Original Article

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Study of Histopathological Changes in Fibroadenoma of the Breast

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Abstract

Background: Fibroadenoma of the breast is a relatively frequently occurring tumor. Although often considered a benign tumour, several reports describe a higher risk of subsequent breast carcinoma in patients diagnosed with fibroadenoma. Increased risk depends on presence of complex changes within fibroadenoma, presence of hyperplasia and positive family history for breast cancer.

Aims and Objectives: Our main aim was to study the histological variations within the fibroadenoma of the breast and also to identify those lesions with the possible risk of malignancy.

Methods: Descriptive study of three years. A total of 250 cases of fibroadenoma were studied. Slides were stained with Hematoxylin and Eosin (H & E) and were thoroughly reviewed. Slides were screened for proliferative epithelial changes, fibrocystic epithelial changes, stromal changes and various other changes such as foci of tubular adenoma and phyllodes tumour. Slides with invasive malignancies were excluded from the study.

Result: Apocrine change among fibrocystic changes was the commonest variation within the fibroadenoma. Complex fibroadenoma, moderate and atypical ductal hyperplasia was seen in older age groups.

Conclusion: Increased risk of breast cancer is seen patients with presence of hyperplasia and complex fibroadenoma of the breast. So exclusive study of histopathological changes in epithelial and stromal elements of fibroadenoma is required and are essential to be reported so as to alert the clinician for follow up of the patient. This will help in timely management to reduce morbidity and mortality.

***Keywords**: Breast cancer, Fibroadenoma, Fibrocystic changes, Hyperplasia.*

Introduction

Fibroadenoma of the breast is a benign tumour arising from the epithelium and stroma of terminal duct lobular unit. Most common breast tumour in adolescent girls and young women, constituting one third of all benign breast lesions. [1] It may occur at any age, but peak incidence falls during the second and third decade of life. Both epithelial and stromal cells exhibit estrogen and progesterone receptor. Hence these proliferate among reproductive age and undergo atrophic changes in menopause. [2] Fibroadenoma exhibits a wide range of cytologic and histologic patterns; the epithelial components can vary from absence of hyperplastic activity to carcinoma in situ. It has been found that as compared with women of similar age in the general population, women with fibroadenoma have two to three times the risk of breast cancer. Increased risk of breast cancer depends on the presence of complex changes within fibroadenoma (cysts larger than 3mm, sclerosing adenosis, epithelial calcifications or papillary apocrine changes), benign proliferative disease in the surrounding parenchyma and a positive family history of breast cancer.[3] Malignant transformations in the epithelial components of fibroadenoma generally considered rare.[4] However in very few cases, malignant transformation has been reported on histopathological examination.[5] Since there are evidences that fibroadenoma indicates higher risk of subsequent carcinoma and not much is known about the lesions occurring within and adjacent to fibroadenomas, the aim of this study was to describe various histologic features of the epithelium and stroma within breast fibroadenomas and also to identify lesions with possible risk of malignancy in a large group of cases.

Material and methods

Source of Data: All specimens of fibroadenoma of breast subjected for histopathological examination in Karnataka Institute of Medical Sciences, Hubballi. Around 250 consecutive specimens of clinically suspected and pathologically proven fibroadenoma of the breast in females were included in the study from June 2018 to May 2021

Method of Collection of Data: All specimens of clinically suspected fibroadenoma were sectioned, processed and subjected for Haematoxylin and Eosin staining. Slides were screened for proliferative epithelial changes (hyperplasia, carcinoma in situ [CIS], invasive carcinoma), fibrocystic epithelial changes (apocrine metaplasia, cysts, squamous metaplasia, sclerosing adenosis, microglandular adenosis, tubular adenosis, papilloma, lactational changes, calcifications), stromal changes (foci of pseudoangiomatous stromal hyperplasia, presence of smooth muscle, hyalinization, myxoid change), and various other changes such as foci of tubular adenoma and phyllodes tumor.

Informed consent of the patient for the present study was not required as it is a prospective and retrospective laboratory study.

Statistical Analysis: Data is presented in the form of mean, standard deviation, frequencies & percentages and by diagrams. Relations between age and histologic findings were studied using the Student t test. The chi-square test was used to study relations between hyperplasia within the fibroadenoma, hyperplasia in adjacent parenchyma, and complexity of the fibroadenoma. P values less than 0.05 were regarded as significant.

