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Cytomorphologic features of Phyllodes tumour of breast: A cytological dilemma to distinguish from Fibroadenoma

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Abstract

Background: Phyllodes tumour is a rare fibroepithelial neoplasm accounting for less than 1% of all breast tumours. The cyto-diagnosis of Phyllodes Tumour often poses a dilemma as it needs to be differentiated from fibroadenoma, which is the most common benign breast neoplasm. Pre- operative categorisation of fibroepithelial neoplasms with cellular stroma is crucial for proper surgical planning, appropriate management and avoidance of recurrence. However, reliable cytological features differentiating Phyllodes tumour from Fibroadenoma with cellular stroma still remains a challenge.

Objectives: To evaluate various cyto-diagnostic features that can help to differentiate phyllodes tumour from fibroadenoma. Also, to determine the statistical significance of these features in categorising fibroepithelial neoplasms.

Methods: FNAC findings of 45 cases of histologically proven phyllodes tumour and an equal number of fibroadenomas were reviewed. Various cytomorphological features were analysed which include cellularity and cellular details of both the epithelial and stromal components to differentiate into appropriate category.

Conclusion: Amongst the various features identified and analysed in the present study, the statistically significant relevant features that favoured a diagnosis of phyllodes tumour over fibroadenoma included plump nature of the stromal cells, presence of fibroblastic pavements and >30% elongated spindly cells in the background dispersed population. While dis-cohesiveness of stromal fragments and pleomorphism increased with increase in tumour grade. These features

need to be considered and applied while dealing with fibroepithelial neoplasms.

Keywords: Phyllodes tumour, Fibroepithelial lesion (FEL), epithelial component, stromal component, Fibroadenoma

Introduction

Various reports have repeatedly questioned the reliability of the diagnostically significant cytomorphological features of Phyllodes Tumour (PT).[1,2] Phyllodes Tumour is a part of the spectrum of fibroepithelial lesions (FEL) of breast which are a heterogeneous group of biphasic neoplasms in which there is a proliferation of both epithelial and stromal components.[3] Fibroadenoma too is a part of this spectrum and is very common as compared to PT. PT and Fibroadenomas are great clinical, radiologic and morphologic mimickers of each other. But while PT has a high risk of recurrence and metastasis depending on its grade, Fibroadenoma is totally benign. Hence their management differs. PT is managed by wide local excision (WLE) or by simple mastectomy and Fibroadenoma can be managed by conservatively or by simple enucleation. Hence an accurate pre-operative diagnosis crucial for their management.[2]

Triple test is the standardised approach for assessing breast lumps and arriving at a pre-operative diagnosis and includes clinical examination, USG guided imaging / Mammography and Fine Needle Aspiration (FNA) or Core Needle Biopsy (CNB) results.[2] However various reports indicate that FNA generally has high false negative rate for diagnosis of PT. Recent research (MiB-1, p53, Ki-67, p63, p40) has focused on predicting behaviour of PT, but its reliable preoperative diagnosis is still limited.[2] This lack of reliable cyto-diagnostic features, emphasizes the need for assessing various cytologic criteria that can help in accurate pre-operative diagnosis of PT.

Aims And Objectives

This study was conducted to evaluate various relevant cytomorphologic features of PT with special emphasis on diagnostic features that can help differentiate PT from fibroadenoma. And to determine the statistical significance of these features in categorising these fibroepithelial neoplasms.

Material And Methods

This study was conducted in Government Medical College, Nagpur over a 5year period. 45 histo-pathologically proven cases of PT were retrieved along with their respective preoperative cytology smears and relevant clinical data, and cytology smears of 45 cases of histopathologically confirmed fibroadenoma were taken as control.[4]

The histopathological diagnosis of PT and fibroadenoma was done as per criteria of WHO.[3]

The cytology smears of PT and fibroadenoma were studied by two observers. The first observer assessed all the smears of PT and fibroadenoma (45 cases each) for a defined set of cytological features and the statistical significance of each feature was calculated. Thereafter the second observer independently and blindly assessed mixed set of same smears (45 cases each of PT and fibroadenoma) for the same defined set of cytological features and offered a diagnosis. The number of PT and fibroadenoma cases correctly identified was compared with values before study.

