disease (FCD) - 6 (15.8%) cases were diagnosed histologically that were characterized by cyst formation, apocrine metaplasia (Fig. 3, 4) and variable fibrosis, epitheliosis and adenosis. On cytology, 2 cases were reported as FCD, 2 as benign cysts and one as fibroadenosis, all of which are the varied manifestations of the spectrum of changes seen in FCD of the breast. In one case smears were unsatisfactory for evaluation. So with FNAC 5 of the 6 cases (83.3%) of FCD were diagnosed accurately.
4. Intraductal papilloma accounted for 3 cases (7.9%). In 2 of these a possibility of intraductal papilloma was suggested on FNAC due to the presence of complex branching sheets of epithelial cells with papillary stromal cores and a background of cystic macrophages. One case yielded smears unsatisfactory for reporting, so a concordance of 66.6% was achieved with histology.

Of the remaining 6 benign lesions, it was possible to correctly diagnose gynaecomastia, lactating adenoma, benign Phyllodes tumour and breast abscess on FNAC. The 2 cases showing discordance were; one case of sclerosing adenosis that was reported as fibroadenosis and another of tuberculosis that was reported erroneously as a non-specific benign breast lesion on FNAC. This could be attributed to the target being missed during aspiration with sampling of the adjacent normal breast tissue.

None of the benign lesions was reported as malignant on cytology i.e. false positive fraction was zero. Thus, a cyto-histologic concordance of 84.2% (32/38) was achieved in benign lesions of the breast.

Malignant Breast Diseases and Their Cyto-Histologic Concordance (Table-3): Of the 12 malignant lesions, 9 (75%) were of infiltrating ductal carcinoma breast (Fig. 5, 6) with variable degree of tubular differentiation, nuclear pleomorphism, mitotic activity, desmoplasia and necrosis on histology. The remaining 3 were one case each of intraductal carcinoma (with both solid and comedo patterns), Non Hodgkin lymphoma (diffuse large cell type)

and squamous cell carcinoma. In one case of infiltrating ductal carcinoma, a false negative report of inflammatory breast lesion was given on cytology. No histopathological confirmation was available in the case of squamous cell carcinoma which was diagnosed solely on cytology as the patient succumbed to the widely disseminated disease soon after FNAC was performed. The smears comprised of dispersed cells and clusters of pleomorphic cells, many with chiselled edges, hyperchromatic nuclei and dense grey-blue (MGG) or deeply orangeophilic (Pap) cytoplasm (Fig. 7, 8). Therefore, cyto-histologic concordance was attained in 10 of the 11 (90.9%) malignant breast lesions.

Diagnostic Accuracy of FNAC (Table-4): From the above observations, it was inferred that FNAC could distinguish benign from malignant lesions of the breast with 91.6% sensitivity and 100% specificity. The positive predictive value of FNAC was 100%, negative predictive value was 97.4%, false positive fraction was zero and false negative fraction was 8.4%.

DISCUSSION: The observations allow a reliable evaluation of the accuracy of FNAC vis-vis the confirmatory histologic diagnosis in breast masses. Benign lesions of the breast (76%) outnumbered the malignant ones (24%) as has been widely reported in literature.[11] It was possible to arrive at the correct specific diagnosis in 32 out of the 38 benign and 9 out of 11 malignant lesions (histology not available in one case), thus achieving a cyto-histologic concordance of 84.2% for benign and 90.9% for malignant lesions of the breast. Majority of the cases of fibroadenoma and fibrocystic disease as well as the cases of gynaecomastia, lactational adenoma, Phyllode's tumour and breast abscess were diagnosed accurately on FNAC. None of the benign lesions was reported as malignant on FNAC i.e. the false positive fraction was zero. It was not possible to pick up the one case of sclerosing adenosis on FNAC which was erroneously reported as fibroadenosis. Core needle biopsy is favoured in such lesions that appear fibrotic or collagenous as these lesions can be paucicellular on FNAC.[12]

