



ULTIMATE FATE OF GREY ZONE (INTERMEDIATE) LESIONS OF BREAST : A CYTO-HISTOPATHOLOGICAL CORRELATION

Pathology

Dr Preethi. K. R* Postgraduate, Department of Pathology, KMCRI Hubballi *Corresponding Author

Dr Kavitha Yevoor Associate Professor, Department of Pathology, KMCRI Hubballi

Dr Anagha. A. S Postgraduate, Department of Pathology, KMCRI Hubballi

ABSTRACT

Introduction : Breast lesions include both benign and malignant conditions, with most being benign. Fine-needle aspiration cytology (FNAC) is commonly the first diagnostic technique used to assess breast masses. The IAC Yokohama reporting system classifies breast FNAC results into five categories. Among these, Category 3 (C3) - "Atypical, probably benign" & Category 4 (C4) - "Suspicious of malignancy" are known as grey zone or intermediate lesions, which require additional evaluation. **Methods :** This study was conducted over a period of 1 and ½ years. Smears prepared from aspirate & were stained with Wright's stain /H & E stain . Histopathological follow up consisting of Excision, Trucut biopsy or MRM was done in these cases. The ROM was calculated for each category as the number of malignant cases confirmed histologically/total number of cases in each category. **Results :** Total of 46 cases were studied, out of which 31 belonged to C3 and 15 to C4. Histopathological correlation was available in 16 cases of C3 and 10 cases of C4. The ROM in C3 was 18.75% and in C4, the ROM was 80%. **Conclusion :** FNAC is a highly effective diagnostic tool, but it has its own limitations, especially with gray zone lesions. Therefore, these lesions should be carefully evaluated and supplemented with histopathological examination and additional radiological investigations to ensure proper patient management.

KEYWORDS

Breast, Fine needle aspiration cytology (FNAC), Grey zone lesions, Risk of malignancy (ROM).

INTRODUCTION

The breast is a specialized organ composed of mammary glands (modified sweat glands) that contain two main structures: ducts and lobules and two types of stroma: interlobular and intralobular. Each of these components can give rise to both benign and malignant lesions.¹

Careful examination and assessment of the lump are crucial for accurate diagnosis and appropriate management of the condition.² While core biopsy is considered the gold standard, FNAC remains widely practiced especially in developing countries like India due to its rapid, minimally invasive, accurate, and cost-effective nature, making it well accepted by patients.³

The IAC Yokohama system for breast cytology provides a uniform and standardized reporting framework for breast FNACs, categorizing into five groups: Category 1 – Insufficient/Inadequate, Category 2 – Benign, Category 3 – Atypical, probably benign, Category 4 – Suspicious for malignancy, and Category 5 – Malignant.⁴ Among them, categories 3 and 4 are referred to as grey zone or intermediate lesions, where it is challenging to provide a definitive diagnosis based on FNAC alone.

Objectives

1. To study the cytomorphological spectrum of breast FNAC cases within the grey zone.
2. To determine the risk of malignancy (ROM) in the grey zone.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Pathology at Karnataka Medical College and Research Institute from July 2022 to December 2023. Cases presented with breast lump were included and FNAC was performed using 22-24 gauge needle and smears were prepared & stained with H&E stain and Wright's stain. IAC Yokohama reporting system was used for cytological evaluation and patients diagnosed as C3 and C4 were selected for the study.

Subsequently, these cases were correlated with histopathology findings. Histopathological specimens received were excised specimens, trucut biopsies and modified radical mastectomies, were fixed in 10% neutral buffered formalin, grossed, processed, and multiple sections were prepared at 3–4 µm thickness, stained with H&E, and examined.

The ROM was calculated for each category as the number of malignant cases confirmed histologically/total number of cases in the diagnostic category.

Chi-square test was used to calculate the p value and the value of 0.05 or less will be considered for statistical significance. The various

statistical parameters were calculated using SPSSv25 (03 atypical cases on histopathology were considered as benign for statistical purpose).

RESULTS

Total 46 breast FNAC cases were included in the study, out of which 31 cases belonged to C3 and 15 cases belonged to C4. The most common age group affected by C3 lesions was between 41 to 50 years (45 % cases) and C4 was between 51 to 60 years (33% cases). In our study, all patients were female. Both C3 and C4 cases showed right sided predominance (54% & 53% cases in category 3 & 4 respectively). The most common breast quadrant involved by both categories was upper outer quadrant (32% & 40% cases in category 3 & 4 respectively).

In C3, the FNAC diagnosis were Phyllodes tumor (18 cases) ADH (12 cases) and 1 case of fat necrosis with atypia.

In C4, the FNAC diagnosis were Suspicious of IDC (9 cases) followed by Suspicious of Papillary neoplasm (6 cases).

