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Original Article

Pathology Section

Morphological Features Predictive of Malignancy in Cytology Smears of Atypical Proliferative Breast Diseases: A Cross-sectional Study

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ABSTRACT

Introduction: Breast lesions comprise about 34-40% of lesions evaluated by fine-needle aspiration in surgical practice. Fine-Needle Aspiration Cytology (FNAC) is increasingly used as a simple and cost-effective method to assess the nature of breast lesions, with high sensitivity and reasonable specificity, which helps in planning further treatment. However, a small percentage of breast lesions cannot be confidently diagnosed as benign or malignant and are termed grey-zone lesions. These include reactive atypia seen in some benign conditions and atypia of malignancy.

Aim: To analyse the cytological features of atypical proliferative breast diseases associated with a malignant diagnosis on histopathologic examination.

Materials and Methods: This was a cross-sectional study involving FNAC smears of all patients diagnosed as proliferative breast disease with atypia in the Department of Pathology, Government Medical College, Kozhikode, Kerala, India, from January 2018 to June 2021. Clinical and cytological features were studied, and patients were followed-up until June 2022. The lesions were classified histologically into benign and malignant lesions. The cytological features in the FNAC smears were studied. The data were entered into spreadsheets in Microsoft Excel, and the variables were analysed using Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows. The Chi-square test was used to evaluate features significantly associated with a histological diagnosis of malignancy.

Results: The study included a total of 162 cases diagnosed as proliferative breast disease with atypia on FNAC. Histopathological follow-up was available for these cases, with 73 benign and 89 malignant. Clinical features that were statistically significant in subjects with malignant histopathological diagnoses included age over 40 years, presence of a hard and fixed breast lump, and nipple changes. Cytological features predictive of a malignant histological diagnosis included clusters with ill-defined borders, loosely cohesive or cribriform clusters, clusters with markedly reduced or absent myoepithelial cells, reduced stromal fragments, numerous singly scattered atypical cells, markedly reduced or absent bipolar bare nuclei in the background, high mitotic rate, and necrosis. The nuclear features that were statistically significant included marked nuclear enlargement, nuclear pleomorphism, irregular nuclear contour, nuclear overlapping, and coarse nuclear chromatin.

Conclusion: The diagnosis of malignancy requires a multifaceted approach, including correlation with clinical, radiological, and pathological features. For an unequivocal cytological diagnosis of malignancy, a constellation of cytomorphological features is needed; a single morphological feature cannot reliably distinguish between benign and malignant lesions. Proper knowledge of the various cytomorphological features of malignancy can help predict malignancy even if all classical cytological features are not present. Cytological study can be a useful adjunct in triaging cases where prompt histopathological assessment is mandatory.

Keywords: Cytological features, International academy of cytology Yokohama system, Masood scoring

INTRODUCTION

Over the years, breast cancer has emerged as the most common cancer affecting females in Kerala. The triple assessment approach, incorporating clinical, radiological, and pathological examination, is the cornerstone for evaluating any breast lesion. FNAC is the simplest and most cost-effective method for assessing the pathological nature of breast lesions and planning further management. It has an accuracy of around 95-100% [1,2] and the advantage of a rapid turnaround time, with fewer complications compared with biopsy specimens [3]. In addition, immunocytochemical tests can also be performed on FNAC samples. However, some breast lesions cannot be diagnosed conclusively as benign or malignant by FNAC alone. These grey-zone lesions most commonly include proliferative breast disorders with and without atypia. Various grading systems have been described, including Masood's scoring index [4,5], which incorporates cytological parameters such as cellular arrangement, cellular pleomorphism, presence of myoepithelial cells, anisokaryosis, chromatin clumping, and nucleoli, to classify breast FNA samples into different categories. A higher score is associated with a higher risk of malignancy. Similarly, in the International Academy of Cytology (IAC) Yokohama classification [6], there are five categories for reporting FNA of the breast, which include grey-zone categories (C3 and C4), where the aspirates cannot be reliably classified into benign or malignant categories. The positive predictive value of malignancy in these C3 and C4 categories varies between 22-39% [7] and 60-95% [8]. Different parameters that give a clue for atypical features include increased cellularity, a greater number of scattered single intact tumour cells, enlarged pleomorphic nuclei, necrosis, mucin, and complex architectural patterns [7]. An unequivocal diagnosis of malignancy can be given only if there is a constellation of these cytological findings. A better understanding of cytological features can help identify cases with higher chances of being malignant, even if all the classical cytological features of malignancy are absent. This study aims to analyse those cytological features in the FNAC smears that can predict a malignant diagnosis on follow-up histopathological evaluation.

