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RESEARCH ARTICLE

DIFFERENTIATING GIANT FIBROADENOMA FROM PHYLLODES TUMOR: A CYTOMORPHOLOGICAL APPROACH

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Abstract

The category of fibroepithelial lesions in the breast includes two key types: fibroadenomas (FA) and phyllodes tumors (PT). Both are biphasic tumors having epithelial and stromal components however the relative composition of both has been a benchmark differentiator in the diagnosis of these tumors. Among these, phyllodes tumors are particula rly uncommon, representing less than 0.5% of breast cancer cases[1]. Typically diagnosed in women in their mid-40s, these tumors can display a variety of biological behavior, with some exhibiting aggressiv e local growth and others having the potential to metastasize[2]. The WHO 5th series defines the phyllodes tumors as a fibroepithelial neopla sm with a prominent intracanalicular architectural pattern and leaf like stromal fronds, capped by luminal, epithelial and myoepithelial layers, accompanied by stromal hypercellularity.

Introduction: -

Histologically, phyllodes tumors may closely resemble benign intracanalicular fibroadenomas, complicating their differentiation, particularly between low-grade phyllodes tumors, giant fibroadenomas and cellular/juvenile fibroadenomas. Giant fibroadenoma, (gFA), a close clinical mimic is defined as fibroadenomas greater than 5 cm in size, or 500 g, constituting approximately 0.5%–2% of all fibroadenomas. They occur more commonly during pregnancy or lactation or in adolescent women.[3]Juvenile fibroadenoma is a rare clinical entity comprising 4% of the total fibroadenomas, of which giant juvenile fibroadenoma constitutes only 0.5%.[4] Additionally, studies have shown a connection between these lesions through shared genetic mutations like MED12.[5]

The distinction of phyllodes tumors from cellular/juvenile fibroadenomas is particularly challenging as the latter may show a cellular stroma. Features such as well-defined stromal fronds and unique growth patterns indicate phyllodes tumors. Correctly diagnosing phyllodes tumors before surgery is crucial, as standard treatment involves a wide local excision with at least a 1 cm margin to reduce recurrence risk. While cytological diagnosis is straightforward for high-grade tumors, low-grade tumors can be more difficult to differentiate from fibroadenomas due to overlapping characteristics.

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Aims and objectives: -

1. This study aims to analyze the cytological features of phyllodes tumors, focusing on identifying distinguishing traits that can help differentiate them from gFA, thereby enhancing diagnostic precision and improving patient management.
2. To assess the sensitivity, specificity and diagnostic accuracy of FNAC in detecting Phyllodes tumors on FNAC.

Materials and Methods: -

In this retrospective study, we analyzed 30 histopathologically proven cases of phyllodes tumor and 14 cases of gFA, total of 44 cases, diagnosed at our centre during last 5 years. The criteria for gFA was 5 cm and above. We included only those cases with available cytology slides. Fine needle aspiration (FNA) was performed on each case using a 23–25-gauge needle with 2–3 passes per lesion. Smears were prepared air-dried and alcohol-fixed and stained with Giemsa, HE and Papanicolaou if required. The demographic data of age, side and size were taken. We assessed smear cellularity as low, moderateor marked, and analyzed the cytomorphology of epithelial and stromal fragments, as well as the dispersed cell population.

For epithelial components, we examined cluster count per 10 fields (>5 or <5), cluster pattern (staghorn, folded sheets, blunt tipped, filiform or tubular) and epithelial cluster borders (frayed, smooth or equivocal). Mitosis and apocrine metaplasia were also noted. In stromal components, we analyzed fragment count per 10 fields (>5 or <5), stromal borders (smooth, frayed, equal), nature of oval nuclei in stroma (absent, fibroadenoma like, minimal fibrocellular or hypercellular), presence of spindle cells in stroma(less than five clusters or more than five clusters), background spindle cells (absent or present), presence of abundant myoepithelial cells (yes or no) and presence of bipolar cells (present, absent). Other parameters as degree of stromal atypia, Pseudoangiomatous stromal hyperplasia, metaplastic change and myxoid change were also noted.

