Original Article

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Utility of Pattern Analysis in Breast Lesions and their Systematic Categorisation Based on Fine Needle Aspiration Cytology

Pathology Section

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ABSTRACT

Introduction: Fine Needle Aspiration Cytology (FNAC) has its definite value in the diagnosis of various mass lesions including breast lesions. Pattern is a regular and intelligible form or sequence discernible in the way which suggests a particular lesion. Patterns observed on cellular morphology in the aspirate are limited and need categorisation, as the risk of malignancy differs with the patterns.

Aim: To study and analyse patterns of various breast lesions on FNAC. To categorise various breast lesions according to patterns. Also, to compare sensitivity and specificity of different patterns with histopathology as a gold standard and to assess risk of malignancy in individual patterns.

Materials and Methods: This was a retrospective and prospective study in which patterns of various breast lesions on FNAC were studied. The data of 800 patients attending the OPD and IPD of Indira Gandhi Government Medical college Nagpur, over a period of 3 years (2015-2017), was analysed. The patterns evaluated were biphasic, inflammatory, fluid rich, epithelial cell rich, spindle cell rich, small round cell rich and pleomorphic.

Results: The lesions were classified as per patterns followed by evaluation of accuracy and risk of malignancy associated with each pattern. We found that the risk of malignancy varies with patterns.

Conclusion: Systematic pattern analysis and systematic categorisation of the breast lesions as per patterns, assists the cytopathologists to reach the final impression. Each pattern has its own implications for management and has a variable risk of malignancy.

Keywords: Intelligible, Reproducible, Triple test

INTRODUCTION

FNAC has its definite value in the diagnosis of various breast lesions as it is minimally invasive, safe and cost effective [1-3]. FNAC is used to evaluate not only palpable mass and cyst of breast but also non palpable mammographic abnormalities. FNAC is highly accurate for palpable mass [4,5].

FNAC is a part of 'triple test' for diagnosis of carcinoma breast. The 'triple test' is a multidisciplinary approach which analyses the pathologic features in conjunction with clinical and radiologic findings to diagnose the lesion and determine the best treatment plan [4].

The use of FNAC significantly lowers the costs of health care by decreasing the number of open surgical biopsies, without sacrificing early detection [6]. In benign lesions, further procedures are avoided or delayed and also it helps in diagnosing the recurrence, obtaining material for IHC and other ancillary studies. It is useful for evaluation of local chest wall recurrences and permits a number of ancillary studies such as flow cytometry, hormone receptor analysis and molecular studies [7].

Pattern is a regular and an intelligible form discernible in the way which suggests particular lesion. Patterns observed on cellular morphology in the aspirate are limited and need categorisation as risk of malignancy differs with patterns. The cell type, background and material aspirated decide the pattern and thus we can focus on group of pathologies in each individual pattern.

The patterns in breast pathology can be fitted to a limited number and once a pattern is identified the entities in each pattern can be differentiated.

MATERIALS AND METHODS

This was a retrospective and prospective study. The cases were taken as retrospective cases for two years (2015-2016) and prospective cases of one year (2017) from Indira Gandhi Government medical College and Hospital, Nagpur, Maharashtra, India. Ethical approval for the study was taken from Institutional ethical committee. There were no ethical issues in the study as it evaluated smears performed for diagnostic purpose and no intervention was done.

For prospective analysis all the patients with palpable lumps referred from surgical OPD were included. In retrospective analysis all cases of breast lump FNAC in which cytological impression could be given were included in the study.

Patients having only nipple secretions with undetectable breast lump even on ultrasonography, patients who were not willing to undergo FNAC and FNAC smears with inadequate cellularity were excluded from study.

In retrospective analysis case details were recorded from case records, cytology and histopathology forms. Past, present history examination findings, lymph node status and histopathology reports were taken into consideration. In prospective analysis, before doing the procedure detail past and present history was taken and thorough examination of breast lesion and lymph nodes (if enlarged) was done. Radiological reports were taken into consideration. In few cases with low cellularity, repeat aspiration was performed under USG guidance.

Pattern analysis is a qualitative data and all breast aspirates were categorised in patterns based on available literature and parameters under study, retrospective cases were added and evaluated till no value addition was possible with additional cases. Thus, with one year prospective and two year retrospective data we reached a sample size of 820 cases.

