Original Research Article

A study of cytohistological correlation of equivocal or atypical proliferative breast lesions at a tertiary care institution of North India

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ABSTRACT

Background: Fine needle aspiration cytology is the mostly the first diagnostic test used for the diagnosis of breast masses. But there is morphological overlap among the sequential lesions from the precancerous group to frank carcinoma known as "grey zone". This grey zone in cytology is estimated to constitute 8.9% of cases.
Methods: Smears were prepared from the fine needle aspirates and stained with Leishman/Giemsa. Trucut biopsy, mastectomy or MRM specimens of patients diagnosed as having on cytology benign with atypia (C3) /suspicious of malignancy (C4) were subjected to histopathological evaluation and cytohistopathogical correlation was done in these cases.
Results: 75% of patients who belonged to category C3 had benign lesions, whereas about 90% of those in category C4 had malignant diagnosis. This difference was statistically significant.
Conclusions: Combination of the mammography and cytology along with the clinical findings (the "triple test") allows for proper management for each patient, determining which patient should undergo surgery and which patient needs close follow-up, hence avoiding an unnecessary surgery. And the patients in cytology category C4 must have the diagnosis confirmed by histological examination.

Keywords: Breast carcinoma, FNAC, Grey zone lesions

INTRODUCTION

Breast lesions account for one of the largest group of conditions necessitating pathological, radiological and surgical intervention.[1,2] The most common palpable lesions are invasive carcinomas, fibroadenomas and cysts. Despite best efforts, the accurate diagnosis of some lesions is nearly impossible using cytology smears; these are known as "grey zone lesions".[3,4]

The true grey zone lesions comprise both benign and malignant lesions including fibroadenoma, fibrocystic disease of the breast, papilloma and other papillary lesions of the breast, proliferative breast disease with or without atypia like radial scar and sclerosing adenosis, fat necrosis, phylloides tumor, lactating breast, tubular carcinoma, lobular carcinoma, mucinous carcinoma, low grade in situ carcinoma or ductal carcinoma. Gynaecomastia in male breast is also a lesion that causes a dilemma in some cases.[5] Although grey zone accounts for a smaller percentage, considering the increasing incidence of carcinoma breast and the importance of its early diagnosis and management, even a minor pitfall would have a larger impact on the patient's care.[6,7]

In most cases the first diagnostic modality employed for the diagnosis of breast masses is FNAC. However, it has disadvantages like interobserver and intra-observer variability and this is further complicated by the grey zone lesions.[8,9] This grey zone in cytology is estimated to

constitute 8.9% of cases.[10,11] It can be further divided as three categories technical limitations (4.5%), inexperience of the cytopathologist (2.4%) and overlap of cytological features of benign vs. malignant (2%). Different studies have shown the percentage of "true grey zone lesions" (lesions which pose diagnostic difficulty due to the presence of atypical/suspicious cells and not because of technical limitations) to be close to 2% of all the breast Fine Needle Aspiration cases examined.[12-15]

Use of FNA is frequently limited to establish the benign and malignant characters of a given lesion. The most widely used cytological reporting protocol consists of a 5 tier categorical system which contains the following categories: C1 (non-diagnostic), C2 (benign), C3 (atypical), C4 (suspicious) and C5 (malignant). This reporting system is endorsed by the Britain's National Health Service Breast Screening Programme (NHSBSP), the National Cancer Institute (NCI) of the USA and The Royal College of Pathologists of Australasia (RCPA).[16-18]

Among these categories, C1, C2 and C5 do not pose much of a difficulty to the pathologists and leads to a good inter observer comparability. The shortcomings in FNAC are to differentiate invasive from in situ cancers and the presence of grey zone categories C3 and C4 in which there exists significant inter observer variation in the diagnosis, as no strict criteria is present for the diagnosis of these categories. Some authors have suggested the use of term "equivocal" for such cases.[19-21]

Aims and objectives

Aim of the current investigation was to study the cytomorphological spectrum of equivocal or atypical proliferative breast lesions and their categorization. Objectives of the current study were to evaluate the morphological features of C3 and C4 categories of breast FNAC and their histological correlation.

METHODS

This is a prospective type of study that was carried out at PGIMS Rohtak from June 2016 to May 2018. The present study was carried out on 40 randomly selected cases. This sample size was based on the average number of samples received in above mentioned duration after filtering cases through inclusion and exclusion criteria. Cases included were those females from age 20-65 years presenting with breast lump for fine needle aspiration or already having cytology report of benign with equivocal/atypical proliferative lesions and without any previous surgery or treatment of the same. Patients with definitive benign or malignant diagnosis on FNAC were excluded from the study. This study has got ethical approval from the ethical committee of our institution. After selection of cases a detailed clinical, cytological and histopathological evaluation of these cases was subsequently done. Smears were prepared from the fine needle aspirates and stained with Leishman/Giemsa.