All the slides were reviewed by a Senior Pathologist (NS) and data was documented in the SPSS 21.0 software, appropriate statistical tests were applied including one-way Anova for qualitative parameters and chi square test for qualitative parameters followed by binary logistic regression model to identify independent cytological predictors distinguishing gfa from PT. The sensitivity specificity and diagnostic accuracy was calculated using appropriate statistical tests.

Results: -

The demographic parameters were analysed (Table 1)
The left breast was the most common side for both gFA (9/14) and PT (19/30). Clinical assessments showed that the median size of gFA was 7.14cm (range being 5-13cm), while PT had a median size of 7.3 cm (range being 3-16cm) ($p = 0.026$).

Table 1: Age & Size statistics

HPE Diagnosis		N	Minimum	Maximum	Mean	Std. Deviation
Giant Fibroadenoma	Age	14	16	63	34.57	14.810
	Size	14	5.0	13.0	7.143	2.9051
	Total	**14**				
Phyllodes Tumor	Age	30	13	65	32.37	16.243
	Size	30	3.0	16.0	7.300	2.8995
	Total	**30**				

Cytological parameters were evaluated and showed that the cellularity was mild to moderate in 78.6% of gFA cases and moderate to marked in 90% cases of Phyllodes Tumor, with marked cellularity more likely in PT ($p = 0.006$). Among stromal fragments, stromal overgrowth was seen in 20.4 % of Phyllodes Tumor and 21.4% cases of gFA. Increased stromal fragments were found more frequently in PT (23.3%) than in gFA (14.3%), (Table4). Stromal fragments borders were also more frayed than smooth in gfa (57.1%) and both being equivocal in 46.7% of Phyllodes Tumors(p=0.016). The stromal spindle cells were more abundant in cases of Phyllodes Tumor with 43.3% cases having more than 5 clusters with spindle cells however only 7.1%cases of gFA had more than 5 clusters with spindle cells$p$= 0.019 (Table 5)

Table 2: Cellularity statistics

HPE diagnosis		Frequency	Percent	Valid Percent	Cumulative Percent
Giant Fibroadenoma	Less than5	7	50.0	50.0	50.0
	5-10 clusters	4	28.6	28.6	78.6
	More than 10 clusters	3	21.4	21.4	100.0
	Total	**14**	100.0	100.0	
Phyllodes Tumor	Less than 5	3	10.0	10.0	10.0
	5-10 clusters	8	26.7	26.7	36.7
	More than 10 clusters	19	63.3	63.3	100.0
	Total	**30**	100.0	100.0	