Amongst the malignant breast lesions, 9 out of the 10 ductal carcinomas were diagnosed accurately and so was the one case of non Hodgkin lymphoma. There was one false negative case wherein a carcinoma breast was wrongly reported as an inflammatory breast lesion. No histologic confirmation was available in the case of squamous cell carcinoma. The single case of intraductal carcinoma in this series was simply reported as carcinoma breast on FNAC. Though, inability to assess invasion is an inherent limitation of FNAC, CNB is not significantly more reliable than FNAC for excluding focal invasion in these lesions.[6] Zajdela et al[13] and Singh et al[14] achieved a cyto-histologic concordance of 89.2% and 93.5% respectively in the diagnosis of benign breast lesions and a concordance of 88% and 85% respectively in the diagnosis of malignant breast lesions. Bell et al[15] observed FNAC to be more accurate in arriving at a specific diagnosis in malignant breast lesions but did not find it to be a reliable procedure for benign lesions.

In this study, FNAC was observed to be a highly accurate diagnostic procedure for distinguishing benign from malignant lesions of the breast with a sensitivity of 91.60%, specificity of 100%, positive predictive value of 100%, negative predictive value of 97.40%, a false positive fraction of zero and a false negative fraction of 8.4%. The reported sensitivities, specificities and positive and negative predictive values for FNAC vary depending on how insufficient samples are considered (as positive, negative or excluded) and how atypical samples are categorized (positive or negative). When insufficient samples and atypical and benign findings are presumed to be negative, sensitivities range from 43.8% to 95%, specificities from 89.8% to 100%, positive predictive values from 76.2% to 100% and negative predictive values from 46.3% to 98.8%. If insufficient samples are excluded, sensitivities and specificities improve to a range of 58.3%-100% and 55%-100% respectively with a slight change in negative predictive value to between 46.6% and 98.6%.[6] The aim should be a sensitivity of no less than95% which can be achieved with increasing experience. Sensitivity is lower for low-grade carcinomas (invasive and in situ), for lobular carcinoma, and for very small and very large cancers. The positive predictive value of a malignant diagnosis is approximately 99%, and, although rare, occasional false positive diagnoses of malignancy are recorded in most series.[6,16,17,18]

The study supports the view that the death knell need not be sounded for FNAC in the investigative sequence of breast masses. Though core needle biopsy has been reported to provide better sensitivity and specificity than FNAC, with an ability to give an unequivocal diagnosis of invasion and a more type-specific diagnosis in both benign and malignant breast masses, it has its own limitations.[6,19,20] CNB requires local anaesthesia (with large bore needles) and sterile conditions with a higher risk of local complications as compared to FNAC.[6] It is a much more expensive procedure than FNAC and when applied to the large volume of work generated by breast cancer screening, the costs can be enormous.[21] Moreover, approximately two-thirds of cancers detected during breast cancer screening programmes are given a definitive cancer diagnosis by FNAC as a part of 'triple diagnosis' with only one-third requiring further investigation by CNB or open biopsy.[6]

It can be concluded that breast FNAC and CNB are complementary techniques and both should be available in any modern multi-disciplinary hospital. However till adequate facilities for core needle biopsy are established in our institution, FNAC on its own, can ably shoulder the burden of being the first line investigation in diagnosis of palpable breast masses.

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Total No. of cases	**Benign**		**Malignant**	
	Number	Percentage	Number	Percentage
50	38	76%	12	24%

Table 1: DISTRIBUTION OF BENIGN AND MALIGNANT BREAST LESIONS

Benign Breast lesions											
Cytologic Diagnosis	**Histologic diagnosis**										
	Fibroadenoma	Fibroadenomatosis	Fibrocystic disease	Intraductal papilloma	Lactational adenoma	Sclerosing adenosis	Gynecomastia	Phyllodes tumour	Breast abscess	Tuberculosis	Total
Fibroadenoma	15	3									18
Fibroadenosis	1	3	1			1					6
FCD/ benign cyst			4								4

Intraductal papilloma				2							2
Lactating breast					1						1
Gynaecomastia							1				1
Phyllodes tumour		1						1			2
Breast abscess									1		1
Non specific										1	1
Unsatisfactory smear			1	1							2
Malignant											0
Total	16	7	6	3	1	1	1	1	1	1	38
% of benign	42.1	18.42	15.79	7.89	2.63	2.63	2.63	2.63	2.63	2.63	100

