

Original Research Article

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An audit and clinicopathological study of fibroepithelial lesions of the breast at a tertiary care centre and comparison with WHO grading

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ABSTRACT

Background: Mammary fibroepithelial lesions encompass a wide spectrum of tumors ranging from an indolent fibroadenoma to potentially fatal malignant phyllodes tumor (PT). The criteria used for their classification based on morphological assessment are often challenging to apply and there is no consensus as to what constitutes an adequate resection margin. The aims of the study were to study histopathological spectrum of fibroepithelial lesions of breast at tertiary care centre, to stratify and classify various fibroepithelial lesions into fibroadenomas and PT, reclassify all confirmed cases of PT seen in the study period according to standard histopathological WHO criteria.

Methods: Records and slides of fibroepithelial lesions of the breast received at the department between January 2016 and August 2019 were retrieved and reviewed.

Results: A total 891 fibroepithelial lesions of breast were diagnosed during this duration. Out of these, 826 (92.7%) were fibroadenoma and its variants, 34 (3.8%) cases were of fibroadenomatoid mastopathy and 31(3.5%) were PT. Among all PT, 8 (25.8%) were borderline and 4 (12.9%) were malignant, rest (61.3%) were benign.

Conclusions: Fibroepithelial tumours of the breast are a heterogeneous group of lesions ranging from fibroadenoma at the benign end of the spectrum to malignant PT. There are overlapping histologic features among various subtypes, and transformation and progression to a more malignant phenotype may also occur. Given the significant clinical differences within various subtypes, accurate pathologic classification is important for appropriate management. Although some immunohistochemical markers may be useful in this differential diagnosis, histomorphology still remains the gold standard.

Keywords: Fibroadenoma, Fibroepithelial lesions, Phyllodes tumours

INTRODUCTION

Neoplastic proliferation of the specialised stroma of the breast occurs leading to secondary distortion of lobules and ducts, incorporating them within the mass. The resulting tumour contains epithelial elements, but only the stromal component is neoplastic. They are morphologically and behaviourally heterogeneous tumour with different clinical behaviours and treatment protocols. These are classified into two major categories i.e. fibroadenoma (FA) and phyllodes tumour (PT).¹ FA

which is by far more common accounts for the vast majority of benign breast tumour occurring in second & third decade of life.² PT, on the other hand, is a rare fibroepithelial breast neoplasm that resembles FA but has a totally different clinical course and management. It accounts for 0.3-0.9% of all primary breast tumours & occurs in older age group.^{3,4} PT was originally described in 1838 by Muller, who believed the lesion to be benign but called it cystosarcoma because of its cystic change and fleshy cut surface cited by Bumpers et al.⁵ PTs are

graded into benign, borderline and malignant according to WHO classification.⁶

Aims and objectives

The aims of the study were to study histopathological spectrum of fibroepithelial lesions of breast at tertiary care centre, to stratify and classify various fibroepithelial lesions into fibroadenomas and PT, reclassify all confirmed cases of PTs seen in the study period according to standard histopathological WHO criteria.

METHODS

The present study was a retrospective analysis of the data on fibroepithelial lesions (FELs) of breast, which involved the archival tumour blocks and clinicopathological data; and didn't involve any patient's personal information or any implication on the management protocol. The study included 891 cases of FELs diagnosed in the department of pathology at a tertiary care centre, over 3.8 years (January 2016 to August 2019). Lumpectomy, excision biopsies, trucut biopsies, mastectomy specimens which were later on categorized as FELs were included in the study irrespective of the age and sex. 10% formalin fixed specimens were subjected to routine haematoxylin and eosin stains. The tumours were reassessed and categorized into fibroadenoma, fibroadenomatoid hyperplasia and phyllode tumour. PT further graded according to the WHO 2012 classification.