Aim

To identify the morphological features that can predict malignancy in cytological smears of atypical proliferative breast diseases.

Objectives:

1. To describe the clinical and cytological features of atypical proliferative breast diseases;
2. To analyse the cytological features of atypical proliferative breast diseases which are associated with a diagnosis of malignancy on histopathologic examination.

MATERIALS AND METHODS

This was a cross-sectional study involving FNAC smears of all patients diagnosed as proliferative breast disease with atypia in the Department of Pathology, Government Medical College, Kozhikode, Kerala, India, during January 2018 to June 2021. The patients were followed-up until June 2022. Informed consent of the subjects was taken. Ethical clearance was obtained from the Institutional Ethics Committee of Government Medical College, Kozhikode (Ref no: GMCKKD/RP 2021/IEC/198 dated 16/07/2021).

Inclusion criteria: All cases diagnosed as proliferative breast disease with atypia on FNAC smears were included in the study.

Exclusion criteria: Cases diagnosed as proliferative breast disease without atypia on cytology and cases where follow-up histopathology diagnosis was not available were excluded from the study.

Study Procedure

Clinical details of the subjects were obtained from case sheets. Collected data included age, site of lesion, clinical presentation, duration of symptoms, size of the lesion, and axillary lymph node status. Papanicolaou- or Giemsa-stained cytology smears were studied. Cellularity was graded into low, moderate, and high: low (<10 clusters per LPF), moderate (10-20 clusters per LPF), and high (>20 clusters per LPF) [7]. The architecture of clusters was assessed and classified as tightly or loosely cohesive, antler-horn clusters, papillary and micropapillary structures, tubular and cribiform patterns. The percentage of single cells in the smears was also assessed [7]. Nuclear size was assessed and categorised as mild, moderate, or marked enlargement: mild <1.5× the size of an RBC; moderate 1.5-2× the size of an RBC; and marked >2× the size of an RBC [7]. Other features assessed included nuclear contour, nuclear crowding, nuclear chromatin texture, nucleolar size, N:C ratio, presence of myoepithelial cells within and around the clusters, background, stromal component, and mitotic activity.

Follow-up and histopathology: These patients were followed-up for at least one year, and the histopathology diagnosis was studied. Patients were subdivided into histologically benign and histologically malignant lesions. The various cytomorphological features in the FNAC smears of histologically malignant cases were compared with those of histologically benign cases.

STATISTICAL ANALYSIS

Data were entered into open-source spreadsheets and analysed using SPSS version 16.0 for Windows. The results were tabulated and analysed statistically. Quantitative variables were expressed as means and qualitative variables as percentages. The association between variables was analysed using the Chi-square test, and p-values were calculated. A p-value <0.05 were considered statistically significant.

RESULTS

During the study period, 2983 breast FNA cases were performed, of which 218 cases (7.3%) were reported as proliferative breast disease with atypia. A total of 56 cases (1.8%) were excluded due to unavailability of follow-up histopathology diagnosis. The remaining 162 cases had follow-up histopathology diagnoses and were included in the study. This accounted for 5.4% of the total breast FNAs during this period.