Table 2: Cytology Vs Histology In Benign Breast Lesions

Malignant Breast Lesions					
Cytologic Diagnosis	**Histologic Diagnosis**				
	Infiltrating ductal carcinoma	Intraductal carcinoma	Non Hodgkin lymphoma	Histology not available	Total
Ductal carcinoma breast	8	1			9
Non Hodgkin lymphoma			1		1
Squamous cell carcinoma				1	1
Inflammatory lesion	1				1
Total	9	1	1	1	12
% of malignant	75	8.3	8.3	8.3	100

Table 3: Cytology Vs Histology in Malignant Breast Lesions

Cytology	**Histology**	
	Benign	Malignant
Benign	38	1
Malignant	0	11

Table-4: Diagnostic Accuracy Of FNAC In Breast Lesions

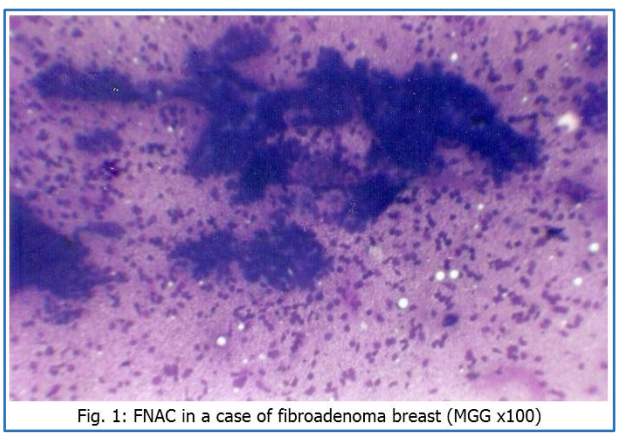

Fig. 1: FNAC in a case of fibroadenoma breast (MGG x100)

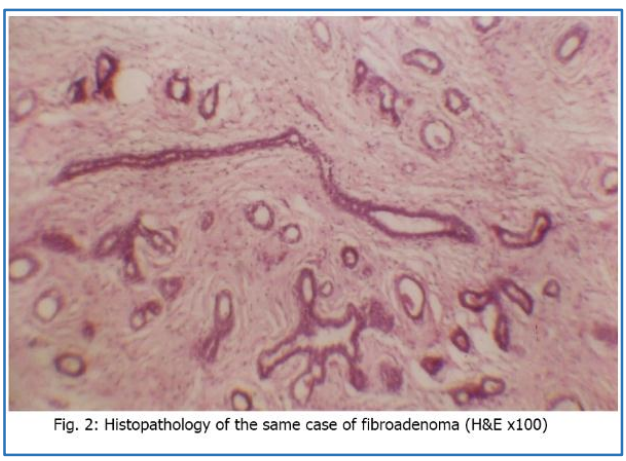

Fig. 2: Histopathology of the same case of fibroadenoma (H&E x100)

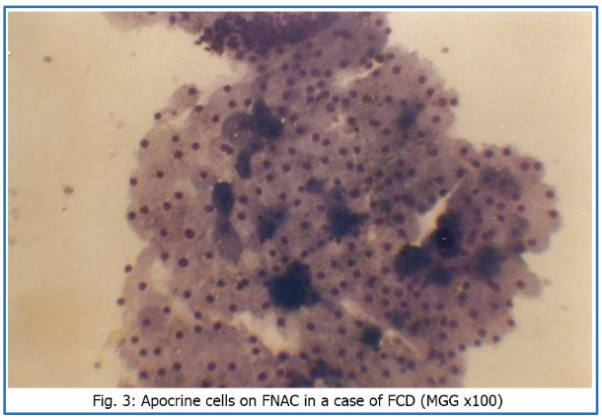

Fig. 3: Apocrine cells on FNAC in a case of FCD (MGG x100)