Informed consent was taken from the patients and FNAC was done using 23G needle and 5 mL syringe. Material was smeared immediately on clean glass slides. Whenever fluid was aspirated, it was centrifuged and smears were made from the sediment for getting maximal cellularity. Hematoxylin and Eosin and Papanicolau staining was done for alcohol fixed slides and May-Grunewald Giemsa staining was done for air dried smears. Ziehl-Neelsen staining was done for acid fast bacilli in suspected cases of tuberculosis.

Pattern analysis on cytology was done for 820 cases and histopathological correlation was available for 276 cases. After collecting the data, sensitivity and specificity in each pattern was calculated.

Patterns were identified based on following parameters

1) Cell: Size (small/large/pleomorphic), Shape (round/oval/spindle)

2) Nuclear Features: presence or absence of nuclear features of atypia or malignancy

3) Background Material: Presence of mucin/proteinaceous material/naked nuclei/inflammation in background.

Seven patterns were identified and further division of lesions was done depending on additional cytological features. The Patterns are as follows -

1) Biphasic Pattern: It is defined as the pattern showing both epithelial cells and spindle or myoepithelial cells/nuclei. This pattern was further divided into two categories-a) Biphasic pattern with myxoid or mucinous background (benign); and b)Biphasic pattern with atypia, dyscohesion (malignant)

2) Inflammatory Pattern: It is defined as the pattern in which inflammatory cells outnumber any other cells. This pattern was further divided into two as- a) inflammatory pattern with necrosis or histiocytes or myxoid background (benign); and b) Inflammatory lesions with atypical ductal cells, pleomorphism, dyscohesion (malignant). Lymphocyte rich patterns were excluded from this.

3) Fluid Rich: It is defined as the pattern showing proteinaceous or mucinous material in background. This pattern was further divided into two as- a) Fluid rich with normal ductal/acinar/apocrine cells (benign); and b) Fluid rich with atypical ductal cells (malignant)

4) Epithelial Cell Rich: It is defined as the pattern showing largely epithelial cells with paucity or lack of spindle cells. This pattern is divided as- a) Epithelial cell rich with papillary structures, with ductal proliferation with or without atypia; and b) Ductal cells with overt malignancy.

5) Spindle Cell Rich: It is defined as the pattern showing largely spindle cells with paucity or lack of epithelial cells. It is further divided as- a) Spindle cell rich lesion with myxoid or mucinous background without nuclear atypia (benign); and b) Spindle cell rich lesion with nuclear atypia, dyscohesion (malignant)

6) Small Round Cell Rich: It is defined as the pattern showing presence of small round cells with scanty cytoplasm. This is again divided as- a) Lymphocyte rich (benign and malignant); and b) Smaller dyscohesive ductal cells.

7) Pleomorphic Pattern: It is defined as the pattern showing presence of atypical pleomorphic cells singly or clustered. It is further divided as- a) Pleomorphic pattern with lipophages or inflammatory cells (benign); and b) Pleomorphic pattern with necrosis/dyscohesion/other features of malignancy (malignant)

RESULTS

The lesions were classified as per patterns followed by evaluation of accuracy and risk of malignancy associated with each pattern. We found that the risk of malignancy varies with patterns [Table/Fig-1].

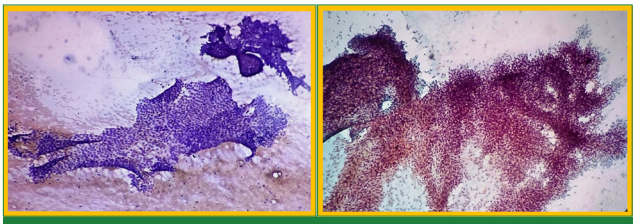
Pattern	Most Common
Biphasic	Fibroadenoma (Benign)
Inflammatory	Fibrocystic disease (Benign)
Fluid-rich	Breast cyst, galactocele (Benign)
Epithelial cell-rich	Carcinoma (Malignant)
Spindle cell-rich	Phyllodes, fibroadenoma (Benign)
Small round cell-rich	Carcinoma (Malignant)
Pleomorphic	Carcinoma (Malignant)

[Table/Fig-1]: Pattern-wise prevalence of the lesions.