Type of study: Descriptive Study

Inclusion criteria: All slides of fibroadenoma and fibroadenomatoid metaplasia of breast in females.

Exclusion criteria: Slides showing any other lesion without fibroadenoma or fibroadenomatoid metaplasia and slides with invasive malignancies were excluded from the study.

Results

Patients: A total of 250 specimens of fibroadenoma processed between June 2018 to May 2021 in the Department of Pathology, Karnataka Institute of Medical Sciences, Hubballi, were studied. The average age of the patients was 27.1 years (range 18-52 years). About 70% were in second and third decade of their life, which was statistically significant (p value<0.005). Table 1 shows age distribution of patients with fibroadenoma.

Table 1: Age distribution of patients with fibroadenoma

Age group	No. of patients
≤20	83
21-30	92
31-40	51
41-50	18
51-60	6
61-70	2

Most of the patients (97.2%) presented with lump without pain in the breast. Few presented with lump with pain (2.8%). Many patients presented within ten months of presentation. Patients who had pain presented earlier than those who didn't have pain. Most of them were left side (129) compared to right (109) The mean size of the fibroadenoma, expressed by the largest diameters varied between 1.0 and 13 centimeters, with a mean of 3.5 centimeters. Most breast lumps were seen in upper outer quadrant (38%).

Histopathology: Slides were stained with hematoxylin and eosin (H&E) (on average 3) and were thoroughly reviewed. Fibroadenomas were screened for proliferative epithelial changes (hyperplasia, carcinoma in situ [CIS], invasive carcinoma), fibrocystic epithelial changes (apocrine metaplasia, cysts, squamous metaplasia, sclerosing adenosis, microglandular adenosis, tubular adenosis, papilloma, lactational changes, calcifications), stromal changes (foci of pseudoangiomatous stromal hyperplasia, presence of smooth muscle, hyalinization, myxoid change), and various other changes such as foci of tubular adenoma and phyllodes tumor.

According to Dupont et al [3], complex fibroadenomas were defined as fibroadenomas harboring one or more of the so-called complex features: epithelial calcifications, papillary apocrine metaplasia, sclerosing adenosis and cysts larger than 3 mm.

Criteria defined by Page et al [6] and Holland et al [7] were used in diagnosing hyperplasia and Carcinoma In Situ. Only the advanced lesion of usual ductal hyperplasia (mild, moderate or florid) was scored, eg, if moderate and florid ductal hyperplasia were both present, only florid ductal hyperplasia was scored.

Distinction between hyperplastic epithelium and tangential sectioning is difficult and appearance of myoepithelial cells throughout a duct, was used as an additional criterion in favour of tangential sectioning. Rosen [8] described a pitfall where in artificial hyperplasia- like pattern caused by detachment of the epithelium with subsequent curling, leading to widened duct filled with epithelial strands.

Phyllodes tumour was distinguished from fibroadenoma using Rosen's criteria [9] i.e, expansion and increased cellularity of the stromal component with often a leaf like stromal growth pattern. In phyllodes areas of fibroadenomas, stromal mitoses were counted per 10 high power fields (HPF; 400x magnification, - 1.6mm²).

Finally, fibroadenomas were classified as pericanalicular or intracanalicular [Figure 1 and 2] when 90% of the tumor displayed that particular type of growth pattern. If neither type could be assigned to a tumor, it was diagnosed it as mixed histological type.

Changes within the fibroadenoma: The frequencies of histopathological changes found within the fibroadenomas are shown in Table No.1. 47.2% of fibroadenomas were of the pericanalicular type, 24% were classified as

intracanalicular and 28.8% were of the mixed histological type.

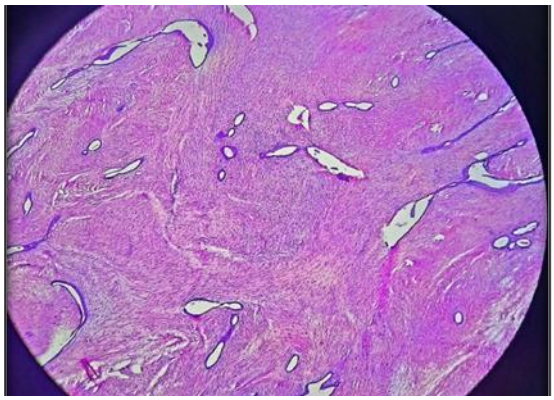

Figure 1: Pericanalicular pattern of fibroadenoma [10X, H&E]