The defined set of cytological features includes a) Smear Cellularity b) Epithelial Characteristics, c) Stromal Characteristics and d) Dispersed cell population.[5,6]

a) Smear cellularity was expressed as sparse, moderate or marked. The cytological features of the

epithelial and stromal component as well as the dispersed cell population in the background were studied in details.

b) For the epithelial component, the following features were considered: number of sheets or clusters per slide (less than 5 or more than 5 epithelial clusters per smear) [Fig.1a & 1b]

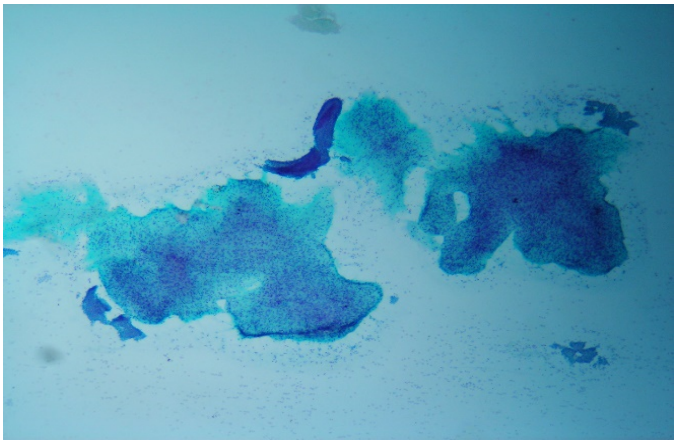

Fig.1a: Smear show 5 sheets of epithelial cell per smear.

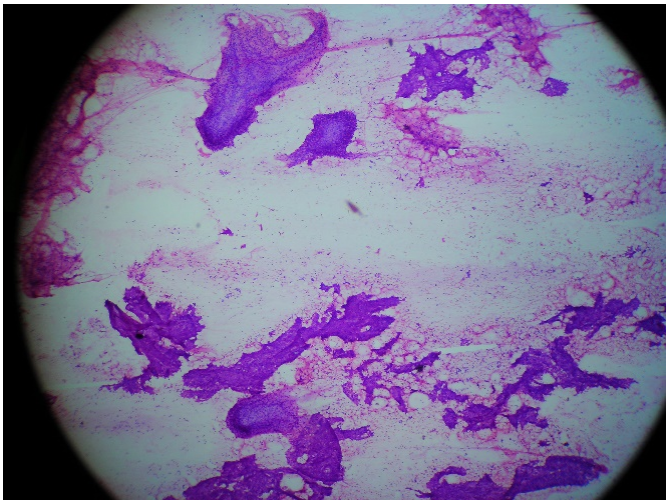

Fig.1b: Smear shows 5 sheets of epithelial cells per smear.

c) and others features like nuclear atypia (present or absent), apocrine metaplasia (present or absent) [Fig2] and pattern of sheets (antler- horn pattern [Fig3], folded sheets[Fig4]) were also noted.

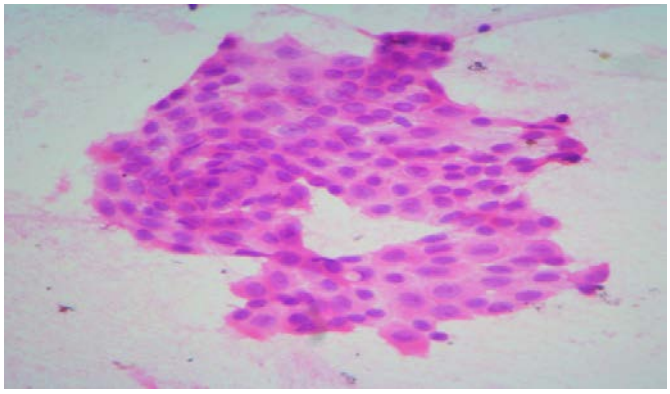

Fig.2: Smear shows apocrine change in epithelial cells.

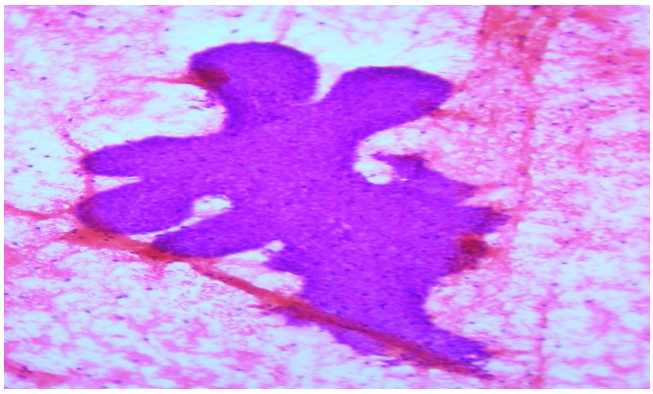

Fig.3: Smear shows Antler-Horn pattern of epithelial cells.