Trucut biopsy, mastectomy or MRM specimens of patients diagnosed as having on cytology benign with atypia (C3)/suspicious of malignancy (C4) were subjected to histopathological evaluation and cytohistopathogical correlation was done in these cases.

FNAC was carried out using the standard procedure with a 20ml syringe, and 23 gauze needle using negative pressure. The material from needle was expelled on to a clean slide and a good thin smear was made on it. Smears was made by placing another slide on top of the material and performing a firm and quick swiping movement and alcohol-fixed smears were prepared and stained by Leishman/Giemsa and hematoxylin and eosin respectively

Fixing was done by air drying for smears that were stained by Leishman stain. The amount of stain sufficient to cover the smear was added. After about 2 minutes, double the amount of buffered water was added and mixed with the stain present. A proper time is elapsed according to the stock used (about 8-10 minutes) and the slide was washed off. Smears that had to be stained with H&E stain were fixed with isopropyl alcohol for 10-15 minutes. The slide was stained first with hematoxylin for 15-20 minutes and then washed. Then, 1% acid alcohol was added for differentiation and the slide was washed in running tap water. The slide was then placed in water for 5 minutes for blueing. Finally, the slide was dipped in Eosin for 3-4 dips for counterstaining and washed off. NCI guidelines (1996) was used for cytological evaluation and patients diagnosed as atypical, probably benign (C3), suspicious, favour malignancy (C4) will be selected for further study.

Atypical, probably benign (C3) category

Smears have characteristics of a benign with any or a combination of nuclear pleomorphism, some loss of cellular cohesiveness nuclear and cytoplasmic changes will be considered in category C3.

Suspicious of malignancy (C4) category

When the aspirates contain few cells showing features of malignancy, where the material is not diagnostic of malignancy due to poor quality of specimen or aspirates showing some malignant features of greater degree than those observed in category C3 without the presence of definitive malignant cells or aspirates showing an overall benign pattern with large numbers of naked nuclei and/or cohesive sheets of cells, but with occasional cells showing malignant features will be considered category C4. Biopsies liketrucut biopsy/excision biopsy/ mastectomy were reviewed for correlation with the FNAC diagnoses. Chi-square test was used to assess the diagnostic value of cytological diagnosis by comparing the percentage of benign and malignant histological diagnosis in categories C3 and C4. The p value of 0.05 or less will be considered for statistical significance. All the

statistical analysis was performed using statistical package for social sciences (SPSS) statistics for Windows (version 20.0. Armonk, New York: IBM Corporation). Spearman correlation coefficient was calculated between the qualitative variables. Sensitivity, specificity, accuracy, false positive rate, false negative rate, positive predictive value, and negative predictive value of different cytological categories were calculated. The FNA materials submitted for cytological study was used up in preparing slides and the tissue biopsies submitted for histopathological study was used up in Preparing wax blocks and slides. The respective blocks were preserved up to ten years and slides up to five years in the department. All biomedical waste generated was discarded as per biomedical waste management rule 2016.[22]

RESULTS

Out of 40 cases 18 cases were of C3 category and 22 cases belonged to C4 category. As shown in (Table 1), cases of benign with atypia category (C3) were more common in premenopausal age group (83%).

Table 1: Correlation of both cytological categories C3 and C4 with menopausal status.

Cytological Category	Premenopausal N (%)	Postmenopausal N (%)	Total
Benign with atypia (C3)	15 (83)	3 (17)	18
Suspicious of malignancy (C4)	8 (36)	14 (64)	22
Total	23	17	40

Table 2: Cyto-histological correlation of cytological diagnosis of C3 and C4 categories.