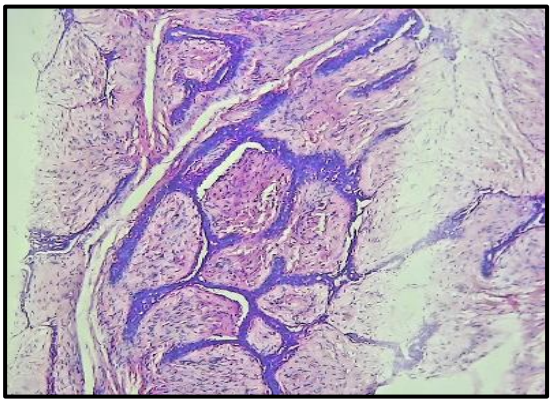

Figure 2: Intracanalicular pattern of fibroadenoma [10X, H&E]

Among proliferative epithelial changes, mild ductal hyperplasia was found in 12% of cases. Moderate ductal hyperplasia was seen in 9.2% and florid ductal hyperplasia in 1.6% of cases. Atypical ductal hyperplasia (ADH) and Atypical lobular hyperplasia (ALH) was detected in two cases and one case respectively. All together, in 22.8% of fibroadenomas some form of hyperplasia was found. However, since in the otherwise normal breast an elevated risk for invasive carcinoma has been proven only for moderate, florid and atypical hyperplasia, we excluded mild ductal hyperplasia from further considerations.

Within fibroadenomas, hyperplasia of higher grade than mild was found in 11.6% of fibroadenomas, and was present in older age groups (mean age- 38 years), which was statistically significant (p value<0.05)

Lobular carcinoma in situ (LCIS), Ductal carcinoma in situ (DCIS) was not found in our series.

Complex features were frequently seen in fibroadenoma, among those complex features, apocrine metaplasia being most frequent (22.4%) [Figure 3]. Taken together, 31.2% of fibroadenomas in this series were complex. Complex fibroadenomas were seen more often at higher age (mean age- 35 years), which was also statistically significant (p value<0.05). Stromal Hyalinization was seen in 19.2% of fibroadenomas. Myxoid change was seen in 21.6% of cases [Figure 4].

In eight cases we observed foci of tubular adenoma [figure 5]. In four fibroadenomas we detected a part of the tumor which had to be classified as a focal phyllodes tumor, which was benign.

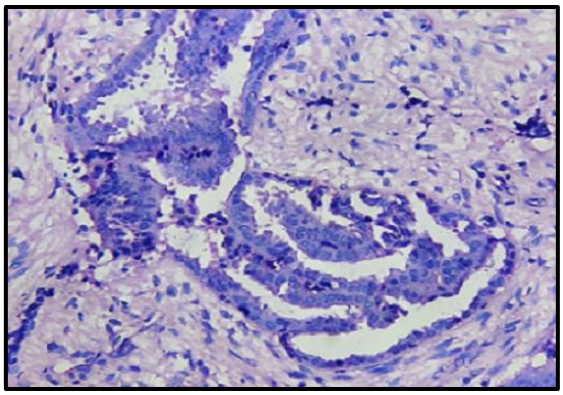

Figure 3: Apocrine change [40X H and E]

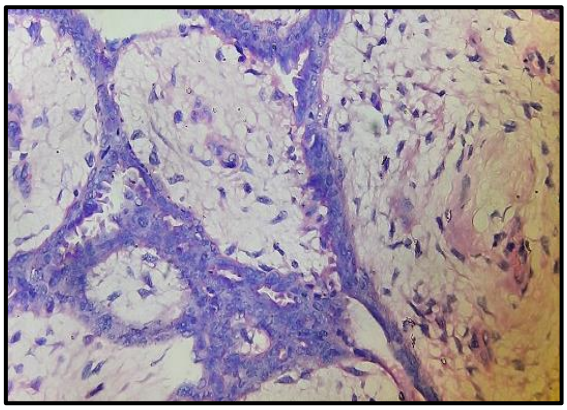

Figure 4: Myxoid Change [10 X H and E]