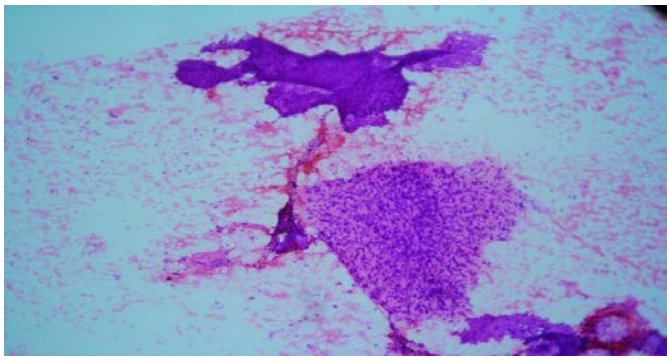

Fig.4: Smear shows folded sheets of epithelial cells.

d) For the stromal component following features were studied: the number of stromal fragments per smear (less than 5 or more than 5 stromal clusters per smear)[Fig 5a & 5b], cellularity of the fragments (sparse, moderate, or marked), nature of the fragments (loose fibromyxoid) [Fig 6] , dense or hyalinised [Fig 7], predominant stromal cell type (thin spindly[Fig 8], plump fibroblastic [Fig 9] or pleomorphic [Fig 10]) and other features that

included: mitosis [Fig 11], fibroblastic pavements [Fig 12] and dyscohesiveness of stromal fragments [Fig 13].

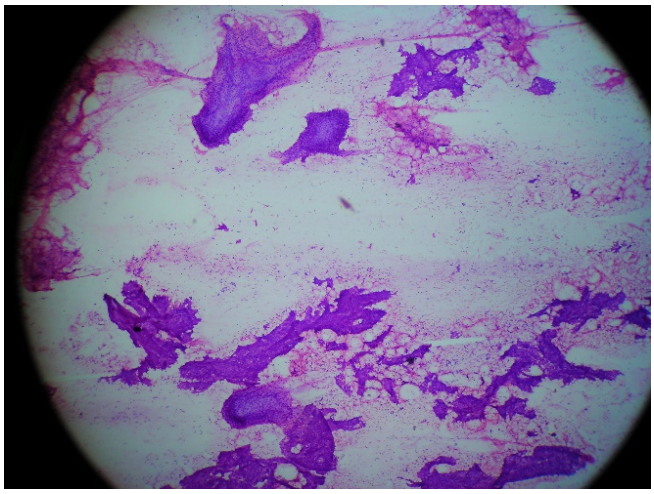

Fig. 5a: Smear shows less than 5 stromal fragments per smear.

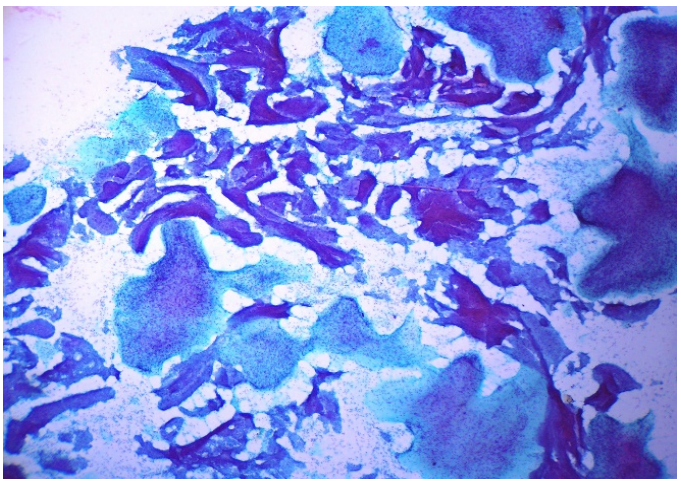

Fig.5b: Smear shows 5 stromal fragments per smear

d) For dispersed cell population the features that were assessed included: cellularity (sparse, moderate & marked), dispersed elongated spindly cells [Fig 14] in the background (less or more than 30% of total dispersed cells per smear) and other features (spindly cell atypia, macrophages and giant cells). [Fig15]

Observations

Relevant data revealed that the maximum number of PT cases were in 5th decade while cases of FA were a decade earlier. Average size of lump in PT was more than 12 cm & in Fibroadenoma it was less than 3 cm.