The cytological features were reviewed and recategorised according to the IAC Yokohama system and included 77 (47.5%) cases with C3 and 85 (52.5%) cases with C4. On histopathological follow-up, 73 cases (45.1%) showed benign histology and 89 cases (54.9%) showed malignant histology. Malignant histology follow-up was observed in 27 of 77 C3 lesions (35.1%) and in 62 of 85 C4 lesions (72.9%). The histopathology follow-up of the subjects is shown in [Table/Fig-1].

IAC Yokohama category	Histopathology diagnosis	
	Benign (n=73)	Malignant (n=89)
C3 (n=77)	Fibroadenoma (n=23) Fibrocystic disease (n=13) Benign Phyllodes tumour (n=5) Benign breast tissue (n=4) Inflammatory lesion (n=2) Cellular solitary fibrous tumour (n=1) Lobular granulomatous mastitis (n=1) Epidermal cyst (n=1)	Invasive carcinoma of no special type (n=24) Ductal carcinoma in situ (n=1) Atypical ductal hyperplasia (n=2)
	Total: n=50	Total: n=27
C4 (n=85)	Fibroadenoma (n=9) Fibrocystic disease (n=7) Phyllodes tumour (n=2) Usual ductal hyperplasia (n=2) Intraductal papilloma (n=1) Sclerosing adenosis (n=1) Adenomyoepithelioma (n=1)	Invasive carcinoma of no special type (n=55) Mucinous carcinoma (n=3) Invasive carcinoma with medullary like features (n=1) Invasive lobular carcinoma (n=1) Solid papillary carcinoma (n=1) High-grade Ductal carcinoma in situ (n=1)
	Total: n=23	Total: n=62

[Table/Fig-1]: Histopathology follow-up of C3 and C4 lesions.

The age ranged from 17 years to 80 years, with a mean age of 46.7 years. The most common presenting complaint was swelling, seen in 153 (94.4%) subjects, followed by pain in 7 (4.3%) subjects and nipple discharge in 2 (1.2%) subjects. The duration of symptoms varied from one week to 16 years, with a mean of 8.5 weeks.

Left breast was involved in 85 (52.5%) subjects, while the right breast was involved in 77 (47.5%) subjects. The size of the swelling varied from 0.4 cm to 8 cm, with a mean size of 2.9 cm. The clinical characteristics are summarised in [Table/Fig-2].

Clinical characteristics		Histopathology diagnosis		p-value
		Benign	Malignant	
Age (years)	Upto 40	33	17	0.0003
	>40	40	72	
Size of tumour (cm)	<2	14	13	0.1636
	2-5	52	73	
	>5	7	3	
Mobility	Mobile	49	26	0.0000034
	Fixed	24	63	
Skin	Dilated veins	2	1	0.1938
	Nodule	0	1	
	Normal	70	76	
	Pigmentation	0	1	
	Puckering	1	6	
	Redness	0	1	
	Ulceration	0	3	
Consistency	Firm	59	49	0.0005
	Hard	14	40	
Nipple	Discharge	1	0	0.0186
	Excoriation	0	1	
	Normal	71	76	
	Retraction	1	12	

Family history	Absent	71	85	0.5563
	Present	2	4	

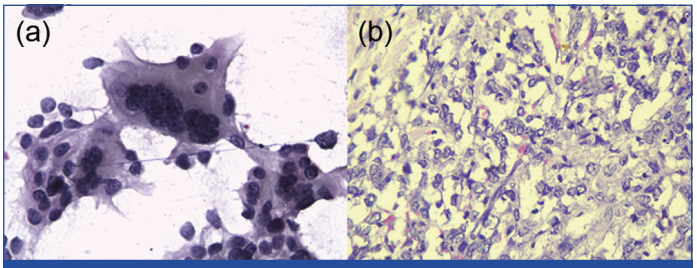
[Table/Fig-2]: Comparison of clinical characteristics of histologically diagnosed benign and malignant cases.