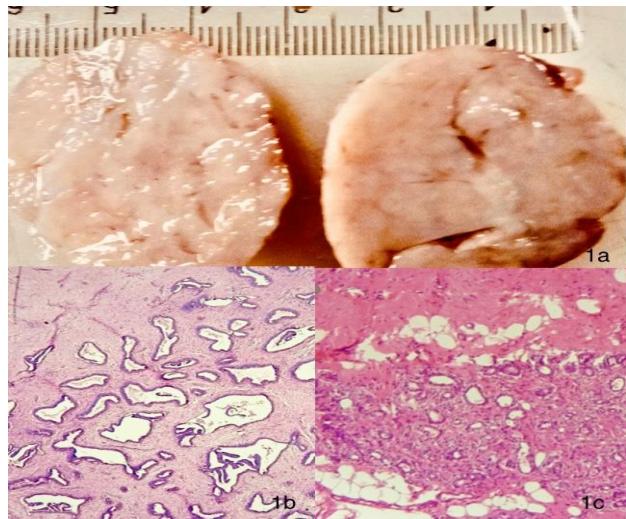


Figure 1: (a) Fibroadenoma gross-encapsulated and cut surface is grey white and lobulated; (b) microphotograph showing pericanalicular pattern of growth in fibroadenoma and (c) microphotograph showing proliferation of multiple adjacent lobules in a fibroadenomatoid mastopathy (H & E, X100).

Statistical analysis

The data were analysed with statistical software SPSS version 16 using frequency, cumulative frequency,

independent sample t- test and fisher's statistical tests. In this study, $p < 0.05$ was considered statistically significant.

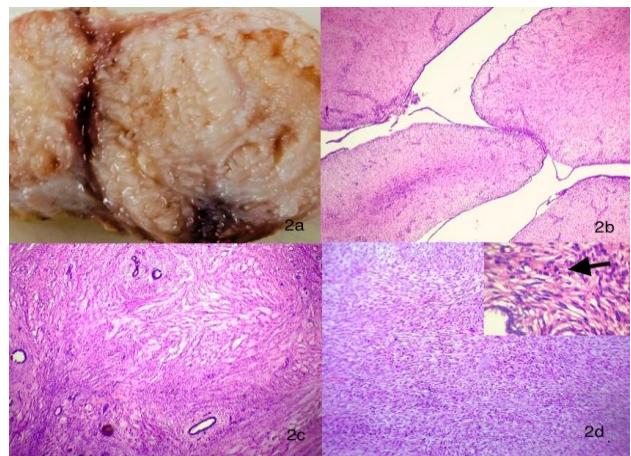


Figure 2: (a) PT-cut section shows bulging tissue with frond-like excrescences; (b) benign PT showing tongue like protrusion formed by stromal overgrowth. (H&Ex100); (c) photomicrograph of borderline phyllodes showing moderate increase in stromal cellularity with entrapped ducts (H and E, x100); (d) photomicrograph of malignant phyllodes showing increase in stromal cellularity along with mitotic figures (inset) (H and E, x100 & X400).

RESULTS

A total 891 fibroepithelial lesions of breast were diagnosed during this duration. Out of 891 cases of fibroepithelial lesions (Table 1) in our study 826 were fibroadenomas accounting for 92.7% of total cases. There was a wide age range of 2.5 to 70 years in our cases. Size varied from as small as less than 1 cm (0.5 cm) to as big as 12.5 cm. Grossly all the fibroadenomas were round, nodular, discrete firm swellings with cut surface showing homogenous firm greyish white surface with slit like spaces. A wide variety of proliferative changes can be seen in the epithelial components of fibroadenoma. A lot of the common microscopic variations of fibroadenoma were encountered in our study also. Out of these usual fibroadenoma, which had no other pathological association was seen in 87.9% of cases (Figure 1 a and b). The most common pathological association was fibrocystic change seen in about 25 cases (3.02%) followed by epithelial hyperplasia which was seen in 18 cases (2.18%) of fibroadenomas (Table 2). All cases initially diagnosed as FAs did not change on review.