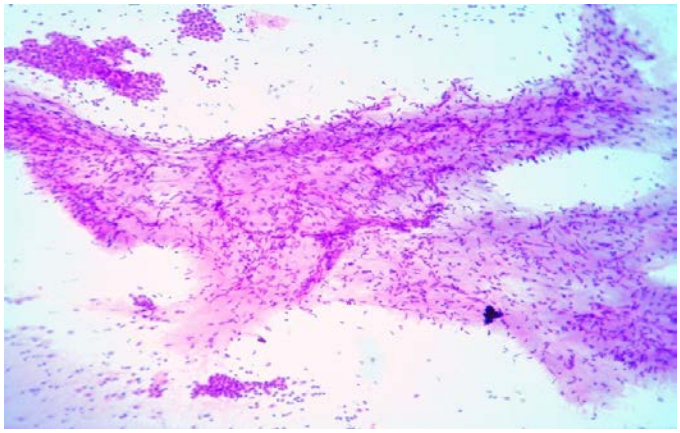

Fig. 6: Smear shows loose fibromyxoid nature of stromal fragments.

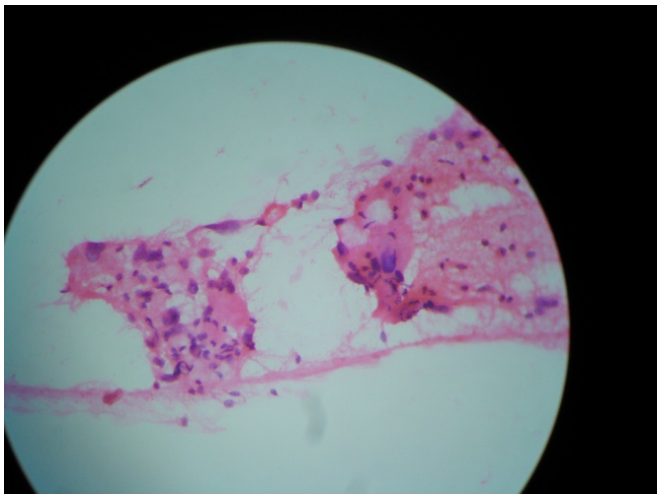

Fig.7: Smear shows hyalinized nature of stromal fragments.

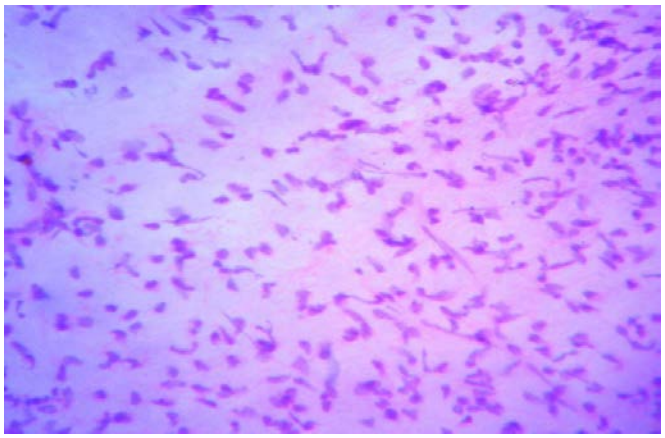

Fig.8: Smear shows thin, spindly, wavy stromal cells type.

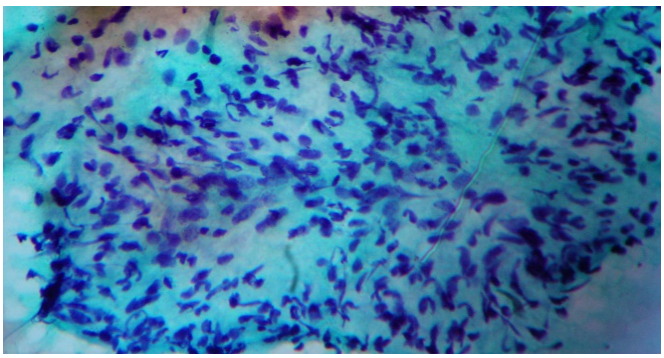

Fig.9: Smear shows plump fibroblastic stromal cells.