Clinical features found to be statistically significant in subjects with malignant diagnoses included older age, presence of a hard and fixed breast lump, and nipple changes including nipple excoriation and retraction.

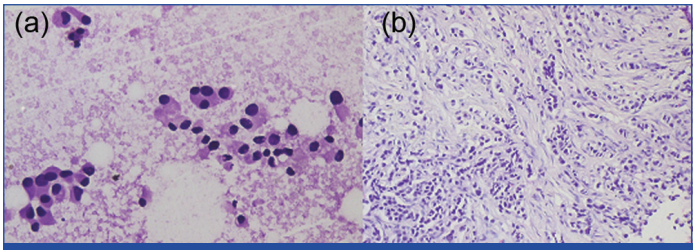
The cytological features are summarised in [Table/Fig-3]. Cytological features that showed a statistically significant association with malignant histopathology included ill-defined cluster borders, loosely cohesive clusters, cribriform architecture, markedly reduced or absent myoepithelial cells within clusters, high N:C ratio, marked nuclear enlargement with nuclear pleomorphism, irregular nuclear contour, coarse chromatin, nuclear overlapping, presence of numerous singly scattered atypical cells [Table/Fig-4,5], markedly reduced or absent bipolar bare nuclei in the background, reduced stromal fragments, high mitotic rate, and necrosis [Table/Fig-6a,b]. However, cellularity, presence of nuclear inclusions, nucleoli, and lymphocytic infiltration around the cell clusters did not show a statistically significant association.

Cytomorphological features		Histopathology diagnosis		p-value
		Benign	Malignant	
Cellularity	Low	31	38	0.1010
	Intermediate	17	32	
	High	25	19	
Border of clusters	Well defined	48	32	0.0002
	Ill defined	25	57	
Cohesion of cells	Loose	30	63	0.0004
	Focally loose	16	6	
	Tight	27	20	
Cribriform architecture	Absent	60	61	0.047
	Present	13	28	
Percentage of single cells	0%	51	32	0.0003
	1-9%	16	29	
	10-19%	2	8	
	20-49%	3	16	
	>50%	1	4	
N:C ratio	<1/2	38	30	0.0044
	1/2 - 1	19	15	
	2-3	15	40	
	>3	1	4	
Nuclear enlargement	Absent	21	9	0.00002
	Mild	30	23	
	Moderate	17	26	
	Marked	5	31	
Nuclear overlapping	Absent	34	23	0.0060
	Present	39	66	
Nuclear pleomorphism	Absent	23	12	0.000001
	Mild	35	20	
	Moderate	11	31	
	Marked	4	26	
Nuclear contour	Regular	58	31	0.0000001
	Irregular	15	58	
Nuclear inclusions	Absent	54	69	0.4976
	Focal	3	6	
	Present	16	14	
Nucleoli	Absent	52	56	0.0677
	Micronucleoli	20	24	
	Macronucleoli	1	9	
Chromatin pattern	Fine	61	59	0.0126
	Coarse	12	30	
Myoepithelial cells	Absent	38	79	0.0000
	Reduced	4	3	
	Reduced focally	19	5	
	Present	12	2	
Stromal fragments	Absent	23	43	0.0156
	Rare	36	41	
	Moderate	4	3	
	Many	10	2	
Mitotic rate (/10 HPF)	<1	66	61	0.0194
	1-2	3	16	
	2-3	2	7	
	3-4	1	3	
	>4	1	2	
Necrosis	Absent	67	76	0.0278
	Present	6	13	
Bipolar bare nuclei	Absent	21	59	0.00001
	Reduced	20	15	
	Present	32	15	

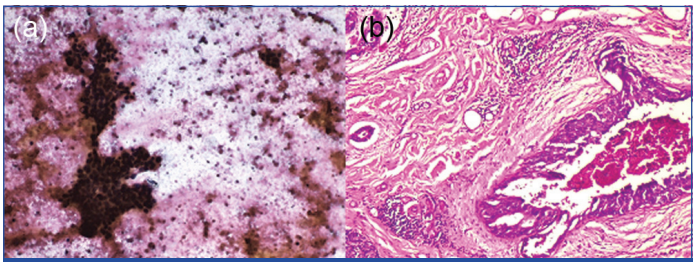
[Table/Fig-3]: Comparison of cytomorphological features in histologically benign and malignant lesions.