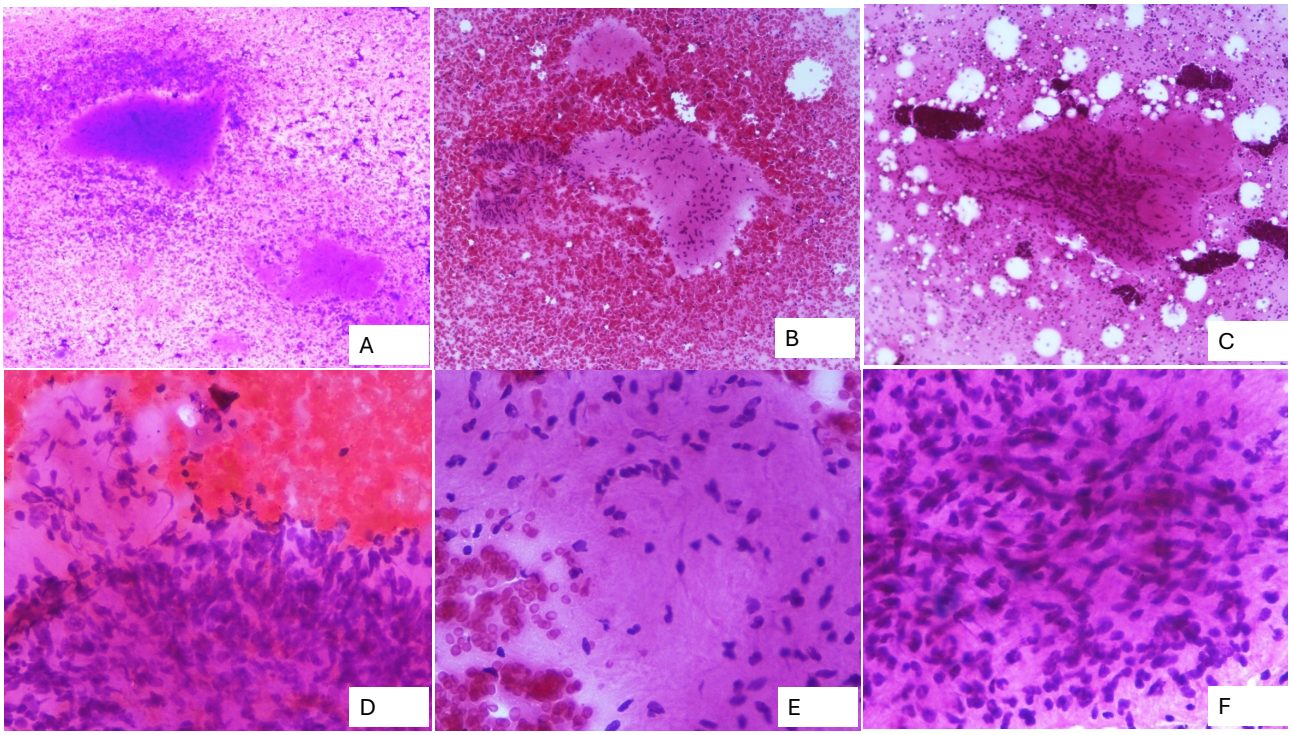
Table 3: Stromal borders

HPE diagnosis		Frequency	Percent	Valid Percent	Cumulative Percent
Giant Fibroadenoma	NA	5	35.7	35.7	35.7
	F>s	8	57.1	57.1	92.9
	F<s	1	7.1	7.1	100.0
	Total	**14**	100.0	100.0	
Phyllodes	NA	3	10.0	10.0	10.0
	F=s	14	46.7	46.7	56.7
	F>s	13	43.3	43.3	100.0
	Total	**30**	100.0	100.0	

Table4: Stromal fragments

HPE diagnosis		Frequency	Percent	Valid Percent	Cumulative Percent
Giant Fibroadenoma	Absent	4	28.6	28.6	28.6
	Poor	8	57.1	57.1	85.7
	More	2	14.3	14.3	100.0
	Total	**14**	100.0	100.0	
Phyllodes	Absent	4	13.3	13.3	13.3
	Poor	19	63.3	63.3	76.7
	More	7	23.3	23.3	100.0
	Total	**30**	100.0	100.0	

Figure 1 Stromal features

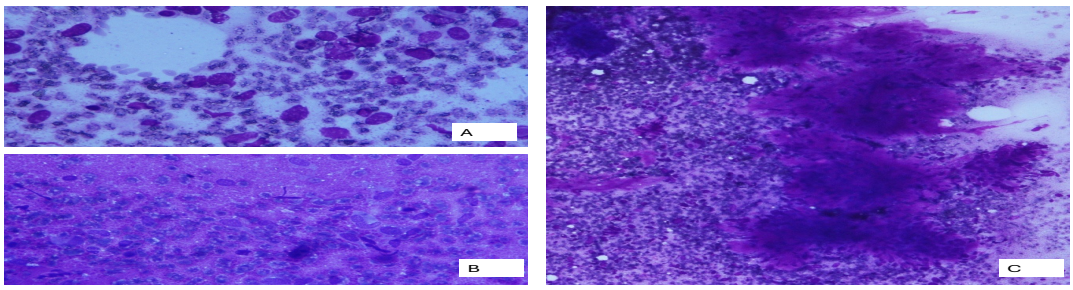


A- Hypocellular with smooth borders
B- Frayed borders and mildly cellular
C- Smooth borders with internal capillaries
D- Frayed borders
E - Stroma with mixture of oval and spindle cells
F - Hypercellular spindle cell predominant

Table5: Stromal Spindle Cells

		Frequency	Percent	Valid Percent	Cumulative Percent
Giant Fibroadenoma	Less than 5	13	92.9	92.9	92.9
	More than 5	1	7.1	7.1	100.0
	Total	**14**	100.0	100.0	
Phyllodes	Less than 5	17	56.7	56.7	56.7
	More than 5	13	43.3	43.3	100.0
	Total	**30**	100.0	100.0	