1. Biphasic Pattern: On cytology most of the biphasic pattern lesions (n=165) were reported as benign lesions (164), further diagnosis was confirmed by histopathology as mentioned in [Table/Fig-2]. In biphasic pattern, most common lesion was fibroadenoma (n=156) [Table/Fig-3a] followed by benign phyllodes (n=3) [Table/Fig-3b] and tubular adenoma (n=3).

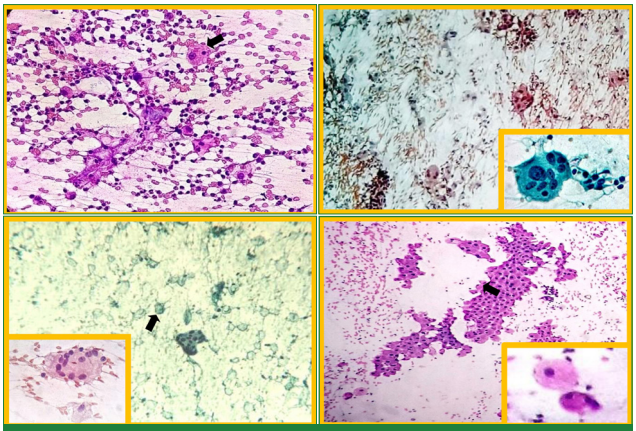
Category	Pattern	Additional Cytological Features	Cytology Diagnosis	Histopathology Diagnosis
I	Biphasic (165)	Myxoid/mucinous background	Benign (164)	Fibroadenoma (156) Benign phylloide (3) Tubular adenoma (3) Gynecomastia (2) Malignant phyllode (0)
		Atypia, dyscohesion	Suspicious (1)	IDC (1) Metaplastic carcinoma (0)
II	Inflam-matory (16)	Necrosis/myxoid background/histiocytes	Benign (16)	Acute Mastitis (3) Granulomatous mastitis (2) Fat necrosis (1) Fibrocystic disease (9) FA with cystic change (1)
III	Fluid-rich (5)	Normal ductal/acinar cells	Benign (4)	Galactocele (2) Breast cyst (2)
		Atypical ductal/acinar cells	Malignant (1)	Mucinous Carcinoma (1)
IV	Epithelial cell-rich (81)	Papillary structure	Papillary neoplasm (3)	IDC (2) Duct papilloma (1) Nipple adenoma (0)
		Ductal proliferation±atypia	PBD±atypia (14)	IDC (11) ADH (2) PBD with adenosis (1) Adnexal tumour (0)
		Ductal cells with features of malignancy	Malignant (64)	IDC (63) Medullary Carcinoma (1)
V	Spindle cell (2)	Myxoid/mucinous background	Fibroadenoma (2)	Fibroadenoma (1) Benign Phylloide (1) Sarcomas (0)
VI	Small round cell-rich (2)	Smaller ductal cells with dyscohesion/small round cells	Malignant (2)	Lobular Carcinoma (2) Lymphomas of breast (0)
VII	Pleomorphic (5)	Lipophages/inflammatory cells	Benign (1)	Fat necrosis (1)
		Necrosis/dyscohesion/features of malignancy	Malignant (4)	IDC (1) Lobular Carcinoma (1) Medullary Carcinoma (2)

[Table/Fig-2]: Clinical diagnosis with cyto-histopathological correlations.



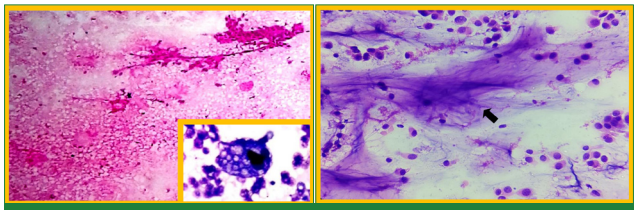
[Table/Fig-3a,b]: a) Fibroadenoma-biphasic pattern showing both epithelial and spindle myoepithelial cells/nuclei in a myxoid background (H and E, 100X); b) Benign Phyllodes-biphasic pattern with hypercellular stroma (H and E, 100X).