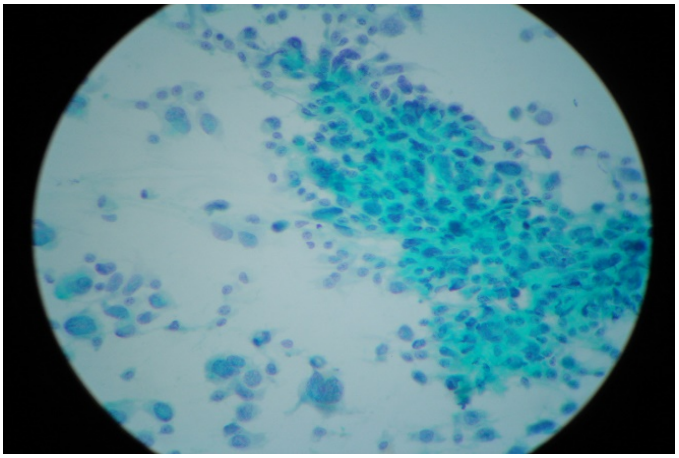

Fig.10: Smear shows pleomorphic stromal cells.

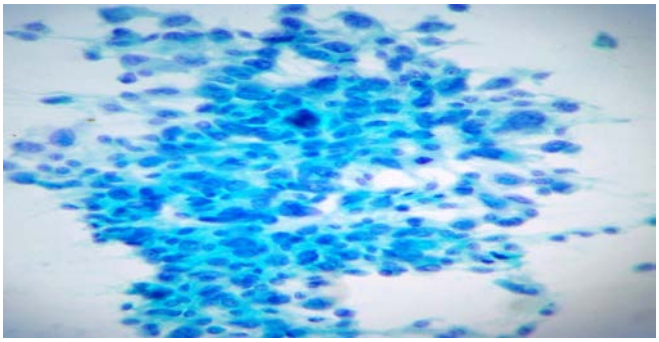

Fig.11: Smear shows mitosis in stromal cells.

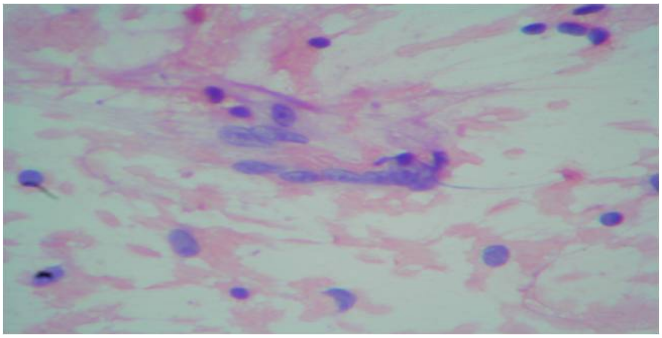

Fig.12: Smear shows fibroblastic pavements.

