Original Research Article

Fibroadenoma/benign phyllodes: a cytologic diagnostic challenge

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ABSTRACT

Background: To study and compare cytomorphological features of histologically proven cases of benign phyllodes and cellular fibroadenoma.

Methods: Smears of histologically-proven cases of benign phyllodes and cellular fibroadenoma in one year, were reviewed. The cellular fibroadenoma had epithelial and/or stromal hypercellularity. The stromal and epithelial components as well as the background cells were qualitatively and quantitatively analyzed.

Results: Number, cellularity and type of stromal fragments varied significantly in two groups. Higher number, intermediate to large-sized and hypercellular stromal fragments were commonly seen in phyllodes. Hypercellular (3+ cellularity) fragments were seen in 100% cases of phyllodes against 11.1% cases of fibroadenoma. Large-sized stromal fragments were found in 100% of phyllodes while in only 11.1% cases of fibroadenoma. The ratio of number of epithelial to stromal fragments was significantly high (58.5:1) in fibroadenoma against phyllodes (1.3:1). The epithelial architecture, atypia, apocrine metaplasia and presence of cystic macrophages did not very much in the two groups. The cellularity of the dispersed cells in background did not reveal significant difference though the type of cells varied; the proportion of long and short spindle cells was higher in PT group while proportion of oval cells was higher in FA group.

Conclusion: The number, cellularity and nature of stromal fragments, ratio of epithelial to stromal fragments, cellularity and type of background cells are helpful in distinguishing benign phyllodes from cellular fibroadenoma. The identification of these features can improve the pickup rate of phyllodes tumor, thereby assisting proper management.

Keywords: Benign phyllodes, Breast, Cellular fibroadenoma, Fibroepithelial tumors

INTRODUCTION

Fibroadenoma (FA) and phyllodes are biphasic fibroepithelial tumors, which resemble clinically, radiologically as well as morphologically.[1,2] The diagnosis of benign phyllodes tumor and its distinction from fibroadenoma (especially cellular fibroadenoma) on fine needle aspiration is a diagnostic challenge due to morphological diversities and overlapping features of these lesions. Since a preoperative categorization of phyllodes tumor is crucial for their appropriate management, an effort has been done to improve the outcome of fine needle aspiration cytology (FNAC) by identifying distinguishing features.

METHODS

This retrospective as well as prospective observational study was conducted in the department of Pathology for a span of one year (June 2016 to May 2017) at FMHS, SGT University, Gurgaon, Haryana, India. The inclusion criteria were adequate material on aspiration and histologically confirmed cases.

The cellular fibroadenoma was diagnosed when epithelial and/or stromal hypercellularity was found in smears. The cases with scant cellularity on smears or the ones who did not turn up for excision of lump and henceforth could not be proved histologically, were excluded. FNA smears of three proven cases of benign phyllodes tumor and nine cases of cellular fibroadenoma, respectively, were reviewed. The stromal and epithelial components as well as the background cells were qualitatively and quantitatively analyzed.

Specific criteria's were used for salient features, as follows:

1) Epithelial component was examined for the following features:

- Cellularity of epithelial fragments: considered 'many' if > 10 fragments, each of >10cells were observed per slide and and 'few' if ≤10 fragments present/slide with total of not >2 slides.
- Architecture: simple if no/only minimal branching sheets/clusters seen, and complex if complex branching sheets seen in most cellular slide.
- Apocrine metaplasia (present or absent), epithelial atypia (present or absent) and mitosis (present or absent).

2) Stromal components, which usually are displayed as stromal fragments and individual dispersed cells in the background, were evaluated separately.

- Stromal fragments were examined, numbered and considered 'many' if average of >10 fragments and 'few' if ≤10 fragments were observed per slide.
- Stromal fragments were categorised as fibromyxoid fragment (with prominent matrix and scant cellularity) or fibroblastic fragments (comprising monolayered sheets of fibroblastic/spindle cells with scant matrix).
- Size : small (<1/4 of low power field area), intermediate (1/4 to ½ LPF area) or large (if occupies >½ LPF area) fragment.
- Cellularity of fibromyxoid was graded on a scale of 1+ to 3+.