2. Inflammatory Pattern: Total 16 inflammatory cases were showing inflammatory cells. All were benign in nature in cytology as well as histopathology. On histopathology reported as acute mastitis [Table/Fig-4a], granulomatous mastitis [Table/Fig-4b], fat necrosis [Table/Fig-4c], fibrocystic disease [Table/Fig-4d] and fibroadenoma with cystic disease. No case was positive for malignancy.In current study, sensitivity, specificity and accuracy for inflammatory pattern is 100%.



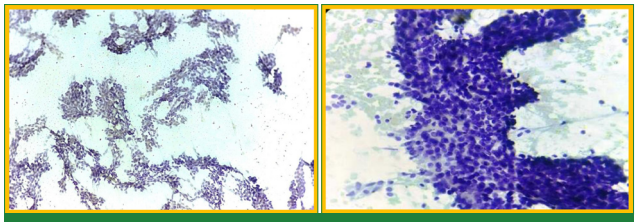
[Table/Fig-4a-d]: a) Acute Mastitis-inflammatory pattern showing many polymorphs histiocytes (arrow) with paucity of ductal cells (H and E, 100X). b) Granulomatous Mastitis-inflammatory pattern showing granulomatous reaction showing giant cells in Inset (PAP, 100X). c) Fat Necrosis-inflammatory pattern showing lipophages, adipocyte with fatty necrotic background and paucity of ductal cells. Giant cell in Inset Arrow shows a foamy macrophage. (PAP, 100X). d) Fibrocystic Disease-inflammatory pattern showing macrophages (inset) with apocrine cells (arrow) (H and E, 100X).

3. Fluid Rich Pattern: In fluid rich pattern out of 5 cases with histopathological correlation, 4 were reported as benign. Four cases showed fluid rich background with normal looking ductal or acinar cells, were reported as benign and on histopathology reported as breast cysts (n=2), galactocele (n=2) [Table/Fig-5a]. One case showing small monomorphic round cells with lot of thick mucin and transgressing capillaries in background, was diagnosed as mucinous carcinoma [Table/Fig-5b], confirmed on histopathology. Sensitivity, specificity and accuracy for this pattern are 100%.



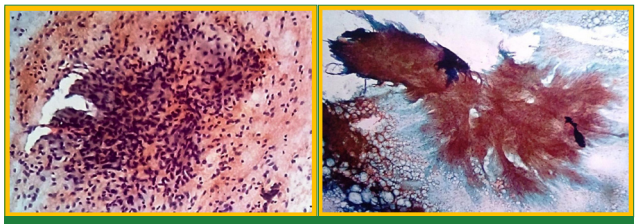
[Table/Fig-5a,b]: a) Galactocele-fluid rich pattern shows macrophages with fatty lipid background with degenerate acinar cells (lipophage in inset) (H and E, 100X); b) Mucinous Carcinoma-fluid rich pattern shows atypical ductal cells with abundant background mucin (arrow) (MGG, 400X).

4. Epithelial Cell Rich Pattern: Out of 81 epithelial cell rich patterns, 64 were reported as malignant on cytology. Histopathology confirmed malignancy in all cases. The type was Infiltrative Duct Carcinoma (IDC) in 63 cases and medullary carcinoma in 1 case. In cases where typical papillary structures were seen and were reported as papillary neoplasm (n=3) [Table/Fig-6a] on cytology, histopathological diagnosis was IDC (n=2) and duct papilloma (n=1). Proliferative epithelial lesions were reported as Proliferative Breast Disease (PBD) with or without atypia (n=14) [Table/Fig-6b]. Histopathological confirmation using core biopsy was obtained in these cases. Out of 11 cases of PBD with atypia all cases were found malignant on histopathology sensitivity and accuracy was 79% and 89.5% respectively, while specificity was 100%.