Histological diagnosis	C3 N (%)	C4 N (%)	Total
Benign	14 (77.78)	02 (9.09)	16
Malignant	04 (22.22)	20 (90.91)	24
Total	18	22	40

Cases suspicious of malignancy category (C4) were more common in postmenopausal age group (64%). Sensitivity was 83.33% and specificity was 87.5%. Positive predictive values came out to be 90.91% whereas Negative predictive value was 77.78%. The p value was <0.0001 (significant). Cytohistological correlation of cytological diagnosis of C3 and C4 (Table 2) shows that 77% cases of category C3 were benign (Figure 1-3).
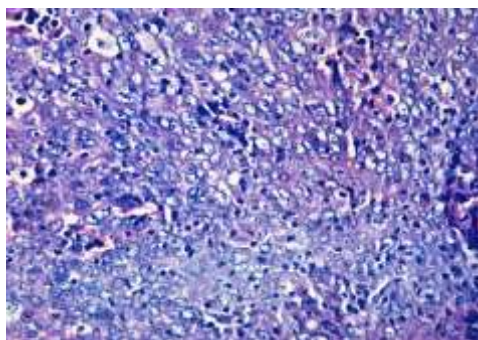

Figure 1: Case diagnosed as c3 on cytology showing mild atypia and loose cohesive clusters along with few bare nuclei in background (Leishman;100X).

90% cases of category C4 were malignant. (Figure 5-6). As depicted in (Table 3), Fibroadenoma was the most common diagnosis in C3 category (5 cases). While fibroadenosis was the 2nd most common diagnosis (4 cases). Histological diagnosis of malignant cases of category C3 showed 2 cases having infiltrating ductal carcinoma, one case of eachcomedo carcinoma and medullary carcinoma (Figure 4, Table 4). As shown in (Table 5), Only 2 cases belonged to category C4 were diagnosed benign on histology. One case diagnosed as cellular fibroadenoma of age 50 years. Other case diagnosed as borderline phylloidestumor of age 54 years. 20 cases were diagnosed malignant on histology of category C4.19 cases werediagnosed as having IDC. One case was diagnosed comedo carcinoma (Table 6).
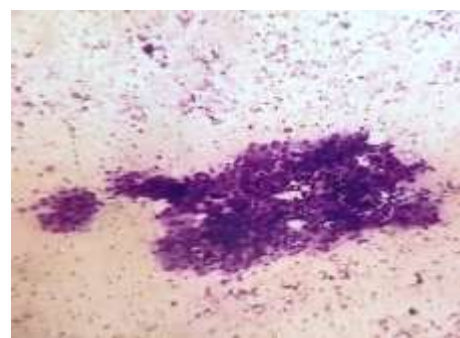

Figure 2: Histopathology of case exhibiting pericanalicular fibroadenoma that was diagnosed as C3 on cytology (HE; 200X).

DISCUSSION

Breast lump is a very common complaint in patients presenting at the surgery outpatient department in all healthcare facilities. It is a cause of anxiety to the patient & her family members no matter whether it is benign or malignant. Although histopathological diagnosis is a universally accepted confirmatory mode for the diagnosis & follow up, FNAC of breast masses is an important part of triple assessment (clinical examination, imaging, and FNAC).[23] FNAC of breast mass is an accepted and established method to determine the nature of the lump and it plays an important role when it is difficult to determine the nature of breast lump by clinical examination. FNAC is the minimally invasive and first diagnostic modality employed for the diagnosis of breast masses. It is simple, useful, quick, highly reproducible, and very cost effective method for the early diagnosis of breast lumps.[24]
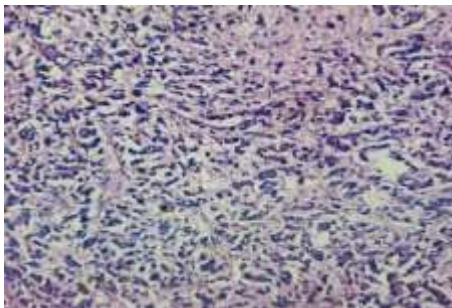

Figure 3: A case diagnosed as C3 on cytology revealing monolayered sheets of ductal epithelial with mild pleomorphism (Leishman;100X).

Table 3: Histological diagnosis of benign cases of C3 category (benign with atypia).

Histological diagnosis	N	%
Phylloidestumor	3	22
Fibroadenoma	5	36
Fibroadenosis	4	28
Sclerosingadenosis	1	7
Fibrocystic disease	1	7
Total	14	100

Our current study was performed only on categories C3 and C4. All patients having palpable lump in breast came to department of pathology for fine needle aspiration cytology. After obtaining informed consent the patients were subjected to fine-needle aspiration cytology. We carefully examined smears and then categorized according to cytological category and only those patients were choosen for study whose fine needle cytology report was benign with atypia (C3)/suspicious of malignancy (C4). Biopsies from subsequent operation by excisional biopsy mastectomy/modified radical mastectomy on these cases were reviewed for correlation with the FNAC and to observe how accurate fine needle aspiration cytology was in assessing C3 and C4 category.