3) Ratio of number of stromal fragments to epithelial fragments was evaluated (in smear with maximum cellularity).

4) Dispersed cells in background were evaluated for

- The cellularity of individual stromal cells being expressed as mild (0-50/HPF), moderate (50-100/HPF) and severe (>100/HPF).
- The cells in the background were classified as either oval (ovoid cells with blunt ends smaller than two times the size of a small round lymphocyte), spindle (thinner ends smaller than two times the size of a small round lymphocyte) or as long spindle (tapered ends with long cytoplasmic processes & two times the size of a small lymphocyte).
- The proportion of each component was recorded and expressed as a percentage.
- Dispersed cell nuclear atypia (present or absent) and mitosis (present or absent) were also noted.

5) Other cells assessed in the background included apocrine cells, cystic macrophages and multinucleated giant cells.

Note: the scattered round epithelial cells were excluded.

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois).

- Continuous variables were presented as mean ± SD, and categorical variables were presented as a absolute numbers and percentage.
- Continous variables were compared using the Mann-Whitney U test. Categorical variables were analysed using the Fisher's exact test.
- For all statistical tests, a 'p' value less than 0.05 was taken to indicate a significant difference.

RESULTS

The age of patients with cellular fibroadenoma (FA) was 14 to 35 years with a mean age of 21 and those with benign phyllodes tumor (PT) was 12 to 38 years with a mean age of 29. The average size of lump in FA and PT groups was 2.9 cm and 4.7 cm, respectively.

Number, cellularity and type of stromal fragments varied significantly in two groups.

The ratio of number of epithelial to stromal fragments was significantly high (58.5:1) in fibroadenoma against benign phyllodes (1.3:1). Higher number of stromal fragments as well as intermediate to large-size hypercellular stromal fragments were commonly seen in phyllodes. (Figure 1B and 1D) Hypercellular (3+ cellularity) fragments were seen in 100% cases of phyllodes against 11.1% cases of fibroadenoma.

Large-sized stromal fragments were found in 100% cases of phyllodes against only 11.1% of fibroadenoma cases.

Table 1: Cytological findings in patients with fibroadenoma and benign phyllodes.

Cytological features			Fibroadenoma (n=9)	Benign phyllodes (n=3)	p value
Epithelial fragments	Cellularity (Figure 1A)	≤10	0(0%)	2(66.6%)	0.045
		>10	9(100%)	1(33.3%)	
	Epithelial architecture	Simple	3(33.3%)	0(0%)	0.509
		Complex	9(100%)	3(100%)	-
	Epithelial atypia		3(33.3%)	1(33.3%)	1.000
	Mitosis		0(0%)	0(0%)	-
	Apocrine metaplasia (Figure 3D)		5(55.5%)	2(66.7%)	1.000
Stromal fragments	Number of fragments (Figure 1B)	>10	1(11.1%)	3(100%)	0.018
		≤10	8(88.8%)	0(0%)	
	Type (Figure 2A&2B, 3A)	Fibromyxoid	9(100%)	3(100%)	-
		Fibroblastic	2(22.2%)	3(100%)	0.045
	Size	Small (mean±SD)	9(100%) 9.1±5.5	3(100%) 15±6.2	0.13
		Intermediate (mean±SD)	4(44.4%) 1.3±2.0	3(100%) 12.3±1.5	0.012
		Large (mean±SD)	1(11.1%) 1.1±3.3	3(100%) 19.7±2.5	0.004
	Cellularity (majority of fragments)(Figure1C&1D,3B)	1+	7(77.8%)	0(0%)	0.04
		2+	1(11.1%)	0(0%)	1.000
		3+	1(11.1%)	3(100%)	0.018
Number of epithelial : Stromal fragments (Figure1A&B)			58.5±38	1.3±0.2	0.012
Background	Cellularity of dispersed population	Mild	4(44.4%)	1(33.3%)	1.000
		Moderate	2(22.2%)	1(33.3%)	1.000
		Marked	3(33.3%)	1(33.3%)	1.000
	Type of cells (Figure 2C&2D)	Oval (mean±SD)	9(100%) 91.77±5.65%	3(100%) 53.33±10.11	0.015
		Spindle (mean±SD)	8(88.8%) 6.22±3.49%	3(100%) 34.33±4.04%	0.016
		Long spindle (mean±SD)	6(66.6%) 2.0±2.54%	3(100%) 12.33±6.43%	0.025
	Cystic macrophages		5(55.5%)	2(66.7%)	1.000
	Multinucleated giant cells (Figure 3C)		3(33.3%)	0	0.509