Figure 2: Background Population



A - Mix population of oval and spindle cell in the background
B -Predominantly oval cells
C -Predominantly spindle cells

Table 6: Nature of oval nuclei

		Frequency	Percent	Valid Percent	Cumulative Percent
Giant Fibroadenoma	NA	1	7.1	7.1	7.1
	Pink acellular	4	28.6	28.6	35.7
	Fal like few oval cells	5	35.7	35.7	71.4
	Mixed minimal fibrocellular	4	28.6	28.6	100.0
	Hypercellular fibrocellular	0	0	0	
	Total	**14**	100.0	100.0	
Phyllodes	NA	4	13.3	13.3	13.3
	Pinkacellular	8	26.7	26.7	40.0
	Falike few oval cells	2	6.7	6.7	46.7
	Mixed minimal fibrocellular	7	23.3	23.3	70.0
	Hypercellular fibrocellular	9	30.0	30.0	100.0
	Total	**30**	100.0	100.0	

Background spindle cells were more abundant in cases of Phyllodes 26.4% than that of Fibroadenoma, 21.4 % cases (***p***=0.046). The nature of oval nuclei in stroma was documented in all cases. Most cases of fibroadenoma has few oval cells 35.7% whereas majority of Phyllodes Tumor had hypercellular oval nuclei (30%). However none of the cases of fibroadenoma had hypercellular stroma with increased oval nuclei. Abundant myoepithelial cells were found in only 14.3% cases of gfa whereas 40% cases of PT had abundant myoepithelial cells(***p***=0.019). Bipolar cells were present in57.1 % 86.6% cases of gfa and PT respectively Myxoid change was present in 14.3% cases of gFA, however 26.7% cases of PT showed myxoid change.

Vascularization was present in 7.1% cases of gfaand 16.7 % cases of PT. Stromal giant cells were present in 14.3% and 10% cases of gFA and PT respectively. Stromal atypia was seen in 21.4% and 16.7% cases of gFA and PT respectively. No statistical significance could be established for these parameters. Epithelial cell cluster pattern of various types were as follows- Abundant monolayered pattern was seen in 57.1% cases of gFA and 40% cases of PT and it was the major epithelial cell cluster pattern in both types (Table 7). Frayed epithelial borders were more prominent in gFA (57.1%) and smooth epithelial borders were more prominent in PT (40%). No statistical significance could be established for these parameters.

Table 7: Epithelial Cell Cluster Patterns

Pattern	**Giant Fibroadenoma**	**Phyllodes**
Abundant Monolayered	57.1	40
Abundant folded	14.3	16.7
Abundant blunttip branching	10	0
Abundant filiform	14.3	16.7
Abundant tubular	0	3.3

To identify independent predictors for distinguishing PT from gFA, a binary logistic regression model was developed (Table 8). The logistic regression was performed and it was found that amongst all parameters with noticeable significance, only the cellularity, stromal borders, spindle cell component in stromal clusters, presence or absence of oval nuclei in hypercellular fragment and type of epithelial cell borders were the notable predictors. (significance 0.019)

Table 8 : Logistic regression

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	.762	.324	5.545	1	.019	2.143

Discussion:-

Phyllodes tumor (PT) of the breast was first described by Chelius in 1827 and later termed cystosarcoma phyllodes by Johannes Muller in 1838[6,7]. Classifying PT remains challenging due to difficulties in distinguishing it from benign fibroadenomas and categorizing the recognized grades of PT. Some benign fibroepithelial neoplasms do not fit neatly into the categories of fibroadenoma or PT. PT can be benign or malignant, with the World Health Organization (WHO) classifying them based on histologic features such as stromal cellularity, mitotic activity, nuclear atypia, and stromal overgrowth.[7] While most pts are benign, the risk of local recurrence ranges from 17% for benign cases to 27% for malignant ones, with up to 22% potentially metastasizing.[8] Distinguishing benign pts from fibroadenomas can be particularly difficult, especially given that fine needle aspiration (FNA) cytology has variable sensitivity for PT, reported between 32% and 83.3%.[9-11] The majority of benign and borderline pts are often misdiagnosed as fibroadenomas, whereas malignant pts are more straightforward to diagnose.