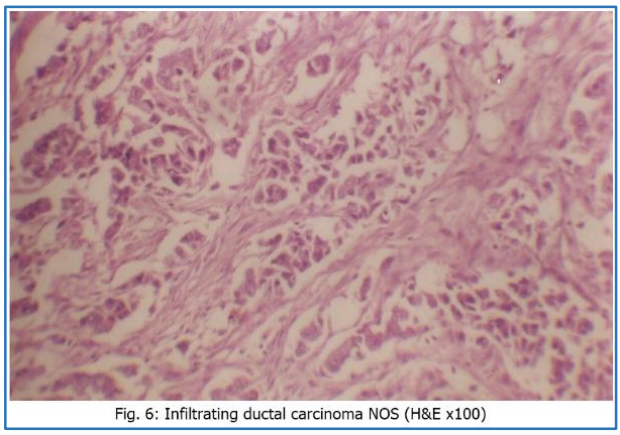

Fig. 6: Infiltrating ductal carcinoma NOS (H&E x100)

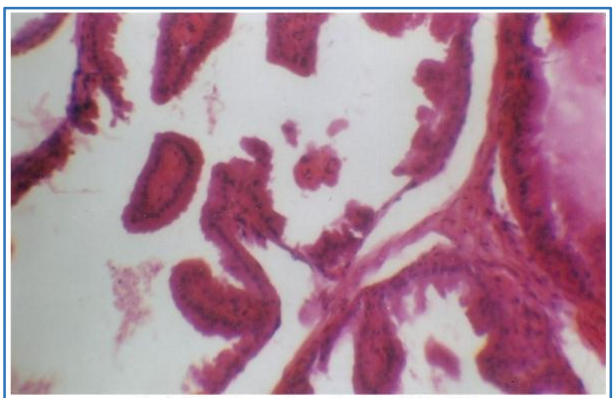

Fig. 4: FCD with apocrine metaplasia (H&E x100)

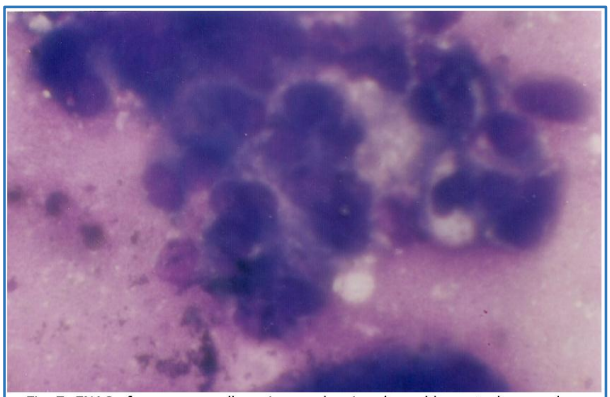

Fig. 7: FNAC of squamous cell carcinoma showing dense blue cytoplasm and hyperchromatic nuclei (MGG x400)

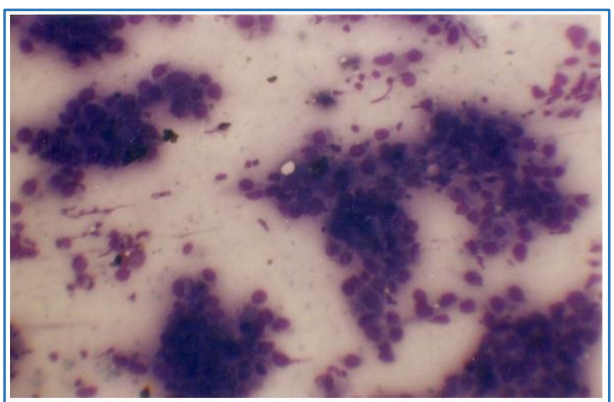

Fig. 5: Common malignant pattern of breast cytology (MGG x100)

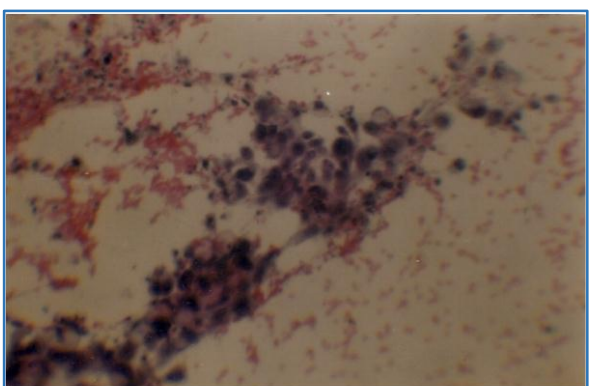

Fig. 8: Pap stained smear of the same case as above showing cytoplasmic orangeophilia (Pap x100)