Original article

Evaluation of Cytomorphological Patterns of Fibroadenoma on Cytology: Emphasis on Pattern based approach to avoid misdiagnosis

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Abstract:

Background: Fibroadenoma (FA) is a frequently occurring breast lesion diagnosed on fine needle aspiration cytology (FNAC) with a bimodal picture comprising of epithelial and/or stromal component. It can have a gamut of differential diagnosis depending on the predominant cellular features reflected on cytological smears, thereby it is important that the cytologist should be well versed with the various patterns of fibroadenoma to avoid diagnostic errors. ***Materials and methods*:** The present study was conducted over a period of two years including all cases of fibroadenoma diagnosed on cytology (n=234). The detailed cytomorphological spectrum was analysed to study the different patterns of fibroadenoma on cytology. Out of these (234), cyto-histological correlation was performed in 197 cases. ***Results:*** The incidence of fibroadenoma among all the breast FNACs was 50% (234/468). The different patterns observed were: epithelial predominant, stromal predominant, FA with giant cells, apocrine change, cyst macrophages, granuloma, acute inflammation and atypia. Cytohistologic concordance was observed in 173/197 cases (87.8%). Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 98.8%, 92.3%, 87.8%, 94.5% and 88.8% respectively. ***Conclusion*:** Although fibroadenoma can be diagnosed with ease on cytology in most of the cases, However, at times in addition to classical features, morphological variations are observed such as giant cells, cyst macrophages, apocrine change, granulomas, acute inflammation and atypia wherein it maybe misdiagnosed as benign phyllodes, hyperplasia, fibrocystic disease etc.. This pattern based approach for the cytological diagnosis of FA is re-emphasized in the index article so as to create awareness about these varied patterns among the young cytopathologists.

Keywords: Fibroadenoma; bimodal; Fine needle aspiration cytology; cytomorphological; cytohistological

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Introduction:

Fibroadenoma (FA) is one of the most frequently occurring benign breast lesions. They are benign, biphasic tumours (usually epithelial and stromal components) and comprise about 50% of all breast biopsies, and 75% for biopsies in women < 20 years of age.[1]

Fine needle aspiration cytology (FNAC) is the most significant first line diagnostic method for pathological

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assessment of breast disorders. The main objective of breast FNAC is to distinguish between benign and malignant lesions. FA is one of the few benign lesions wherein a prompt and accurate diagnosis on FNA is possible. Since a reliable diagnosis of FA may mean no excision (non-operative/conservative management), diagnostic criteria must be strictly observed.[2]

Histopathological examination by core or open biopsy has been a gold standard in the evaluation of breast lumps.[3]However, open or core needle biopsy techniques are relatively more costly and traumatic. FNAC has been shown to be safe, rapid, reliable and cost-effective technique in diagnosing breast lesions.[4] Though, histopathological examination (HPE) of excised breast lumps/excision biopsy is considered as the final diagnosis, FNAC in conjunction with ultrasound (USG) turn out to be significant initial methods of assessment (included in the triple assessment of breast lumps).[5]

Clinical examination is the first step in the assessment of breast disorders. With the advent of imaging modalities, USG of breast has become an important diagnostic tool. Fine needle aspiration cytology (FNAC) and radiological imaging- mammography and ultrasonography – as complements to clinical examination (triple test) have become the standard approach to investigations of palpable breast lump.[5]

The present study aims to bring to the forefront the crucial role FNAC plays in diagnosing FA along with highlighting its diverse cyto-morphological patterns. The present study was performed to analyze the cytomorphological variations of fibroadenoma, various causes of its over and under diagnosis to avoid diagnostic errors and cyto-histological correlation wherever possible.

Material & Methods:

A retrospective audit was conducted at ESIC Medical College & Hospital, Faridabad. The study was approved by Institutional ethics committee. A total number of 468 females visiting the cytology department for FNA of breast lump (both blinded and image guided) were included in the study. Duration of the study was two years (July 2016 to August 2018). General characteristics of the patients were recorded. The lump was palpated and fixed, area was sterilised and FNA was performed using 22-gauge needle. Both air dried and alcohol fixed smears were prepared, stained with Giemsa and Papanicolaou respectively. Cases of Fibroadenoma (234/468) were segregated and their cyto-morphological features were studied in detail. Histopathological examination (biopsy/ excised lumps) was done in 197 out of 234 cases.

Sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy were calculated.