Our study analyzed 44 cases (14 fibroadenomas and 30 pts) over three years. Consistent with previous findings, fibroadenomas were more common in patients under 30, while pts typically occurred in individuals aged 40 to 50, with a median age of 39 years in our PT cases. This suggests that patient age can aid in evaluating cellular fibroepithelial lesions. The left breast was the most commonly involved site, aligning with existing literature. Epithelial features did not significantly differ between fibroadenomas and pts, but we noted a statistically significant presence of large folded epithelial fragments in pts, reflecting exaggerated intracanalicular proliferation. Tumuddi et al have reported the statistical significance in the spectrum of epithelial cell pattern unlike our findings.[12]Previous studies have indicated that an increased number of stromal fragments and hypercellularity favor PT diagnoses.[12.]
In our study, 84% of PT cases exhibited moderate to marked background cellularity, with 96% showing more than 10% spindle cells and 50% displaying cytologic atypia and mitosis. While spindle cells can appear in fibroadenomas, they typically do not exceed 30% of the total cell population.[12]

Despite no significant differences in cyst macrophages or apocrine metaplasia between the two lesions, our findings align with previous studies indicating their limited diagnostic utility.[12] Distinctions between cellular fibroadenomas and benign pts have been explored, with increased stromal cellularity in pediatric fibroadenomas being a potential diagnostic clue. Features favoring PT over fibroadenoma include tumor size greater than 3 cm, mitotic counts above 3/10 HPF, and stromal overgrowth.

Table 9(A): Comparision of our study with Tummudi et al[12].

Parameters	**Fibroadenoma**	**Phyllodes**	***p* value** Tummudi et al	***p* value** Our study
Age	34	32	**0.066**	**<0.001**
Side Left (Lt); Right (Rt)	Lt -64%	Lt 63.3%		
Size in cms	7.143	7.300	**0.026**	**<0.001**
Cellularity: <5fragments 5-10 fragments >10 fragments	 50 28.6 21.4	 10 26.7 63.3	**0.006**	0.549
Stromal Border: NA S=f F>s S>f	 35.7 0 57.1 7.1	 10 46.7 43.3 0	**0.016**	**0.040**
Abundant myopeithelial Cells	14.3	40	**0.019**	
Bipolar Cells				**0.019**

Table 9(B):Comparision of our study with Tummudi et al[12].

Features	**Fibroadenoma**	**Phyllodes**	***p* value** Tummudi et al	***p* value** Our study
Stromal spindle cell				
<5	92.9	56.7	**0.019**	**0.011**
>5	7.1	43.3		
Background spindle cell	21.4	26.4	**0.046**	**<0.001**
Nature of oval nuclei:				
NA	7.1	13.3	**0.046**	NA
Pink acellular	28.6	26.7	**0.04**	
Fa like few oval cells	35.7	6.7		
Minimal fibrocellular	28.6	23.3		
Hypercellular	0	30		
Epithelial Borders:				
NA	7.1	10	**0.03**	NA
F=S	35.7	13.3		
F>S	57.1	36.7		
F<S	0	40		
Epithelial cell cluster pattern				
Abundant monolayered	57.1	40	0.5	**<0.001**
Abundant folded	14.3	16.7		
Abundant blunt tip branching	10	0		
Abundant filiform	14.3	16.7		
Abundant tubular	0	3.3		

Overall diagnostic accuracy has been 68.18% which is comparable with the other workers.[10,13,14]
Traditionally, PTs have been excised with wide margins, often recommended at 1 cm. However, recent studies suggest a more conservative approach may be appropriate for benign pts that are initially enucleated without margins, as their recurrence rate is low.

Conclusion:-

This study highlights that while core biopsies are increasingly recommended, FNA remains a viable option in resource-limited settings. Our findings indicate that features such as frayed stromal borders, increased spindle cell predominance, and large folded epithelial sheets can help distinguish PT from fibroadenoma.

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