A significant proportion of category C3 showed malignancy (23-37.5%) and smaller percentage (12.5-13.33%) of category C4 revealed benign lesions as well. Furthermore, patients with category C3 lesions may not necessarily be subjected to surgical biopsies if their clinical examination and mammographic findings are suggestive of benign outcomes as well. However, patients with category C4 lesions should always be subjected for histopathological examination because of a higher malignancy rate. In present study, we found 77.78% of benign lesions in category C3 and 90.91% of malignancy in category C4. This difference was statistically significant (p=0.001). And present study was in concordance with the study done by Manasmadan et al.[26]
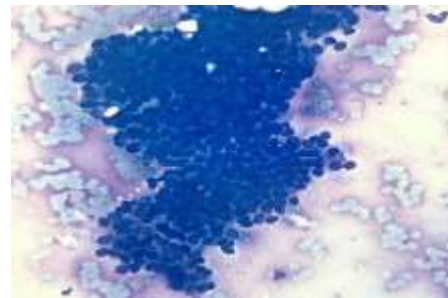

Figure 4: Histopathology of a case revealing infiltrating ductal carcinoma that was diagnosed as c3 on cytology (HE;100X).

Table 4: Malignant cases of C3 category (benign with atypia)

Histological diagnosis	N
Infiltrating ductal carcinoma (IDC)	2
Comedo carcinoma	1
Medullary carcinoma	1
Total	4

Figure 5: Case diagnosed as c4 on cytology having moderate nuclear atypia, lack of bare nuclei and loss of cohesion of cells (Leishman; 200X).

The sensitivity, specificity, positive predictive value, negative predictive value and p value of C4 category in the diagnosis of malignancy in the present study were 83.33%, 87.5%, 90.91%, and 77.78%, respectively. Comparison of sensitivity, specificity, positive predictive value, and negative predictive value of C4 category in the

diagnosis of malignancy with previous studies showed that our present study was in concordance with the studies previously done (Table 7-8).

Table 5: Histological diagnosis of benign cases of C4 category (suspicious of malignancy).

Histological diagnosis	N
Borderline phylloidestumor	1
Cellular fibroadenoma	1
Total	2

Table 6: Histological diagnosis of malignant cases of C4 category (suspicious of malignancy).

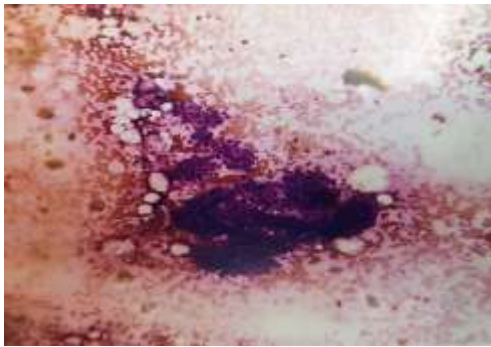| Histological diagnosis	N	%
IDC	19	95
Comedo carcinoma	1	5
Total	20	100

Figure 6: Histopathology showing poorly differentiated infiltrating ductal carcinoma with prominent nucleoli and occasional mitotic figure, same case was diagnosed as C4 on cytology (HE;400X).

In our study 20/22 cases of C4 and 4/18 cases C3 shows malignant diagnosis on histology. Out of 24 cases 21 (88%) cases were having IDC, 2 (8%) cases of comedo carcinoma and 1 (4%) case of medullary carcinoma. IDC is much more common than any other carcinoma. Similar observations were made by previous three studies.(Table 9) In C3 category, where 4/18, 4 cases turned out to be malignant (4/18= 22%) and thus were considered false negative (FN). This result also corroborated well with the range established by other studies (62.5-77%). The reasons for these false negative cases can be sampling error, small tumor size, low-grade tumor, less cellularity or low grade well differentiated carcinomas arising in cystic lesions. These 4 FN cases were again reviewed after histopathological diagnosis. All of these cases showed mainly cohesive sheets of ductal epithelial cells, bare nuclei with few clusters showing cellular crowding and lack of cohesiveness. Thus patients with C3 diagnosis need not undergo a surgical procedure if the proper clinical and mammographic correlation is done and they too suggest a benign lesion. Benign histological diagnosis between both categories included fibroadenoma (05 cases), fibroadenosis (04 cases) phylloidestumor (03 cases) sclerosingadenosis (01 case) borderline phylloides (01case) fibrocystic disease (01 case) and cellular fibroadenoma (01case). Two out of 22 cases showed benign pathology on histopathological examination and were considered false positive (FP). Of these one was highly cellular fibroadenoma and one was borderline phylloidestumor. These cases showed dyscohesive clusters, cellular overlapping and moderate cellular and nuclear pleomorphism. These results also correlate with the other studies, which show a range of 86.2-87.5% for malignancies in this category. Some degree of atypia, dyscohesion and nuclear pleomorphism can be seen in fibroadenomas and along with increased cellularity can cause diagnostic difficulty.