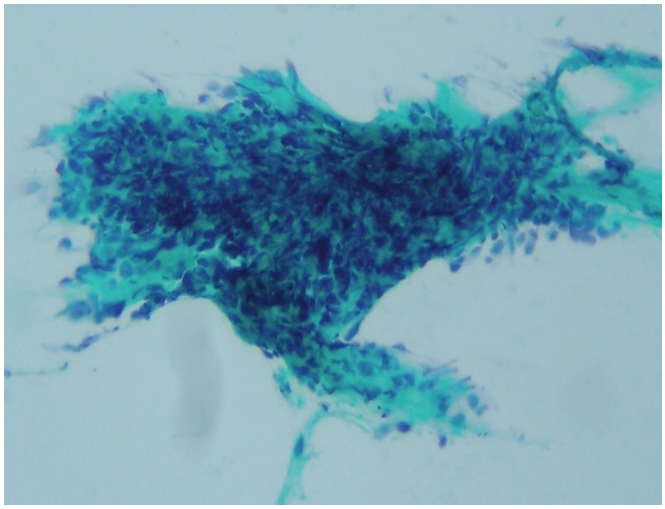

Fig.13: Smear shows dyscohesiveness of stromal fragments

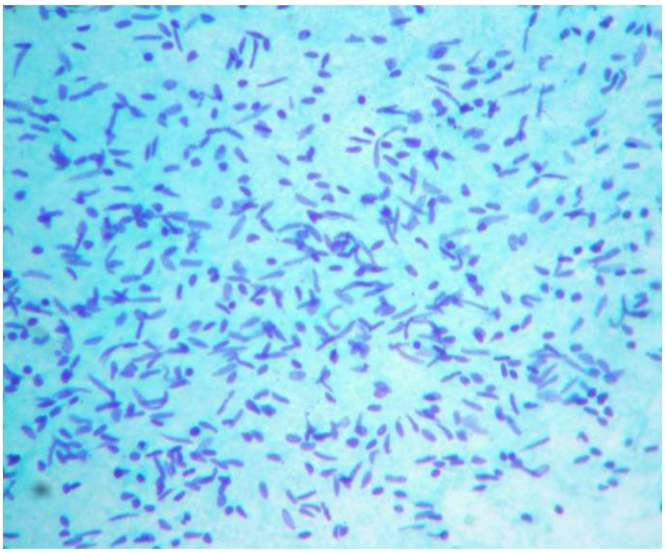

Fig.14: Smear shows 30% dispersed elongated spindly cells in the background.

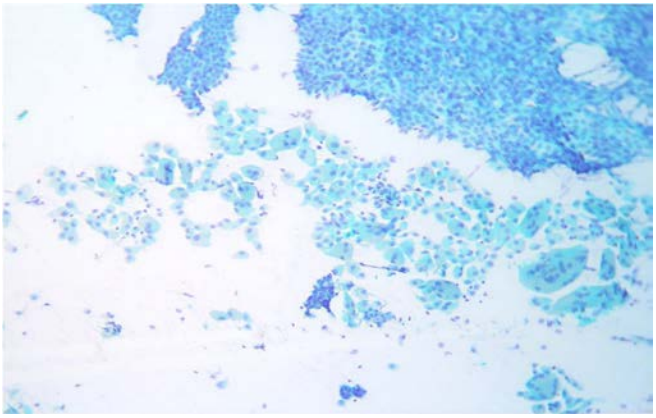

Fig.15: Smear shows macrophages and giant cells.

Table 1: Shows histopathologically confirmed cases of PT and fibroadenoma with initial preoperative cyto-diagnosis

Histopathologically confirmed cases of PT& FA with initial pre- op Cytodiagnosis							
Histopath diagnosis	Cases No (%)	Cytodiagnosis					
		PT			FA	?FA/ ?PT	PBD
		Benign	Boderline?Malignant	Malignant			
Benign PT	33(73.3)	18	-	-	8	4	3
Borderline PT	8(17.8)	5	2	-	-	1	-
Malignant PT	4(8.8)	-	1	3	-	-	-
Total (%)	45(100)	23(51.1)	3(6.6)	3(6.6)	8 (17)	5(11.1)	3(6.66)

(FA- fibroadenoma, PT-phyllodes tumour, PBD-proliferative breast disease)As shown in Table 1, cytology smears of 45 histologically proven cases of PT were studied by first observer before the application of defined set of cytological features. Out of 45 cases, 29 cases were correctly diagnosed as PT on cytology while 8 cases were diagnosed as fibroadenoma, 3 cases as proliferative breast disease and 5 cases as ? PT/? Fibroadenoma. Thus 51.11% of PT were correctly diagnosed and sub typed before using the defined set of cytological features.

Table 2: Smear Cellularity and Characteristic of Epithelial Component

Cytological Features	Phylloides Tumour- n	Fibroadenoma- n
Cellularity	Sparse – 7 Moderate-22 Marked-16	Sparse -3 Moderate-20 Marked-22
No. of epithelial characteristic	>5 epithelial sheet/smear-25 <5 epithelial sheet/smear-20	>5 epithelial sheet/smear-30 <5 epithelial sheet/smear-15
Other Features	Antler Horn- 11 Folded sheets-34 Apocrine metaplasia-3	Antler Horn- 28 Folded sheets-27 Apocrine metaplasia-8

(n- Number of cases)As shown in Table 2, there was no significant difference in the smear cellularity between PT and Fibroadenoma. They were equally moderate to markedly cellular in majority of cases. More than 5 epithelial sheets or clusters per smear were more commonly seen in Fibroadenoma than PT. Of the various features, antler horn pattern / branching clusters was significantly more in fibroadenoma than PT while other features namely folded sheets and apocrine metaplasia were not helpful in distinguishing between PT and fibroadenoma.