Total 26 cases were correlated histopathologically and ROM for C3 was 18.75% and ROM for C4 was 80% [Table 1].

In this study, the p-value obtained was 0.002, indicating statistical significance. The sensitivity was 81.25%, and specificity was 80.00%. The positive predictive value was 86.67%, while the negative predictive value was 72.73%, resulting in a diagnostic accuracy of 80.77%.

TABLE 1 : Histopathology diagnosis and Risk of malignancy (ROM) in C3 and C4.

IAC Yokohama category	No: of cases (n=46)	Histopathology correlated cases				ROM (%)
		cases correlated	B	A	M	
C3	31	16	11	02	03	18.75
C4	15	10	01	01	08	80.00

B- Benign, A- Atypical, M- Malignant

DISCUSSION

Breast lump can be benign or malignant but causes anxiety to the patient as breast cancer is the most prevalent cancer among females worldwide and in India, which is a significant cause of both mortality and morbidity.⁵

IAC Yokohama system of breast cytology which was initiated in Yokohama at the 2016 International Congress of Cytology, which is similar to Bethesda reporting system of Thyroid cytology provides uniform reporting of breast FNAC.⁶ Among 5 categories, C3 & C4 are considered as grey zone lesions as these are difficult to diagnose on cytology. Hence triple test approach consisting of clinical

examination, ultrasonography and FNAC is recommended for evaluating breast lesions.

C3 - "Atypical, probably benign" is given when smears shows predominantly cytological features of benign processes or lesions, but with the addition of some features that are uncommon in benign lesions and which may be seen in malignant lesions.⁴

C4 - "Suspicious of malignancy" is given when smears shows cytomorphological features which are usually found in malignant lesions, but with insufficient malignant features, either in number or quality, to make a definitive diagnosis of malignancy.⁴

In the present study, C3 was seen in 67.40% and these breast lesions exhibited loose cohesive clusters with mild atypia and few benign bipolar nuclei in the background, some cases showed overcrowding and overlapping of nuclei as shown in Figure 1. C4 was seen in 32.60% and these breast lesions showed dyscohesive clusters and papillary fronds of cells with high N : C ratio, irregularly clumped chromatin and scant to moderate cytoplasm. Some cases showed few clusters having intact myoepithelial layer which was against malignancy and some cases showed scant cellularity of atypical cells, leading to the assignment of these cases to C4 as shown in Figure 2.

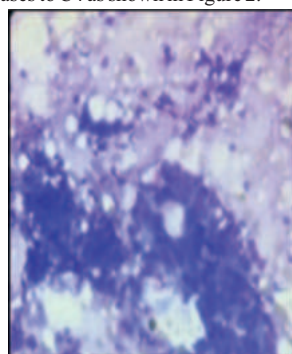
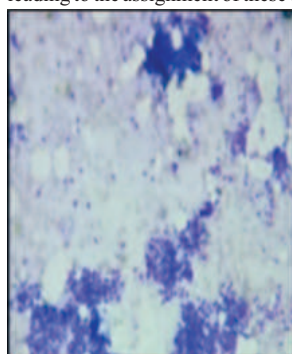


Figure 1a
(Fig 1a : Wright's, 10X, Fig 1b : Wright's, 40X)

A case diagnosed as ADH (category 3) on cytology exhibiting cohesive clusters of ductal epithelial cells with overlapping and overcrowding of nucleus.

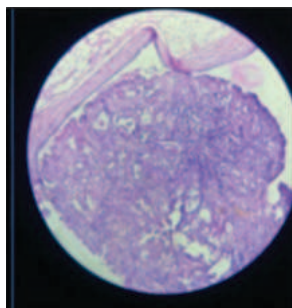
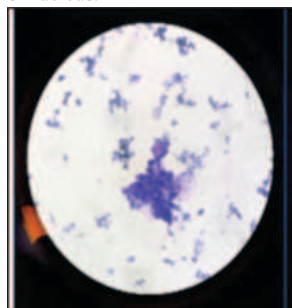


Figure 2a
(Fig 2a : FNAC Wright's, 40X, Fig 2b : HPR H&E, 40X)

Figure 2a A case diagnosed as suspicious of papillary neoplasm (category 4) on cytology showing scant cellularity of tumor cells arranged in 3D cluster.

Figure 2b shows histopathology section showing papillary fronds with fibrovascular core covered by thick capsule which led to the diagnosis of Encapsulated papillary carcinoma

In our study, 11/16 cases of C3 and 1/10 cases of C4 shows benign diagnosis on histology and out of 12 benign cases, fibroadenoma(5), benign phyllodes tumor(5), giant fibroadenoma(1) and duct papilloma(1). On histology 1 case of each C3 and C4 shows ADH and one case of C3 shows borderline phyllodes tumor on histology. 3/16 cases of C3 and 8/10 cases of C4 shows malignancy on histology and out of 11 malignant cases, IDC(8), ILC(1), Papillary carcinoma (2) [Table 2 and 3].