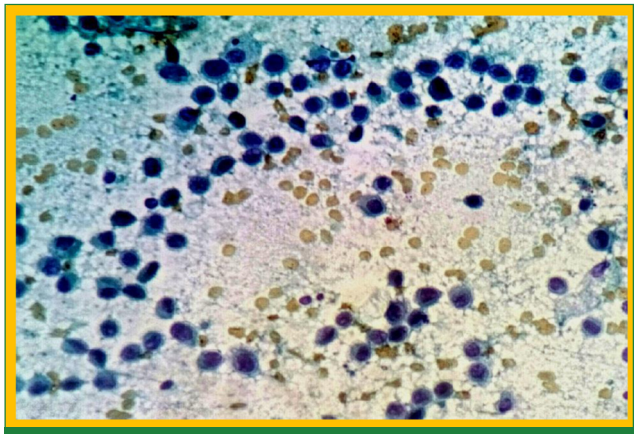
[Table/Fig-6a,b]: a) Papillary Neoplasm-epithelial cell rich pattern shows predominent epithelial cells arranged in papillary structures with paucity of spindle cells (PAP, 100X); b) Proliferative breast disease without Atypia- epithelial cell rich pattern shows predominent epithelial cells showing overlapping with paucity of spindle cells (H and E, 400X).

5. Spindle Cell Pattern: In this pattern out of the two cases one was reported as Fibroadenoma [Table/Fig-7a] on cytology and confirmed on histopathology. Second case of diagnosed as fibroadenoma on cytology was a cystosarcoma phyllodes [Table/Fig-7b] on histopathology.



[Table/Fig-7a,b]: a) Fibroadenoma- spindle cell rich pattern in fibroadenoma showing cellular stromal fragment. (H and E, 400X); b) Benign Phyllodes-spindle cell rich pattern in benign cystosarcoma phyllodes showing many cellular stromal fragment with occasional epithelial fragment (H and E, 100X).

6. Small Round Cell Pattern: Small cell tumours were reported as lobular carcinoma (n=2) confirmed on histopathology. [Table/Fig-8] and no case of lymphocytic mastopathy, malignant small round cell tumour or lymphoma was found in our study.

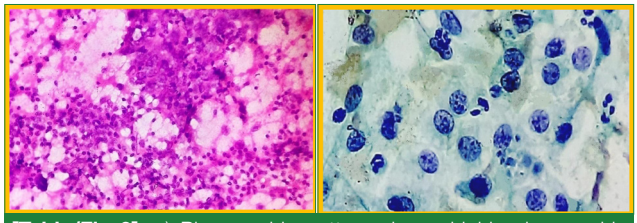


[Table/Fig-8]: Lobular Carcinoma- small round cell rich pattern shows small round slightly pleomorphic cells arranged in Indian file pattern (PAP, 400X)

7. Pleomorphic Pattern: Majority of the pleomorphic pattern were malignant (n=4) on cytology as well as histopathology. On histopathology, they were reported as Invasive lobular carcinoma (n=1) and medullary carcinoma (n=2) [Table/Fig-9a], Duct Carcinoma (n=1) [Table/Fig-9b].

Sensitivity, specificity and accuracy for spindle cell lesion, small cell rich lesion and pleomorphic pattern is 100%.

Epithelial cell-rich pattern has lowest sensitivity in detecting malignancy followed by biphasic pattern [Table/Fig-10]. Risk of malignancy is calculated for each pattern [Table/Fig-11].



[Table/Fig-9]: a) Pleomorphic pattern shows highly pleomorphic cells with lymphocytes in background medullary carcinoma (H and E, 100X); b) Duct Carcinoma- pleomorphic pattern shows single population of highly pleomorphic cells (PAP, 400X).

Pattern	Sensitivity (%)	Specificity (%)	Accuracy (%)
Biphasic	99	100	99.5
Inflammatory	100	100	100
Fluid-rich	100	100	100
Epithelial cell-rich	79	100	89.5
Spindle cell-rich	100	100	100
Small round cell-rich	100	100	100
Pleomorphic	100	100	100
Total	97	100	98

[Table/Fig-10]: Statistics of the present study.

Pattern	Benign	Suspi-cious	Malignant	Total	Risk of Malignancy
Biphasic	164	1	0	165	0%
Inflamma-tory	16	0	0	16	0%
Fluid-rich	4	0	1	5	20%
Epithelial cell-rich	0	17	64	81	79%
Spindle cell-rich	2	0	0	2	0%
Small round cell	0	0	2	2	100%
Pleomor-phic	1	0	4	5	83%
Total	187	18	71	276	40%

[Table/Fig-11]: Pattern wise risk of malignancy.