Ethical Clearance: Obtained from Institutional Ethics Committee

Observation & Results:

A total number of 468 breast FNAs were performed out of which 234 (50%) were diagnosed as Fibroadenoma on cytology. The study population predominantly belonged to the age group 21-30 years (59.4%;139/234). Patients presented with various chief complaints of breast lump (96.5%) followed by pain and tenderness. The lump was single(93.5%) in majority of cases and involving the right breast most frequently (83.7%).Upper outer quadrant was the most common location for fibroadenomas (67.4%). The correlation between clinical and cytological diagnosis was established in 221/234 cases (94.4%). The detailed clinicopathological features are shown in table I.

Table I: general characteristics of fibroadenoma (clinical profile)

CHARACTERISTIC	NO. OF CASES (n=234)	PERCENTAGE (%)
AGE (IN YEARS)		
<20	52	22.2
21-30	99	42.3
31-40	59	25.2
41-50	20	8.54
>50	4	1.70
DURATION OF SYMPTOMS		
<1 month	31	13.2
1-6 months	139	59.4
6-12 months	45	19.23
>1 year	19	8.11
LATERALITY		
Left	103	44.01
Right	110	47
Bilateral	21	8.97
FOCALITY		
Single	217	88.8
Multiple	17	7.26

CHARACTERISTIC	NO. OF CASES (n=234)	PERCENTAGE (%)
CLINICAL DIAGNOSIS		
Fibrocystic disease	41	17.5
Fibroadenoma	171	73
Cyst	5	2.13
Phyllodes	4	1.7
Carcinoma	13	5.5

On detailed evaluation of the cyto-morphological features, the following patterns were observed: Epithelial predominant (82.05%), Stromal predominant (8.11%), FA with giant cells(4.7%), FA with apocrine change (3.8%), FA with cyst macrophages (8.5%), FA with granuloma (0.85%), FA with acute inflammation(0.42%) and FA with atypia (4.28%). The spectrum of various cytological patterns are depicted in table II.

Table II: pattern of cytomorphological variations in cases of fibroadenoma

CHARACTERISTIC	NO. OF CASES (n=234)	PERCENTAGE (%)
CELLULARITY		
Highly cellular	193	82.4
Moderately cellular	35	14.9
Paucicellular	6	2.5
EPITHELIAL CELLS		
Monolayered sheets	192	82.05
Clusters	39	16.6
Others	3	1.3
STROMAL FRAGMENTS		
Abundant	19	8.1
Few	211	90.2
Absent	4	1.7
HISTIOCYTIC GIANT CELLS		
PRESENT	11	4.7
ABSENT	223	95.3
CYST MACROPHAGES		
PRESENT	20	8.5
ABSENT	214	91.4
APOCRINE CHANGE		
PRESENT	9	3.8
ABSENT	225	96.1
GRANULOMA		
PRESENT	2	0.85
ABSENT	232	99.1
ATYPIA		
CELLULARITY		
PRESENT	10	4.27
ABSENT	224	95.7
ACUTE INFLAMMATION		
PRESENT	1	0.42
ABSENT	233	99.57

Histopathology (excision biopsy/lumpectomy) was performed in197 cases, out of which 173 (87.8%) were confirmed as Fibroadenoma on histopathology (concordant) and 37 (18.7%) were discordant. The histopathological diagnoses of all cases are shown in table III. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 98.8%, 92.3%, 87.8%, 94.5% and 88.8% respectively.

Table III: spectrum of histopathological diagnosis of 197 cases

Histopathological diagnosis	No. of cases	Percentage (%)
Benign breast disease	5	2.5
Fibrocystic disease	8	4.06
Galactocoele	3	1.5
Fat necrosis	2	1.01
Granulomatous mastitis	1	0.5
Fibroadenoma	173	87.8
Usual epithelial hyperplasia	2	1.01
Atypical ductal hyperplasia	1	0.5
Benign Phyllodes	2	1.01