[Table/Fig-4]: (a) 40x (Pap smear) show numerous atypical cells with scattered giant cells; (b) 40x (H&E) Sections show dyscohesive sheets of tumour cells with nuclear pleomorphism.



[Table/Fig-5]: (a) 20x- (Pap smear) show numerous singly scattered atypical cells; (b) 10x- (H&E) sections show cords and sheets of tumour cells showing moderate nuclear pleomorphism.



[Table/Fig-6]: (a) 20x- (Pap smear) show atypical cells in a necrotic background. (b) 10x- (H&E) Sections show invasive breast carcinoma with background DCIS and comedo necrosis.

Cytology smears from malignant lesions showed predominantly loosely cohesive clusters (70.8%) compared with benign lesions

(41.1%). Sheets with cribriform architecture were found in 31.5% of malignant cases compared with 17.8% of benign cases.

DISCUSSION

In the present study, proliferative breast disease with atypia constituted 5.4% of total breast FNACs. This frequency ranged from 7.6% in a study by Deb RA et al., to 23.5% in a Nigerian population study by Yusuf I et al., [9,10]. Various studies have suggested that strict criteria should be applied to categorise these gray-zone lesions into C3 and C4 categories [11,12]. The percentage of C3 lesions should ideally be 3-7% of all breast FNACs and should not exceed 15% [9,13,14]. The management guidelines for these categories differ: C3 lesions should undergo a repeat FNA, while histopathological examination should be performed for C4 cases at the earliest [15].

About 35.1% of C3 lesions and 72.9% of C4 lesions showed malignant histology on follow-up. According to studies by Yu SN et al., and Tran PV et al., 30-45% of C3 lesions showed malignant histology [7,16]. The risk of malignancy in the C4 category, as established in various studies, was 81-87% [17,18]. The mean age at diagnosis in this study was 46.7 years. This was concordant with data from the Indian Cancer Registry Programme, where the most common age group diagnosed with breast cancer is 45-54 years [19].

Size of the swelling was not found to be a significant predictor of malignancy; however, the presence of a hard lump fixed to the chest wall was a statistically significant feature suggesting malignancy. Similarly, nipple changes such as nipple excoriation and retraction were significantly associated with malignant disease [20].

The most common benign lesion with atypical cytology was fibroadenoma, followed by fibrocystic disease. This was in concordance with studies by Shabb NS et al., and Mitra S and Dey P, which found fibroepithelial lesions and papillary lesions to be the most common causes of false-positive cytology [21,22]. This can be attributed to hypercellularity, nuclear atypia, and prominent nucleoli seen in cytology smears of fibroepithelial lesions, including fibroadenoma and phyllodes tumour, due to hormonal effects such as lactation, pregnancy, and adolescence.

Invasive breast carcinoma, of no special type, was the most common malignant histopathologic diagnosis. A confident diagnosis of invasive carcinoma could not be made in many cases because of sparse cellularity due to technical reasons or dry taps caused by the dense desmoplastic stroma of the tumour, which can obscure the morphology of malignant cells [23].