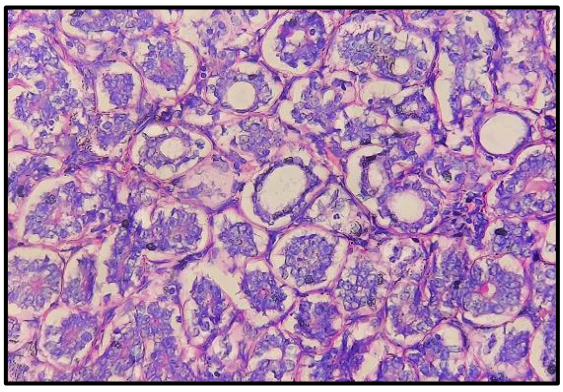

Figure 5: Tubular Adenoma [40X H and E]

Discussion

This study evaluates in detail the histomorphological features of 250 cases of fibroadenoma. Although proliferative changes, fibrocystic changes and stromal changes in fibroadenomas are commonly observed, some of these changes are considered to be of clinical significance.

Fibroadenoma of the breast usually form during menarche (15-25yrs of age) , a time at which lobular structures are added to the ductal system of the breast. [10] The mean age in our series was 27.1 years which was comparable with Carty N.J. et al. [11]. Fibroadenoma can occur anywhere within the breast, including the axillary tail and the retroareolar area, but the majority is found in the upper outer quadrant where most breast tissue is located. [10]

In our series fibroadenoma was most commonly located in the upper outer quadrant which was comparable with Carty N.J. et al. [11]. Most of the patients presented with fibroadenoma when the size was around 2- 3cm. The mean size in our study was 3.5 cm which is comparable to study done by Shabtai M et al [12]

Histopathology: Fibroadenomas are considered to be an abnormality of normal development and involution. They are essentially an exhuberant overgrowth of elements thought to be derived from the terminal duct lobular unit, the epithelial component giving the impression of being compressed (‘intracanalicular’) or not (‘pericanalicular’). [13] Most common pattern was pericanalicular pattern similar to study done by Kuijper et al. [14]

In some cases, the enhanced intracanalicular pattern of some fibroadenoma resembles the clefted architecture of benign Phyllodes tumour which makes occasionally difficult to distinguish between the tumour types. [15] The presence of elongated, branching, and cleft- like ducts within cellular stroma serves as a histological clue to the diagnosis of phyllodes tumour. According to WHO, although fibroadenoma and benign phyllodes tumour present with similar recurrence risks, their distinction is important in the core biopsy setting because of differences in subsequent management. In case of uncertainty, diagnosis of benign fibroepithelial tumour is preferred, especially in a core biopsy. [16]

Comparison of histopathological variations in different series is shown in table no. 2

Hyperplasia within fibroadenoma were frequently seen in our series. Criteria given by Page [6] was used to diagnose hyperplasia and included additional features (dispersed myoepithelial cells), to rule out hyperplasia. Also, hyperplasia-like pattern that is caused by curling of the epithelium of larger ducts when it is disrupted and detached is excluded. Dupont[3] and Page[6] gave RRs for hyperplasia in breast parenchyma ranging from two to five. Proliferative disease in breast epithelium is an established risk factor for breast cancer[3]. Studies shows that proliferative disease in the parenchyma adjacent to a fibroadenoma also has an effect on the risk of breast cancer. Dupont et al[3] found an incidence of 13.7%, which was associated with an RR of 3.9 in the adjacent parenchyma. Likewise McDivitt et al[17] reported an odds ratio of 3.7. Since most specimens did not meet the requirement of 0.5 cm^2 of surrounding tissue we couldn’t study the changes in surrounding tissue. In order to identify women with this risk factor, it would be preferable to include, if possible, a small rim of surrounding tissue when resecting a fibroadenoma.

Table 2: Frequencies of histopathological changes found within fibroadenoma.

Lesion	Frequency
Proliferative epithelial changes	
Mild ductal hyperplasia	12%
Moderate ductal hyperplasia	9.2%
Florid ductal hyperplasia	1.6%
Atypical ductal hyperplasia	0.8%
Atypical lobular hyperplasia	0.4%
Fibrocystic epithelial changes	
Apocrine metaplasia	22.4%
Cysts	8.4%
Sclerosing adenosis	0.4%
Stromal changes	
Hyalinisation	19.2%
Myxoid change	21.6%
Other changes	
Foci of tubular adenoma	3.2%
Foci of phyllodes tumour	2%

Table 3: histopathological variations in different case series.