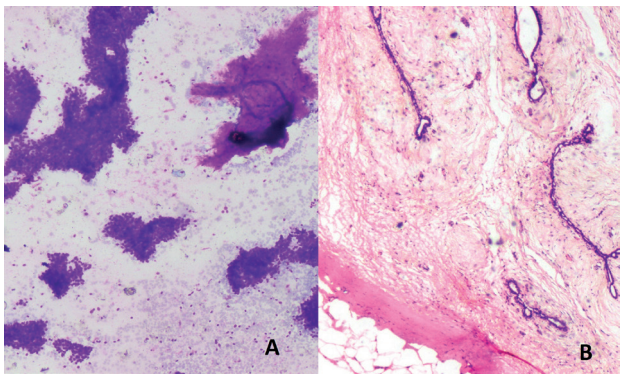

Figure 1: A) Smears show characteristic cytological findings of fibroadenoma- staghorn clusters/ monolayered branching sheets of benign ductal epithelial cells with interspersed myoepithelial cells, fibromyxoid stromal fragments and numerous bare benign bipolar nuclei (Giemsa, 100x) ; B) Characteristic histopathology of Fibroadenoma (Hematoxylin & Eosin, 100x)

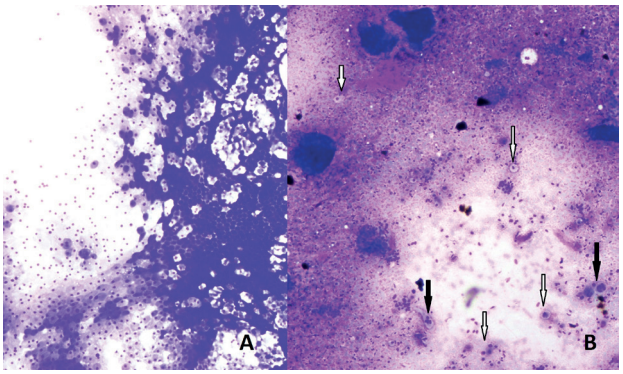

Figure 2: A) Smears show staghorn clusters/ monolayered branching sheets of benign ductal epithelial cells with extensive apocrine change (Giemsa, 100x); B) Smears show characteristic features of FA alongwith multinucleated histiocytic giant cells (black arrows) and scattered macrophages (white arrow with black border) (Giemsa, 40x)

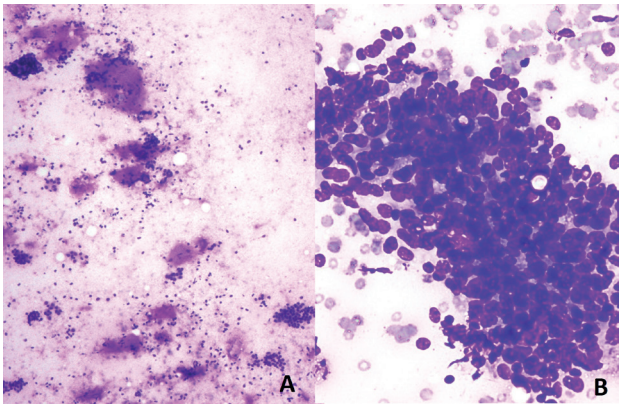

Figure 3: A) Smears show many stromal fragments alongwith sheets of benign ductal epithelial cells (Giemsa, 100x) ; B) Smears show a cluster of ductal epithelial cells showing anisonucleosis, nuclear overlapping (Giemsa, 400x)

Discussion

Fibroadenoma (FA) is the most frequently occurring benign tumour of the breast. The peak incidence is during the second and third decades of life as observed by Bangaru et al[6], Saikia et al[7]and Kuijper et al[8]. In the present study as well, majority of the women belonged to age group 21-30 (42.3%). They clinically present as firm, freely mobile, painless, non tender, well demarcated masses, usually measuring 2 to 3 cms in size, though the size of the lump may range from < 1 cm to greater than 10 cms. Breast lump was the most common clinical presentation noted by Ramesh et al[9], Layfield et al[10], Walters et al[11], Lee Y et al[12] and the current study. The correlation between clinical and cytological diagnosis was established in 94.4% cases in our study, likewise Smallwood et al, Dandapat et al[13] and Furnival et al[14]observed 86.7%, 91.3% and 85% correlation respectively.

The current study revealed that right, left and bilateral breasts were involved in 47%, 44% and 8.9% cases respectively. These findings cases were similar to Singh et al[15]and Bhadani et al[16]. Upper-outer quadrant was the most common location for FA in our study (67.4%) which is in accordance with most of the studies in literature namely Singh et al[15] (59%) and Bhadani et al[16] (39.8%), Yalavarthi et al[17] (59.04%) and Saikia et al[7] (40.8%).