There were 34 cases of fibroadenomatoid mastopathy (Figure 1c) with an age range of 17 to 45 years with a mean age of 24.52 years.

A total of 31 cases of phyllodes tumour were diagnosed during this duration. Of these cases, 7 were trucut biopsies and 24 were lumpectomy and modified radical Mastectomy Specimens. The age of patients ranged from

25 to 70 years with a mean age of 43.90 years. Of the total 31 cases, 19 (61.3%) were benign, 8 were borderline (25.8%) and rest 4 were malignant (12.9%). The standard WHO criteria (2012) for differentiating benign, borderline and malignant phyllodes tumours were used. On trucut biopsies (7 cases) of the patients, the following four stromal features were assessed: stromal cellularity, stromal atypia, mitosis, and relative proportion of the stroma to the epithelium while in rest 24 cases along with above features other histopathological criterias were also studied and P values calculated. (Table 3) Grossly phyllod tumours usually appear as tan to yellow coloured masses and Cut section shows bulging tissue with frond-like excrescences. (Figure 2a) Nearly 100% (19 cases) of

the benign PTs (Figure 2b) had stromal overgrowth, modest stromal hypercellularity, minimal cellular pleomorphism, uniform stroma distribution, without mitotic figures and in lumpectomy and mastectomy specimens 100% (12/12) had well circumscribed margins. All borderline PTs showed marked stromal overgrowth and hypercellularity (Figure 2c), moderate cellular pleomorphism, heterogenous stromal distribution with mitotic counts of 5–9/10 HPF. In 4 cases (50%) of borderline PT margins are infiltrative. The malignant PTs showed all of the latter features in addition to increased mitotic counts of >10/10 HPF, marked stroma overgrowth as well as pleomorphism and infiltrative tumour margins (Figure 2d).

Table 1: Incidence and age distribution of cases.

Category	No. of cases	Age range (years)	Mean age (years)
Fibroadenoma and its variants	826	2.5- 70	23.8
Fibroadenomatoid hyperplasia and mastopathy	34	17-45	24.5
PTs	31	25-79	43.9
Total no of cases	891		

Table 2: Fibroadenoma and variants.

Fibroadenoma and variants	No.
Fibroadenoma usual type	726
Fibroadenoma with cystic change	25
Fibroadenoma with adenosis	10
Fibroadenoma with epithelial hyperplasia	18
Fibroadenoma with apocrine metaplasia	17
Juvenile fibroadenoma	3
Complex fibroadenoma	5
Myxoid fibroadenoma	4
Giant fibroadenoma	0
Fibroadenoma with stromal hyalinization	11
Fibroadenoma with infarct	2
Fibroadenoma with inflammation	2
Fibroadenoma with phyllodes tumor	1
Fibroadenoma with squamous metaplasia	1
Fibroadenoma with tubular adenoma	1

Table 3: Clinicopathological parameters assessed in PTs.

Clinicopathologic features	Benign	Borderline	Malignant	P value
Age (in years)				
<20	0	0	0	
20-50	12	4	1	0.017
>50	1	4	3	
Size (cm)				
<5	2	0	0	
5-20	9.8	6	1	0.072
>20	1	2	3	
Well circumscribed	12	5/8	0/4	0.165
Infiltrative border	0	4/8	4/4	0.029
Hemorrhage	4/12	5/8	4/4	0.458

Continued.

Clinicopathologic features	Benign	Borderline	Malignant	P value
Mucoid degeneration	9/12	5/8	3/4	0.965
Slit like spaces	10	7	4	0.976
Desmoplasia	4	5	4	0.450
Stromal overgrowth	3(+)	5(++)	4(++)	0.308
Infiltrative margin	0/12	5/8	4/4	0.020
Cellularity				
Mild	12	3	0	
Mod	0	5	0	0.001
Severe	0	0	4	
Mitosis	<5/10 HPF	5-10/10 HPF	>10/10 HPF	0.001
Nuclear pleomorphism				
Mild	12	3	0	
Moderate	0	5	0	0.001
Severe	0	0	4	
LVI/NI	0	0	0	NA
Subendothelial stromal condensation	5	5	2	0.873
Skin/nipple/areola	0	1	1	0.303
Metaplasia	0	0	0	NA
Total cases	12	8	4	