The epithelial architecture, atypia, apocrine metaplasia and presence of cystic macrophages did not very much in the two groups. (Figure 3C and 3D) The cellularity of the dispersed cells in background did not reveal significant difference though the type of cells varied; the proportion of long spindle cells (cells with taper ends and thin cytoplasmic projections), and short spindle cells was higher in PT group while proportion of oval cells with blunt ends was higher in FA group.

(A) Lots of epithelial clusters and occasional fibromyxoid stromal fragment (relatively eosinophilic) in fibroadenoma. Giemsa, 40x. (B) predominance of hypercellular stromal fragments in phyllodes. Higher magnification depicting less cellular stromal fragment in fibroadenoma (C) against hypercellular large fragments in phyllodes (D), Giemsa, 100x (Figure 1).
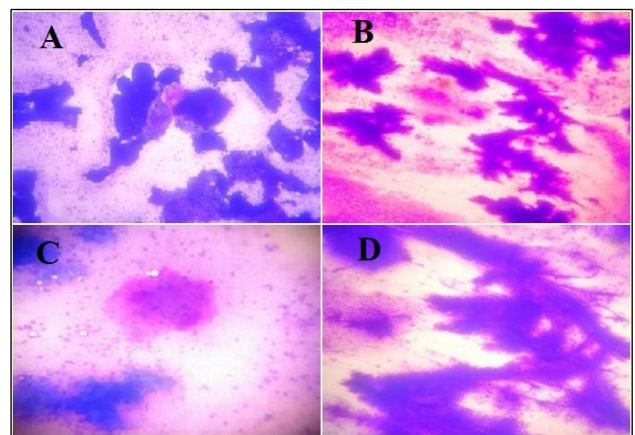

Figure 1: Comparison of epithelial and stromal fragments in fibroadenoma and benign phyllodes tumor.

A. Large fibromyxoid stromal fragment in fibroadenoma versus fibroblastic hypercellular stromal fragment in phyllodes
B. Pap 100x. Numerous oval bipolar nuclei and occasional long spindle cells in background of fibroadenoma smears versus numerous spindle cells in phyllodes (Figure 2).
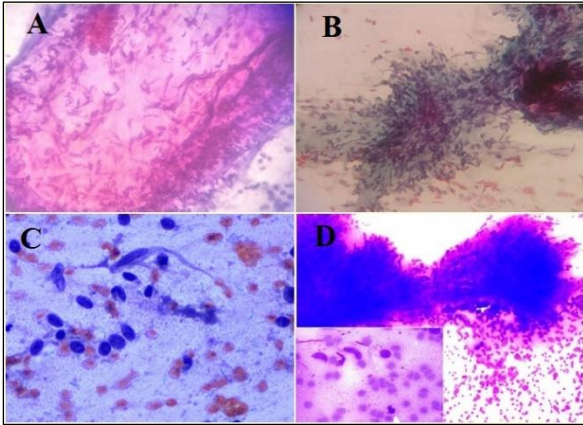

Figure 2: Type of stromal fragments and background nuclei in fibroadenoma and benign phyllodes tumor.
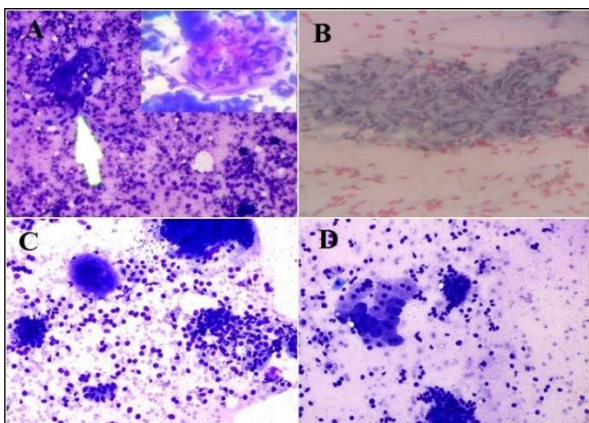

Figure 3: Uncommon findings in cases of fibroadenoma.