Table 7: Cytohistology correlation comparison in various studies.

Fine needle aspiration cytology categories of various studies										
Histological diagnosis	Arul et al.[25] (N=93) (%)		Madan et al.[26] (N=43) (%)		Goyal et al.[27] (N=40) (%)		Vandana et al.[28] (N=213) (%)		Present study (N=40) (%)	
	C3	C4	C3	C4	C3	C4	C3	C4	C3	C4
Benign	64.3	13.8	77	13.33	62.5	12.5	64	19	78	9
Malignant	35.7	86.2	23	86.67	37.5	87.5	36	81	22	90

The benign histological diagnosis in our study is also comparable with the previous studies (Table 10).[25-27] Of the cases in category C3 which resulted in surgery, more than 34% had a malignant diagnosis on biopsy. This result corroborates with reported literature values that range between 8.6% to 52%, with most reports having over 30%. The decision to proceed to biopsy in our centre relies on the "triple test" correlating the FNAC results with the clinical and radiological studies. Hence, the cases in category C3 that had clinical and imaging studies suspicious for malignancy were advised for biopsy,

thereby accounting for the high percentage of malignant cases in this category. Our study is in line with the recommendations of other authors that the use of the "triple test" is important for proper management of patients with FNAC results in category C3, and whether such patients need surgical intervention, or can simply be put on follow up. In case of C4 category, our study showed that approximately 80% of patientswere diagnosed to have malignant lesions, which is similar to the range of 81% to 97% reported by others.[28-30] Hence, as recommended by other studies, we believe that

patients in cytological category C4 should have the

diagnosis confirmed by histological examination.

Table 8: Comparison of result of present study with various previous study.

Study	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value
Goyal et al[27]	40	60.8	88.2	87.5	62.5	<0.001
Yusuf et al[29]	47	76.7	76.5	85.2	65	<0.001
Arul et al[25]	93	84.8	86.7	86.2	64.3	<0.001
Present study	40	83.33	87.5	90.91	77.78	<0.001

Table 9: Comparison of histological diagnosis of malignant cases of both cytological categories C3 and C4 with previous studies.

Histologial diagnosis	Manas et al[26]	Arul et al[25]	Goyal et al[27]	Chaiwun et al[30]	Present study
IDC	100	94	95	98	88
Comedo carcinoma	0	0	0	0	8
Invasive lobular carcinoma	0	6	5	2	0
Medullary carcinoma	0	0	0	0	4

Table 10: Comparison of histological diagnosis of benign cases of both cytological categories C3 and C4 with previous studies.

Histological diagnosis	Manas et al[26]	Arul et al[25]	Goyal et al[27]	Present study
Fibroadenoma	50	59	54	33
Fibrocystic disease	21	41	36	8
Phylloidestumor	0	0	0	18
Fibroadenosis	0	0	0	25
Boderlinephylloidetumor	0	0	0	5
Cellular fibroadenoma	14.5	0	0	5
Proliferative breast disease	14.5	0	0	0
Sclerosingadenosis	0	0	0	5

Hence, the importance of performing surgical procedure (possibly lumpectomy followed by frozen section examination) in C4 category cannot be overemphasized considering the high rate of occurrence of malignancy in such cases. Moreover, our study also underlines the significance of FNAC which is a simple out patients procedure in the rapid and timely diagnosis of such cases thereby ensuring better patient management and survival.

Limitations

Limitation of our study is that sample size was small and hence more studies are needed on a larger scale to conform with the findings of our study.

CONCLUSION

In conclusion, it is important for both clinicians and pathologists to understand the benefits as well as the limitations of cytological diagnosis from FNAC specimens. Evaluation of specimen adequacy immediately after FNAC is useful to reduce equivocal diagnoses. As already discussed that in our study, approximately 75% of cases diagnosed as category C3 had benign lesions, whereas about 90% of patients in category C4 had malignant diagnosis, hence we

recommend to maintain the equivocal diagnostic categories C3 and C4. Combination of the radiological and cytological data together with the clinical features (the "triple test") allows for proper management for each patient, determining which patient should undergo surgery and which patient needs close follow-up, hence avoiding an unnecessary operation. And we also believe that cases of category C4 must have the diagnosis confirmed by histopathology.

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