	Present series	Kuijper et al[14]	Shabtai m et al[12]
Mild ductal hyperlasia	12%	11.6%	
Moderate ductal hyperplasia	9.2%	26.8%	
Florid ductal hyperplasia	1.6%	5.3%	12.9%
Atypical ductal hyperplasia	0.8%	0.3%	
Atypical lobular hyperplasia	0.4%		0.6%
Lobular carcinoma in situ		0.8%	
Ductal carcinoma in situ		1.3%	3.4%
Apocrine change	22.4%	28%	16.35%
Cysts	8.4%	5.1%	
Sclerosing adenosis	0.4%	12.4%	23%
Calcifications		3.8%	14.2%
Microglandular adenosis		0.3%	
Foci of tubular adenoma	3.2%	0.5%	
Foci of phyllodes tumour	2%	0.8%	

Among fibrocystic epithelial changes, 22.4% of cases showed apocrine metaplasia which was also most frequent histopathological changes in fibroadenoma seen in our study. This may be contributed to the large amount of slides available per case, as Azzopardi stated;" no doubt more extensively sampling would reveal its presence even more frequently"[18]. Cystic changes were also seen followed by sclerosing adenosis. Our findings were similar to study done by Kuijper et al[14].

Complex fibroadenoma were first described by Dupont et al[3], who reported that 22% of proven fibroadenoma were complex. In our study 31.2% of all biopsy-proven fibroadenoma were complex. We found that complex fibroadenomas were more frequently seen in older patients with mean age of 35 years, which was statistically significant (p value <0.005), similar to study done by Sklair Levy M et al[2].

Patients with fibroadenoma are 1.3-2.1 times more likely than women in the general population to develop breast cancer. Risk is further elevated for women with complex fibroadenomas who are 3.1-3.72 times more likely to develop breast cancer than women in the general population[2].

Stromal changes revealed hyaline and myxoid changes in majority of cases. These changes are most frequently seen in fibroadenoma, but they do not have any further risk for malignant transformation. Intracanalicular pattern, pericanalicular pattern and mixed pattern was found, there are the basic histological patterns and are not associated with further risk of malignancy. There was no evidence of multinucleated giant cells, smooth muscle changes, pseudoangiomatous like changes, infarct in our study.

A criterion to distinguish between fibroadenoma and phyllodes tumor is rapid growth. Therefore, rapid growth in a tumor previously diagnosed as fibroadenoma should raise suspicion of stromal transformation (and possibly epithelial transformation). Malignancy arising within fibroadenoma should be treated as in the otherwise normal breast. Second, fibroadenoma is associated with a long-standing increased risk of invasive breast cancer. Depending on presence of hyperplasia in adjacent tissue, complexity of the fibroadenoma and a positive family history for breast cancer the RR may rise to four, nearly twice the RR for women with a first degree relative with breast cancer. [19]

There were no cases of Carcinoma in situ (Ductal or lobular) seen in our study.

Diagnosis of fibroadenoma requires triple diagnostic procedure including clinical investigation, mammography/ sonography and fine needle aspiration (FNA)/ needle core biopsy (NCB). The advantage of NCB over FNA may be that it more easily reveals complex changes and epithelial proliferations[14]. Excision of fibroadenomas above the age of 35 years will remove all malignant lesions arising within fibroadenomas. Histopathological changes in epithelial and stromal elements are essential to be reported in the description of the report so as to alert the clinician for close follow up of the patient. This will help in timely management to reduce morbidity and mortality. Surveillance may be warranted for women with a known family history for breast cancer diagnosed with fibroadenoma with complex features or hyperplasia in adjacent tissue on needle core biopsy or excision.

Conclusion

Fibroadenoma of the breast is the most common fibroepithelial neoplasms, occurring in the reproductive age group. Epithelial and stromal elements of fibroadenoma exhibits various changes like proliferative epithelial changes, fibrocystic epithelial changes and stromal changes.

Complex fibroadenoma is defined as fibroadenomas harboring one or more of the so-called complex features: epithelial calcifications, papillary apocrine metaplasia, sclerosing adenosis and cysts larger than 3 mm.

Epidemiological studies shows fibroadenoma to be long term risk factor for breast cancer. Risk is increased in women with complex fibroadenomas, proliferative disease, or a family history of breast cancer.

Histopathological changes in epithelial and stromal elements of fibroadenoma are essential to be reported so as to alert the clinician for close follow up of the patient. This will help in timely diagnosis and management.

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