The important cytological factors predicting malignant behaviour observed in this study included loosely cohesive clusters with ill-defined borders and a high percentage of singly scattered, intact malignant cells displaying nuclear overlap, enlargement, irregular nuclear contours, and coarse chromatin in a necrotic background. Studies by Zhao C et al., also demonstrated the significance of a high percentage of singly scattered, intact malignant cells in making a confident diagnosis of malignancy [24]. Similar results were obtained in studies by Weigner J et al., where a combination of features such as cellular discohesion, nuclear overlap, fewer benign bipolar bare nuclei and myoepithelial cells, and a non cystic background were associated with malignancy [25]. Studies by Narasimha A et al., and Kalhan S et al., have demonstrated alterations in nuclear and cytoplasmic parameters as the disease progresses from benign lesion to ductal hyperplasia, in situ carcinoma, and invasive carcinoma [26,27]. The changes found to be significant in these studies included increases in mean nuclear area, mean cytoplasmic area, the Nuclear-to-Cytoplasmic (N/C) ratio, and nuclear perimeter. Other studies have demonstrated that a constellation of findings such as eccentrically placed nuclei, a high nuclear-to-cytoplasmic ratio, coarse chromatin, and prominent nucleoli are useful indicators of malignancy [7,28]. Similarly, the presence of cribriform architecture was significantly associated with malignancy. In this study, cribriform architecture was found in 31.46% (n=28/89) of malignant cases compared with 17.8% (n=13/73) of benign cases. This was concordant with studies by Yu SN et al., and Shabb NS et al., [7,29]. Similar studies have shown that cribriform architecture is more commonly a feature of low-grade malignancies such as tubular carcinoma, invasive cribriform carcinoma, and adenoid cystic carcinoma of the breast, as well as benign mimics like collagenous spherulosis [30,31]. However, no statistical association for cribriform architecture was derived in studies by Weigner J et al., [25]. Fibromyxoid stromal fragments were found to be more commonly associated with a benign diagnosis [32]. In this study, the absence of fibromyxoid stromal fragments was noted in 48.3% (n=43/89) of malignant lesions compared with 31.5% (n=23/73) of benign cases. Similarly, the presence of myoepithelial cells and benign bipolar bare nuclei were found to be useful pointers for a benign diagnosis [33]. Myoepithelial cells were present but reduced in number in low- and intermediate-grade ductal carcinoma in situ, whereas they were absent in high-grade ductal carcinoma in situ and invasive carcinomas [34,35]. However, in other studies [7,35], loss of myoepithelial cells in epithelial cell clusters was not found to be statistically significant in predicting malignancy.

Presence of a necrotic background can be considered a useful indicator of malignancy. Necrotic background was found in 14.6% (n=13/89) of malignant cases compared with 8.2% (n=6/73) of benign cases. This was concordant with studies by Weigner J et al., where necrosis was found to be associated with 7.9% of malignant cytology but only 2.8% of benign cytology samples [25]. The benign samples in which areas of necrosis were seen in this study included cases of recurrent phyllodes tumour, fibroadenoma with fibrocystic changes, fat necrosis of the breast, usual ductal hyperplasia, and epidermal cyst. Similarly, a myxoid background was observed in only one case, which was histologically diagnosed as invasive breast carcinoma with mucinous change.

Limitation(s)

The study had a few limitations. A total of 56 subjects were excluded due to unavailability of histopathological follow-up. The minimum follow-up period was only one year.

CONCLUSION(S)

In the present study, cytological factors predictive of malignancy in cytology smears included architectural features such as ill-defined, loosely cohesive clusters and a high percentage of singly discohesive atypical cells, cribriform architecture, and nuclear overlapping. Cellular features that were found to be statistically significant were nuclear enlargement, a high nuclear-to-cytoplasmic (N/C) ratio, coarse chromatin, and irregular nuclear contour. Reduced myoepithelial cells in epithelial cell clusters, reduced bipolar bare nuclei, a necrotic background, and absence of fibromyxoid stromal fragments were also found to be significantly associated with malignancy. Thus, careful search for these features in a fine cytological smear will help the pathologist make an early and accurate diagnosis of malignancy and guide patient management without delay. It will also help prevent unnecessary biopsies of benign lesions.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 23, 2025
- Manual Googling: Aug 25, 2025
- iThenticate Software: Aug 27, 2025 (10%)

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- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
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