Table 2 : Histopathological diagnosis of FNAC cases in category 3.

HPR diagnosis	No: of cases (n=16)	(%)
Benign :		
Fibroadenoma	05	31.25%

Giant fibroadenoma	01	6.25%
Benign Phyllodes tumor	05	31.25%
Atypical :		
Atypical ductal hyperplasia	01	6.25%
Borderline Phyllodes tumor	01	6.25%
Malignant :		
IDC with fat necrosis	01	6.25%
IDC with ADH and DCIS components	01	6.25%
Invasive lobular carcinoma (ILC)	01	6.25%

Table 3 : Histopathological diagnosis of FNAC cases in category 4.

HPR Diagnosis	No:of cases (n=10)	(%)
Benign: Duct papilloma	01	10%
Atypical : ADH	01	10%
Malignant :		
IDC, NOS	06	60%
Encapsulated papillary carcinoma	01	10%
Invasive papillary carcinoma	01	10%

In C3 category, where 3 cases found to be malignant were considered false negative (FN). One case was diagnosed as IDC with ADH and low grade DCIS components on histopathology as adjacent tissue had ADH component and only this part was hit by the FNAC needle masking the IDC component which led to the assigning of C3 on FNAC & Other case of C3 was diagnosed as IDC with fat necrosis on histopathology, this was due to aspiration from a non representative site. Similar finding was described by Chetana Babu K Udupa et al.⁸ Hence, for such cases close correlation with USG features and if necessary, USG guided FNAC recommended. 1 case was diagnosed as Invasive lobular carcinoma on histopathology as FNAC smear showed small, monotonous cells with small nuclei and mild atypia led to the assigning of C3 of on FNAC. This finding is described by Menet. E et al.⁹

In C4 category, where 1 case found to be benign was diagnosed as duct papilloma on histology and was considered as false positive (FP). Differentiating between benign and malignant papillary lesions can be challenging with FNAC because the procedure typically targets the center of the lesion, while invasive features are often located at the periphery as described by Deshmukh. P.S et al.¹⁰

In the present study, we got 81.25% of benign lesions in category 3 and 80 % of malignant lesions in category 4 and the p value found to be 0.002 which is statistically significant and these findings are concordance with the study done by Kapil et al.¹¹ In this study, the sensitivity, specificity, positive predictive value, and negative predictive value of the C4 category in diagnosing malignancy were 81.25%, 80.00%, 86.67%, and 72.73%, respectively. A comparison with previous studies indicates that our findings align with those reported in earlier research [Table 4 and 5].

Table 4 : Cyto-histopathological correlation Comparison in various studies.

HPR diagnosis	Kapil et al.11 (N = 40) (%)		Vandana et al.12 (N = 213) (%)		Present study (N = 46) (%)	
	C3	C4	C3	C4	C3	C4
Benign	78	9	64	19	81.25	20
Malignant	22	90	36	81	18.75	80

Table 5 : Comparison of statistical parameters in various studies.

Statistical Parameters	Kapil et al11	Arul et al13	Present study
Sensitivity (%)	83.33	84.8	81.25
Specificity (%)	87.5	86.7	80.00
PPV (%)	90.91	86.2	86.67
NPV (%)	77.78	64.3	72.73

In our study, category 3 had a ROM of 18.75%, which is expected as this category mainly includes benign lesions, but some cases may ultimately be malignant. ROM of this category is similar to the ROM of the study conducted by Wong S et al.¹⁴ but is higher than some studies like Montezuma D et al.¹⁵ which may be due to overlooking malignant cells and category 4 had a ROM of 80%, which is expected as this category mainly includes malignant lesions but some cases may ultimately be benign. ROM of this category is similar to the ROM of the study conducted by Wong S et al.¹⁴ but is lower than some studies like Montezuma D et al.¹⁵ which may be due to over interpreting benign cells as category 4 [Table 6].

Table 6 : Comparison of Risk of malignancy (ROM) in various studies.

IAC Yokohama Category	Wong S et al.,14	Montezuma D et al.,15	Present study
Category 3	15.7%	13%	18.75%
Category 4	84.6%	97.1%	80%

Limitations

A limitation of our study is the small sample size, indicating a need for further research on a larger scale to confirm our findings.

CONCLUSION

Although FNAC is an excellent diagnostic tool, for grey zone lesions it is a diagnostic challenge for pathologists. Thus a combined approach using radiological, cytological data, and clinical features (the "triple test") is recommended for proper management of patients. In the present study, around 81% of cases categorized as Category 3 were found to have benign lesions, while approximately 80% of patients in category 4 were diagnosed with malignancies. Hence histopathology examination must be done in category 4 cases as these are at high risk of malignancy.

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