(A) Occasional cases of fibroadenoma revealing fibroblastic fragment/pavements (white arrow and inset) and occasional hypercellular stromal fragment (B), giant cells (C), and apocrine metaplasia (D) (Figure 3).

DISCUSSION

Phyllodes tumors (PT) and fibroadenomas (FA) are fibroepithelial breast tumors that are characterized by proliferation of both stromal and epithelial cells.[2] FA is an entirely benign neoplasm while the phyllodes tumor encompasses a wide spectrum of morphology and behavior. PT are categorized as benign, borderline, or malignant based on features such as tumor margin (pushing vs infiltrative), degree of stroma overgrowth, stromal cellularity, tumor necrosis, pleomorphism, and the number of mitosis per high-power field. Although the diagnosis of malignant PT on FNA does not pose a problem, the diagnosis of low grade PT and its distinction from FA on FNA is difficult due to overlapping features between the two lesions.[2] The treatment of choice for phyllodes tumors, irrespective of the grade, is surgical excision with wide resection margins or simple mastectomy. Simple enucleation like that performed for FA or incomplete excision would carry a higher risk of recurrence.[1-3] Therefore, a preoperative diagnosis of phyllodes tumors is required to plan the extent of surgery. FNA is a commonly used first-line preoperative test in the investigation of palpable breast mass. Using FNA smears to render a diagnosis of low grade phyllodes tumor can be challenging because both false-positive and false-negative interpretations can occur. So there is difficulty separating benign phyllodes tumor from cellular fibroadenoma on FNA.

Cytological features considered to be helpful in distinguishing benign phyllodes tumor from fibroadenoma include hypercellular stromal fragments, cellular composition of stromal fragments, cellularity of background nuclei and cellular composition and morphology of background stromal nuclei.[3] Jayaram G suggested that presence of at least two large stromal fragments, hypercellular fragments and moderate to large number of dissociated stromal cells can be used as criteria for the diagnosis of benign PT.[4]

Few authors have considered hypercellular stromal fragments referred to as "phyllodes fragments" to be the most important distinguishing feature that occur only in phyllodes tumor,[5-9] while other authors observed hypercellular stromal fragments in both benign phyllodes tumors and fibroadenomas.[2] In our study, hypercellular stromal fragments were noted in 100% cases of benign phyllodes tumor and in only one case of cellular fibroadenoma. (Figure 1B-1D, 3B) Though significant, if only this finding was relied upon to make the diagnosis of phyllodes tumor, we could have misdiagnosed a case of fibroadenoma, as was noted by Dusenbery and Frable.[7] The hypercellular appearance of stromal fragments in such cases of fibroadenoma could be due to increased thickness of fragments and resultant overlapping of the stromal nuclei. Since, apart from benign phyllodes, hypercellular stromal fragments can be seen in few cases of fibroadenoma, hence it is recommended not to use them as unequivocal evidence for diagnosis of phyllodes tumor on FNA smears. The type and cellular composition of stromal fragments also has been described to be different in cases of PT and FA. Imad et al, found fibromyxoid fragments in 100% cases of phyllodes and 66.6% cases of fibroadenoma while fibroblastic pavements were found in phyllodes only (93%). Imad A et al found spindle nuclei in PT and oval nuclei in FA while Savitri et al observed the presence of plump spindle cells in PT and thin wavy spindle cells in FA.[9] Authors observed long, plump, spindle cells with blunt ends in fibroblastic stromal fragments of PT and short oval to

thin, wavy spindle nuclei in fibromyxoid fragments of cases with FA. (Figure 2A,2B,3A), (Table 2) However, this feature is of limited usefulness because it is not always possible to appreciate the morphology of the cells comprising the stromal fragments due to distortion and artefactual changes.