Table 3: The Cytological Characteristics of Stromal Component.

Characteristics	Phylloides Tumour-n	Fibroadenoma-n
No. of fragments /smear	>5 stromal fragments/smear-37 <5 stromal fragments/smear-8	>5 stromal fragments/smear-17 <5 stromal fragments/smear-28
Stromal cellularity	Sparse -04 Moderate-14 Marked-27	Sparse - 29 Moderate-08 Marked-08
Predominant nature of stroma	Loose Fibromyxoid- 4 Dense-30 Combination-09 Hyalinised-02	Loose Fibromyxoid-30 Dense-08 Combination-06 Hyalinised-01
Predominant stromal cell type	Plump fibroblastic-30 Thin wavy-06 Combination-06 Pleomorphic-03	Plump fibroblastic-09 Thin wavy-25 Combination-11 Pleomorphic-00
Other features	Fibroblastic Pavements-30 Dyscohesivness-15 Presence of mitosis-02	Fibroblastic Pavements-00 Dyscohesivness-00 Presence of mitosis-00

(n- Number of cases)

As shown in Table 3, more than 5 stromal fragments/ smear was more commonly seen in PT than fibroadenoma . Markedly cellular stroma was significantly associated with PT and sparsely cellular was associated with fibroadenoma. Among the nature of stroma, dense stroma was significantly more common in PT and fibromyxoid stroma in fibroadenoma. Combination of both (dense stroma & fibromyxoid stroma) and hyalinised stroma was not helpful to distinguish between PT and fibroadenoma. Out of predominant stromal cell type, plump fibroblastic stromal cells were significantly more in PT while thin wavy stromal cells were significantly associated with fibroadenoma. Pleomorphic stroma was exclusively seen in malignant PT. Other features like fibroblastic pavements were exclusively seen in PT while discohesiveness was significantly seen in borderline & malignant PT. Mitosis was exclusively seen with malignant phylloides tumour.

Table 4: Distribution of dispersed cell population between Phylloides Tumour & Fibroadenoma

Dispersed cell population	Phylloides Tumour	Fibroadenoma
Cellularity	Sparse-10 Moderate-12 Marked-23	Sparse-9 Moderate-12 Marked-29

Cell type -Spindly cell (=/ >2 lymphocytes diameter)	<30%(bare bipolar predominantly)- 11>30%- 34	<30%(bare bipolar predominantly)- 35>30%- 10
Macrophages and giant cells	30	12

As shown in Table IV, cellularity of dispersed cell population showed no significant difference to distinguish between PT and fibroadenoma. Dispersed cell population consist of spindly cell type which has size of equal to or more diameter of 2 lymphocytes. >30% dispersed spindly cells was significantly associated with PT, while <30% dispersed spindly cells was significantly seen in fibroadenoma. Macrophages & multinucleated giant cells was significantly associated with PT

Table 5: Cytodiagnosis of cases after independent& 'blind' assessment of slides by 2nd observer with application of the set of cytological features: (45 cases each of PT & FA)

Histopath Diagnosis		Cases No (%)	Blind categorization by 2nd observer (%)					
			PT			FA	?FA/?PT	PBD
			Benign/ Low grade PT	PT? Borderline PT	Malignant PT			
PT (n=45)	Benign PT	33(73.3)	26 (78.8)	-	-	3 (9.09)	1 (3.03)	3 (9.09)
	Borderline PT	8 (17.8)	1 (12.5)	7 (87.5)	-	-	-	-
	Malignant PT	4 (8.8)	-	-	4 (100)	-	-	-
FA (n=45)		45(100)	2 (4.4)	3 (6.6)	3 (6.6)	38 (85)	2 (4.4)	3(6.6)

(FA- fibroadenoma, PT- phylloids tumour, PBD- proliferative breast disease)Table 5. shows cytodiagnosis of cases after independent and blind assessment of slides by 2nd observer with application of set of specific cytological features. 82.22% of PT and 100% of fibroadenoma were correctly diagnosed & sub typed after application of set of cytological features.