	Biphasic	Inflam-matory	Fluid Rich	Epithelial Cell Rich	Spindle Cell Rich	Small Round Cell	Pleom-orphic
Age range (in years)	15-46	16-54	49-70	20- 65	34- 45	48- 71	38-90
Mean age (in years)	29 (lowest)	32	33	46	38	59	63 (high-est)

[Table/Fig-12]: Age distribution of the cytological patterns.

Risk of malignancy was 100% with small round cell pattern followed by pleomorphic pattern which was 83%. Biphasic pattern was most common in 3rd decade (mean age 29 years) and pleomorphic was more in old age i.e., 63 years [Table/Fig-12].

DISCUSSION

FNAC of breast lumps is an important diagnostic tool for the pre-operative diagnosis of breast neoplasm. It provides rapid and accurate diagnosis and has become a cost effective tool for the treatment of breast lesions [7].

Success of FNAC depends upon several important contributing factors like aspirator's experience, skillful cytological interpretation and a rational analysis based upon correlation of cytological and clinical information in the context of the patient [8]. Inadequate sampling, overlapping cytological features and inexperience of cytologist are the limitations in breast cytology study [9].

Pattern identification helps a cytologist to shortlist lesions. Predominant cell pattern, cellular features and background are morphological attributes of aspirates to assist pattern recognition. On the basis of predominant cell pattern, differential diagnosis is suggested and then final diagnosis is narrowed down using cellular features and background. Recognition of pattern reduces inter observer variation. Moreover, diagnosis of pattern is all inclusive and offers a medico legal protection.

Before analysing cellular details and background elements; observation of the cell pattern alone can complement breast cytology study. This approach could be a very good step for a beginner in cytology and also helps cytologist in screening the breast cytology slides [10]. Systematic pattern recognition of breast cytology smears will also be very useful in reducing false positive rates.

In our study epithelial cell-rich, small round cell-rich and pleomor-phic patterns are most commonly associated with malignancy. Most important attribute in case of inflammatory, fluid- rich and epithelial cell-rich pattern is ductal epithelial cells which were used to differentiate between benign and malignant lesions. As there are few limitations for cytological studies, there was difficulty in diagnosing cases like PBD with atypia, papillary lesions, cystosarcoma phyllodes, in situ carcinoma and fibroadenoma with changes secondary to hormone therapy or infarction. The cytologic distinction of intraductal carcinoma insitu from an invasive cancer is not reliable [11].

1. Biphasic Pattern: In this pattern, along with epithelial cells, second population of cell was myoepithelial cells or nuclei of myoepithelial cells. Presence of myoepithelial cells suggests benign nature of lesion, so there wasn't any difficulty in diagnosing these cases. In one case, few atypical cells and dyscohesiveness was seen, so it was reported as suspicious for malignancy which was further reported as IDC on histopathology. Secondary changes in fibroadenoma were metaplastic changes like apocrine change (n=9), cyst macrophages (n=31) and giant cells (n=15).

2. Inflammatory Pattern: In inflammatory lesions, ductal cells need to be examined very carefully. Most of the time, clinically and radiologically mastitis mimics carcinoma of breast, so cytology is very useful to decide further management [7]. As tuberculosis is prevalent in India it is important to do Ziehl-Neelsen staining for acid fast bacilli in these cases.

3. Fluid Rich Pattern: Due to paucity of cells it is difficult to diagnose cases in which aspirate is fluid in nature .Immediate repeat aspiration and smears from centrifuged fluid help to increase cellularity. Apocrine metaplasia favored diagnosis of benign while with mucinous background extensive search is done to rule out mucinous carcinoma. In cases where no distinction possible, may be reported as a mucocele like lesion.