Table 2: Comparison of cytological findings in various studies.

Cytological findings	Name of author of various studies			
	Imad A. El Hag et al,	Banyopadhyay R. et al,	Savitri K. et al,	Present study
Epithelial fragments				
Cellularity	NSD	NSD	NSD	FA>PT
Architechture	NSD	NSD	NSD	NSD
Apocrine metaplasia	FA>PT	NM	NSD	NSD
Stromal:epithelial	NSD	Increased in PT	NM	PT>FA
Stromal fragments				
Number	PT>FA	PT>FA	NSD	PT>FA
Cellularity	NM	PT>FA	NSD	(3+) PT > FA
Size	NM	Larger in PT	NSD	Larger in PT
Nature/border	Fibromyxoid in both Fibroblastic in PT only	More defined borders in PT	More defined borders in FA Large, Club shaped in FA (21%)	Fibromyxoid in both Fibroblastic-PT>FA
Type of cells	Spindle nuclei in PT Plump (FA>PT)	NM	Plump spindle in PT Thin wavy in FA	Long and thick spindle PT>FA Short oval to thin wavy spindle FA>PT
Dispersed population				
Cellularity	NSD	3+ in PT (30%)	NSD	NSD
	>30% in 93% PT <10% in FA	>30% in 50% PT	>30% Long spindle nuclei (57%PT) 10-30% long spindle in both round oval cells in FA	Spindle cells (small and long) in 100% cases of PT, with average of 46.6%

NSD=No significant difference, NM=not mentioned.

As mentioned above, hypercellular stromal fragments may also be present in some cases of fibroadenoma. In these cases, the degree of background cellularity, the composition of these cells and the epithelium to stroma ratio may be useful features in differentiation.[1,2]

Some studies report that the cellularity of the background nuclei usually is increased in cases of PT.[10] Authors noted similar percentage of cases (33.3%) in PT and FA groups to exhibit 3+ cellularity, as has been pointed by Savitri et al. (Table 2)Therefore, the cellularity of the background nuclei was not a reliable feature for the distinction of low grade PT from FA on FNA smears.[2] The composition and nuclear morphology of the dispersed stromal cells in the background, have also been emphasized in literature and is useful in practice.[2] This feature seemed particularly helpful in differentiating benign phyllodes from cellular fibroadenoma. Elongated spindle cells in the background, variably referred to as mesenchymal or fibroblastic cells were observed to be more prominent in PT than FA.[5,11] Shimizu et al, evaluated the average nuclear dimensions of 100 randomly selected background nuclei (17 PTs and 19 FAs) and found them to be smaller in FA than in PT, but this difference was not statistically significant.[8] In our study, we found increased proportions of short and long spindle cells (averaging respectively 34.33% and 12.33% of the dispersed stromal cells) in the background, to occur in all the cases of PT. Short oval to round nuclei characterized most FAs with 88.8% cases exhibiting 4-12% short spindle and 66.6% cases exhibiting 1-8% of long spindle nuclei. (Table 1) One of the cases of fibroadenoma which exhibited maximum number of short and long spindle cells, revealed few phyllodes like areas on histology. (Figure 2C, 2D)

Apart from above findings, the number of stromal fragments was higher (>10 in 100% cases) in cases of benign phyllodes tumor against fibroadenoma (>10 in only one case), and the epithelial to stroma ratio was statistically higher (58.5±38) in fibroadenoma against benign phyllodes (1.3±0.2), (Figure 1A) supporting them as differentiating features, as mentioned by Imad and

Banyopadhyaya et al.[1,2] Limitations of this study was lesser number of cases.

CONCLUSION

The number, cellularity and nature of stromal fragments, ratio of epithelial to stromal fragments, cellularity and type of background cells are helpful in distinguishing benign phyllodes from cellular fibroadenoma.

The identification of these features can improve the pickup rate of phyllodes tumor, if careful examination of the cytological features are done, thereby assisting proper management.

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