FA is a biphasic tumor, composed of both epithelial and stromal components. A specific cytological diagnosis can be given, when the cytological findings of staghorn clusters/monolayered branching sheets of benign ductal epithelial cells with interspersed myoepithelial cells, fibromyxoid stromal fragments and numerous bare benign bipolar nuclei are combined with the clinical finding of a well delineated, freely mobile mass in a young woman. However, at times in addition to classical features, morphological variations are observed such as giant cells, cyst macrophages, apocrine change, granulomas, acute inflammation and atypia. This pattern based approach for the cytological diagnosis of FA is re-emphasized in the index article so as to prevent misdiagnosis. It is necessary to create awareness among the young cytopathologists regarding such variations/additional findings which may sometimes create a diagnostic dilemma. Histopathology remains the gold standard for confirmation of diagnosis in such cases.

Most of the cases (82.4%) in the present study had high cellularity, akin to Kollur et al[18]and Ferrer et al[19]. Our study found the most common arrangement of benign ductal epithelial cells to be monolayered sheets (82.05%), a finding which was predominant in studies conducted by Kollur et al[18]and Singh et al[15]. Stromal predominance occurred in 8.1% cases which was similar to Mendoza et al[20]. Cyst macrophages were seen in 8.5% cases which was comparable to the findings of Mendoza et al[20]. The frequency of apocrine change (3.8%) was in concordance with Saikia et al[7] while granulomas were most infrequently observed in 0.85% cases which was comparable with the results of Mendoza et al[20]. Atypia was noted in 4.27% cases which was similar to Swetha et al[21] and Asirvatham et al[22] however acute inflammation was found in 0.42%cases, as seen by Mendoza et al[20].

The cytomorphological variations observed in cytology of FA may sometimes create a diagnostic challenge for the reporting pathologist. Epithelial predominant smears may mimic epithelial hyperplasia. Highly cellular stromal fragments composed of spindle cells with nuclear atypia in addition to benign sheets of epithelial cells are highly suggestive of benign phyllodes tumour. Presence of Giant cells, granulomas and acute inflammatory cells in some cases can be akin to inflammatory lesions. Apocrine change and presence of cyst macrophages in FA on occasions may lead to misdiagnosis of fibrocystic disease of breast since the classical picture of fibrocystic disease is presence of sheets of ductal epithelial cells of apocrine type in addition to usual bi modal population against a background of cystic macrophages. Accompanying atypical changes with classical fibroadenoma may give rise to a false positive diagnosis of atypical hyperplasia/ carcinoma. Attention must be paid to the overall cytological pattern particularly single, benign bare nuclei and fragments of myxoid stroma to avoid a malignant diagnosis. In such cases with obvious cytological atypia, excision must be recommended. Therefore, it is very important to distinguish FA from other differential diagnosis discussed above as a confident diagnosis of FA does not require excision or further follow up if the diagnostic criteria are strictly observed.

Histopathology (excision biopsy/lumpectomy) was performed in 197 cases, out of which 173 (87.8%) were confirmed as Fibroadenoma on histopathology (concordant) and 24 (12.2%) were discordant. The concordance rate was similar to Bangaru et al[6] (88.02%), Yalavarthi et al[17] (73.68%), Ferrer et al[19] (79.28%), Singh et al[15] (65%), and Kujur et al[23] (97.7%). The individual discordant cases were fibrocystic disease (4.06%) in accordance with Ferrer et al[19] (3.31%) and Bangaru et al[6] (8.38%), benign phyllodes (1.01%) comparable with Ferrer et al[19] (3.59%), Bangaru et al[6] (1.79%), galactocele (1.5%) similar to Bangaru et al[6] (0.59%)

On review of literature, the sensitivity and specificity of FNAC for diagnosis of FA ranges from 81-98% and 79.6-100% respectively[6,15,19,24-29]. The observations in the present study (98.8% and 92.3% respectively)are comparable to other studies.

Conclusion

Fibroadenoma (FA) is the most frequently occurring benign tumour of the breast for which cytology is the first line diagnostic method. At times, in addition to classical features, morphological variations are observed such as giant cells, cyst macrophages, apocrine change, granulomas, acute inflammation and atypia. A pattern based approach for the cytological diagnosis of FA is re-emphasized in the index article to prevent misdiagnosis and to draw attention of young cytopathologists towards such variations/ additional findings which have the potential to create a diagnostic dilemma.

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Contributor's statement:

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