4. Epithelial Cell Rich Pattern: Epithelial cell rich lesions varied from mild atypia to frank malignant features. Cases with clear malignant features on cytology were reported as malignant lesion, confirmed as IDC and medullary carcinoma on histopathology. In papillary lesions/neoplasm FNAC has limitations and was reported as papillary neoplasm of breast (n=3). Final histopathology diagnosis in these cases were IDC (n=2) and duct papilloma (n=1). A study by Pratibha D et al., [12] has found similar overlap in diagnosis of papillary lesions of breast

Cases with scanty cellularity of cells showing features of malignancy were reported as suspicious and those with proliferative epithelial lesions were reported as PBD with or without atypia. Total 11 cases of cytologically diagnosed PBD were malignant on histopathology. These were low grade duct carcinoma where diagnosis of PBD with atypia was given on cytology. When there is epithelial hyperplasia as seen by hypercellularity, dyscohesive cell population, paucity of myoepithelial cells it is extremely difficult to distinguish between atypical ductal hyperplasia and low grade duct carcinoma. Such lesions are grey zones of breast cytology this is in concordance with the Mitra S et al.,[13]. Shabba LS et al., [14] found 20% lesions in true grey zone due to overlap of cytological features of benign and malignant conditions due to nature of lesions. Thus, the loss of sensitivity in this pattern is at the cost of high specificity.

5. Spindle Cell Pattern: Spindle cell rich pattern need to be interpreted carefully due to variable presentation of fibroadenoma. The distinction between phyllodes tumour and fibroadenoma is difficult. Hypercellular stromal fragments are more common in phyllodes tumour but can be seen in fibroadenoma as well. Numerous individual, long, plump fibocystic cells with spindle shaped nuclei are characteristic of a phyllodes tumour [15,16]. Diagnostic difficulty due to overlap of cytological features of fibroadenoma and phyllodes is also noted by Bandyopadhyay R et al.,[17].

Metaplastic carcinoma can mimic a phyllodes tumour because of a prominent spindle cell component, but the benign epithelial component of a phyllodes tumour is absent [18].

6. Small Round Cell Pattern: In lobular carcinoma, are sparsely cellular because of marked stromal fibrosis and predominantly isolated cells with small groups or linear arrays are seen. Lymphomas show monomorphic small cell pattern, in our present study no case of lymphoma or malignant small round cell tumour was found.

7. Pleomorphic Pattern: In cases with pleomorphic cellularity pattern, one case was showing lipophages and inflammatory cells and it was reported as fat necrosis which was confirmed on histology. As fat necrosis mimics like carcinoma clinically, radiologically and on cytology, it is important to look background for other features. While cases with necrotic background and dyscohesive groups were reported as malignant which were high grade invasive duct carcinoma on histopathology. Fat necrosis is a lesion which contributes to indeterminate or erroneous diagnosis on cytology because in this epithelial cells are typically sparse but nuclear atypia may mimic malignancy. Shabba NS et al., [14] also noted similar findings.

The accuracy of present study in diagnosing breast neoplasms is 98.0% which corresponds well with Nggada HA et al., [19] [Table/Fig-13] who reported diagnostic accuracy of 97.7%.The specificity of 100% in our study was similar with studies done by Muddegowda PH et al., [20] and Nggada HA et al., [19] which showed specificity of 98% and 98.7% respectively. The sensitivity of 97.0% correlates with studies done by Nggada HA et al.,[15] and Kuo YL et al.,[21]. They noted sensitivity of 95.7% and 100% [Table/Fig-13]. Pattern analysis is highly reliable and recommended mode of analysis of breast lesion. Each pattern has its implications for management and has variable risk of malignancy.

Parameters	Present Study	Nguansangiam S et al., [1]	Muddegowda PH et al., [13]	Nggada HA et al., [14]	Kuo YL et al., [15]
Sensitivity (%)	97.0	92.5	94.5	95.7	100.0
Specificity (%)	100.0	90.2	98.0	98.7	94.0
Accuracy (%)	98.0	91.2	97.0	97.7	___

[Table/Fig-13]: Statistical comparison with the previous studies.

LIMITATION

The limitations of this study are that very rare condition may not have been categorised. Further studies with large sample size are needed for further validation of the study.

CONCLUSION

Systematic pattern analysis and categorisation of breast lesions as per patterns assist cytopathologists to reach final impression. Recognition of pattern reduces inter observer variation. This study adds to new approach to diagnosis of breast smears which is linked to risk assessment in each pattern

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