DISCUSSION

The fibro epithelial lesions of breast mainly represent those lesions of breast where the lobulocentric architecture is distorted. It is mainly constituted by three types of lesions. The fibroadenoma and its variants are most common breast tumour. Other fibro epithelial lesions are PT and fibroadenomatoid hyperplasia also known as sclerosing lobular hyperplasia. FA and PT are two separate lesions with different clinical behaviors. Despite their histologic resemblance, standard criteria are available to distinctly distinguish these entities.

Diagnosis of fibroadenomas was confirmed when the lesions showed a biphasic pattern, with a bland epithelial component and with the stromal component showing low cellularity, minimal to absent stromal mitoses and the absence of a large frond like growth pattern of the stroma. The core criteria used for the distinction of PT from FA were prominent fronds or leaf like pattern and increased stromal cellularity.⁷ The 2012 World Health Organization criteria for PT diagnosis was used in this review and classified into benign, borderline, and malignant categories relied on the degree of stromal hypercellularity, cellular pleomorphism, mitotic activity, stromal overgrowth, and nature of the margins using the portion with the highest cellular activity and most florid architectural pattern.⁸ Cellular pleomorphism was designated little, modest, or marked, whereas stromal hypercellularity was categorized as modest or marked.⁹ Stromal mitotic activity was quantified per 10 high-power fields (HPF) in the most mitotically active areas of the stroma.⁷ Stromal overgrowth defined as a low power field ($\times 4$ microscope objective and $\times 10$ eyepiece) that comprised only stroma without epithelial elements was

labeled absent or present.⁹ A benign PT was diagnosed when the lesion showed well circumscribed margins, modest stromal hypercellularity, little or moderate cellular pleomorphism, occasional mitoses that numbered up to 4/10 HPF, and no stromal overgrowth.⁷ A malignant tumor was defined by marked stromal hypercellularity and cellular pleomorphism, presence of stromal overgrowth, brisk mitotic activity ($\geq 10/10$ HPF), and invasive margins; the finding of a malignant heterogenous element classifies the tumor as malignant.⁷ Borderline PT showed some but not all characteristics observed in malignant lesions.

In current study most common of all fibro epithelial lesions of breast remains fibroadenoma accounting for about 92.7% and concordant to studies conducted by Wani et al in, Patil et al; but duration of study was different in all of these.^{10,11} The diagnosis of FA is relatively simple and easy except for the cellular variant, which has been reported among even breast pathologist as difficult to distinguish from benign PT. All the FA reviewed in our study did not change which further highlights the unambiguity in the histopathological diagnosis of simple FA. A wide variety of proliferative changes can be seen in the epithelial components of fibroadenoma. A lot of the common microscopic variations of fibroadenoma were encountered in present study. Out of these simple fibroadenoma, which had no other pathological association was seen in 87.9% of cases. The most common pathological association was fibrocystic change seen in about 3.02% followed by epithelial hyperplasia which was seen in 2.18% of fibroadenomas (Table 1). The most frequent association of fibroadenoma with fibrocystic disease was similar to studies as that of Geethamala et al.²

In our study fibroadenomatoid mastopathy cases were 3.82% of total fibro epithelial lesions with a mean age of 24.5 years. These are benign breast lesion with the composite histological features of a fibroadenoma and fibrocystic changes; characterized by microscopic fibroadenomatoid foci intermingled with dilated ducts, epitheliosis and adenosis. These lesions are distinct from the typical well circumscribed fibroadenoma that may have fibrocystic changes.