Results & Interpretation

In present study, average age of patients with PT was 45 years while FA was seen a decade earlier. Average size of lump in PT was 12 cm and of fibroadenoma it was< 3 cm. In present study ,based on specific set of cytological criteria it was found that predominance of cellular stromal fragments were suggestive of PT, but can also be seen in few cases of FA . More diagnostically relevant features (statistically significance) for PT was

a) Nature of stromal cell - Plump fibroblastic stroma associated with PT and thin spindly stroma with fibroadenoma.

b) Fibroblastic pavements was exclusively in PT (67%)

c) >30% spindly dispersed cell population was significantly seen in PT (76%)

d) Discohesiveness of stromal fragments was significantly associated with borderline & malignant phylloides tumour and

e) Mitosis was exclusively seen in malignant PT. Combination of these features strongly favours an accurate diagnosis of PT.

After application of specific set of cytological features,the following results were found:

a) Accurate categorization of Benign PT improved from 54.55% to 78.88%.

b) Sub-typing of Borderline PT improved from 25% to 87%

c) Accurate categorization of fibroadenoma improved from 75.55% to 84.44%

However following pitfall still occurred even after application of specific set of cytological criteria during this study: a) 4 cases of Cellular Fibroadenoma were still incorrectly diagnosed as Benign PT because of overlapping features like markedly cellular , plump spindly stroma & scattered bare bipolar nuclei b)3 cases of Benign PT were diagnosed as fibroadenoma due to large areas of myxoid change that appeared as loose fibromyxoid stromal fragments, which can be considered as sampling error c)3 cases each of Benign PT and FA were incorrectly categorized as PBD due to lack of cellular stroma . This was due to hyalinised stromal fragments.

Discussion

Distinguishing benign PT and fibroadenoma on cytology is very challenging in spite of the recommended defined set of cytologic criteria.[7] However very few published studies have compared FNAC result in terms of distinguishing low grade PT from fibroadenoma. Furthermore cytological features used in those studies were not uniformly applied.

Cytological features considered to be helpful in distinguishing benign PT from fibroadenoma have included smear cellularity, characteristic epithelial component, stromal component and dispersed cell population.

More than 5 epithelial clusters per smear were more commonly seen in Fibroadenoma than PT.

In present study,> 5 stromal fragments per smear were observed in 82% of PT and 37% of fibroadenoma. Krishnamurthy et al[6]found > 5 stromal fragment in 33% of PT cases and 27% in fibroadenoma cases.

Marked stromal cellularity was found in 60% of PT in present study. Similar finding was also noted by Krishnamurty et al.[6]

Dense fibromyxoid nature of stroma was found in 66% of PT while Bhandopadhyay et al[1] found that 70% of PT cases have myxoid material.

In present study predominant stromal cell type was plump, fibroblastic in 66% of PT and thin wavy in 55% of fibroadenoma. Imad etal [5] found spindle fibromyxoid stroma in 100% of PT and plump stromal fragments in 100% of fibroadenoma.

Fibroblastic pavement and discohesiveness were found exclusively in PT while Imad etal[5] observed fibroblastic pavement in 93% of PT.

In our study Background dispersed cell population also play an important role in distinguishing between PT and Fibroadenoma. More than 30% spindly cells favours the diagnosis of PT along with macrophages and giant cells. Krishnamurthy etal[6] also found that increased proportion of long spindle cells averaging > 30% of dispersed stromal cells was found only in PT.

In present study, mild cellularity was seen in 15% , moderate cellularity in 48% and marked cellularity in 35% of PT that were similar to the findings of ElHag etal[5].

More than 5 epithelial clustures per smear was seen in 55% of Phylloides tumour and 66% of Fibroadenoma while El Hag etal[5] found that more than 5 epithelial sheet per smear in 80% of Phylloides tumour and 100% of Fibroadenoma.

Other epithelial characteristics like antler-horn, folded sheets, and apocrine metaplasia were seen more in

relation to Fibroadenoma as compared to PT. El Hag et al[5] stated that apocrine metaplasia was rare in PT (7%) as compared to Fibroadenoma (25%).

Summary and Conclusion

In the specific clinical scenario (age >45years & size >3cm),the features that strongly favour a diagnosis of PT include: stromal fragment predominance with plump fibroblastic stroma ,>30% dispersed elongated spindly cell population, and fibroblastic pavements.

For further sub typing, features that are diagnostic of malignant PT include discohesivness, pleomorphism, nuclear atypia and mitosis. If smear shows few stromal fragments along with discohesivness and mild atypia then it usually favours borderline PT. And when stromal fragments are cohesive with no atypia and mitosis, then it favours benign PT.

These cyto morphological features when applied for the diagnosis of PT prove to be viable and reliable.

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