In present study, PTs accounted for approximately 3.48% of fibro epithelial lesions. PT is a rare fibro epithelial lesion as compared to fibroadenoma, with wide spectrum of morphology. It has risk of local recurrence and uncommon metastasis. Although microscopic distinction between fibroadenoma and PT especially benign PT is difficult, strict histologic assessment of a combination of histologic features with classification help to achieve the correct diagnosis and provide useful clinical information.¹² PTs were classified according to three tier grading system of WHO classification into benign, borderline and malignant. Our findings showed that benign PT is significantly the most common, followed by borderline and malignant PT sequentially accounting for 61.3%, 25.8% and 12.9%, respectively. This proportion is in considerable agreement with other studies showing approximately 40-75% benign tumours, 15-36% borderline, and 7-15% malignant tumours.^{13,14} In the benign PT, the size varied from smallest 4cm to largest measuring >20 cm. The age varied from 20 to 55 years. All benign PT were well circumscribed grossly here in this study. In borderline PT, size varied from 5-20 cm in 6 cases and >20 cm in 2 cases with age ranged from 20 to 60 yrs. 62.5% cases were well circumscribed grossly. In malignant PT category 75% cases (3 out of 4) are in >50 year of age and >20 cm in size. None of case was well circumscribed grossly. On gross, phyllodes appear as solid, lobulated, and gray white in color with hemorrhagic, necrotic, and cystic areas within. Phyllodes tumors are biphasic with both mesenchymal and epithelial components. Characteristic leaves like architecture is present with epithelial components forming benign ducts while the hyper cellular stroma forming the malignant counterpart. These fibroblasts can also differentiate into heterotopous elements such as fat, cartilage, smooth muscle, and striated muscle. The presence of these components indicates poor prognosis. In our study, histologic parameters of stromal cellularity, infiltrative margins, nuclear pleomorphism and mitotic figures were largely adequate to classify PTs, and found statistically significant (p value <0.05). We also assessed other histological parameters such as haemorrhage, mucoid degeneration, slit like spaces, desmoplasia, stromal overgrowth, sub endothelial proliferation and skin or nipple/ areola involvement but no significant association was found in current study (p value >0.05). This discrepancy could probably be due to less number of cases in this study. There was no heterologous element in any of the PTs reviewed. Heterologous elements have been reported to be very uncommon among PT. Our

study had a shortfall of inability to assess margins in the trucut biopsy (7 cases) reviewed. Tumour margin is known to be an important element, especially in predicting local recurrence and has been found to be useful in resolving cases of ambiguity between benign and borderline.

Mammography, ultrasonography, and magnetic resonance imaging (MRI) are routine imaging diagnostic modalities. However, none of them are characteristic of phyllodes and features overlap with fibroadenoma.^{15,16} Surgical treatment is the mainstay of treatment for phyllodes. Wide local excision with at least 1 cm tumour -free margins should be kept. Since excision with required margins is impossible in giant phyllodes, mastectomy should be done for larger tumors and also in cases of recurrent tumours, especially of malignant histology.¹⁷ Mastectomy may also be required for tumours between 5 and 10 cm in diameter depending on the size and location of phyllodes. The clinical implication and surgical management of the three classes differ and as such bear varying prognostic tendencies. The local recurrence rate of PT has been estimated to be about 10-18% with negative and positive resection margins, respectively.¹⁸

CONCLUSION

Fibro epithelial lesions of breast are one of the most common lesions especially in young females. These results show that FAs are quite common & rarely misdiagnosed. The rare PT can cause a lot of clinical concern and cases simply referred to as PT without further classification, limit the patients' access to appropriate management as accurate classification helps in the overall management and prognostication. Moreover the need to differentiate fibroadenomas from Phyllodes tumor due to the different surgical procedures required for these tumours and the tendency of malignancy in Phyllodes needs to be considered seriously. In summary, morphologic criteria when applied in detail can conveniently diagnose fibro epithelial lesions and aid in the classification of PTs into its subtypes except in very few ambiguous conditions where immunohistochemistry may come in handy. It is therefore recommended that standard datasets should be routinely used in reporting these lesions.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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