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EVALUATION OF ER,PR, HER 2 NEU AND KI-67 STATUS IN FIBROADENOMA PATIENTS

General Surgery

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ABSTRACT

Background : One of the most important decisions in the management of breast tumr ,clinician must make was to decide whether to initiate hormone therapy or not, owing to its side effects, and chemotherapy, which is known to have significant risks and morbidity. Consequently, it is essential that the pathologist and operating surgeon accurately and consistently evaluate the ER, PR HER2/neu, and Ki 67 status of breast tumors. Material and method : Fifty excisional/Trucut biopsy samples of breast tissues excised from 50 patients clinically and USG confirmed diagnosed Breast fibroadenoma patients were subjected to immunohistochemistry findings for the ER,PR, Her 2 Neu and Ki-67 markers. The ALLRED scoring system was followed to score qualitatively the expression pattern of ER and PR after immune-histochemical staining of the tissue for ER and PR. The intensity and proportion of the stained cells were assessed and then final results were calculated and reported as follows; 0–1 score as negative, 2-3 score as weak expression, 4-6 as moderate expression and 7–8 as strong expression of ER or PR proteins.**Result :** It was observed that in all the 50 patients the normal and fibroadenoma excised masses were ER and PR positive (100%). We observed a statistically non significant weak inverse correlation of Allred score for ER and size of the lesion .The pearson correlation coefficient of Allred score for ER with size of the lesion was 0.045 (p=0.756) .We observed a statistically non significant weak inverse correlation of Allred score for PR and size of the lesion .The pearson correlation coefficient of Allred score for ER with size of the lesion was -0.0139 (p=0.469).In all the HER2 Neu was negative in normal and fibroadenoma tissue.(100%)/It was observed that presence of ki-67 values were significantly higher (10.55 ±0.06%) in excised masses with fibroadenoma than normal masses (5 ±0.03%).No significant difference was observed between ER ,PR and HER-NEU values amongst normal and fibroadenoma tissues . **Conclusion:** It can be concluded that there was no significant difference in ER ,PR and HER-NEU values amongst normal and fibroadenoma tissues .However,there exist significant strong positive corelation between values of ki-67 and size of the lesion.

KEYWORDS

INTRODUCTION

One of the most prevalent benign breast tumors that are commonly seen in clinical practice is breast fibroadenoma. The highest prevalence of 27.6% was observed in women ages 18 to 40 years.Incidence declines with age and is less common in women who have gone through menopause. The overall incidence of fibroadenoma in the adolescent population is 2.2% [4].

Fibroadenomas are characterized by an abundance of stromal and epithelial cells, and they frequently manifest as palpable breast lumps. The majority of patients with these lesions are women who are fertile, and they are well-known for their clinical heterogeneity, presenting in a variety of ways from discomfort and worry to asymptomatic findings [1-3].

Since breast fibroadenomas were initially reported in medical journals more than a century ago, our knowledge regarding their molecular mechanism, clinical behaviour and histological characteristics has changed significantly. Both glandular (epithelial) and connective tissue (stromal) components are commonly present in these tumors. Both pathologists and physicians have been very interested in the unique histological features and cellular variations of fibroadenomas [4].

It is possible for breast cancer to develop inside a fibroadenoma, however it is quite uncommon. Reports vary on the occurrence of these instances, ranging from 0.125% to 0.02% [5-7]. Under these conditions, invasive carcinomas (eleven percent invasive ductal carcinoma (IDC) and 3.4% invasive lobular carcinoma (ILC)) are shown to be less common than carcinomas in situ (66.9% lobular carcinoma in situ (LCIS) and 12.4% ductal carcinoma in situ (DCIS).[8]

Given the frequency of these aggressive lesions, it is necessary to identify tumor markers when fibroadenoma is present. Numerous tumor markers that help identify malignant potential have been reported in the literature; this paves the way for future tumor management.

One type of marker is the hormone receptors for progesterone and estrogen. The degree of hyperplasia and the level of steroid hormone expression are correlated with benign breast disease. The presence of PR is positively correlated with the proliferation of fibroblasts or epithelial cells. Progesterone receptors are nearly always present in fibroadenomas, while estrogen receptors are present in about 25% of instances.[10–9]

All proliferating cells contain the protein Ki-67, and its use as a proliferation marker has generated a lot of attention. With the exception of the G0 phase, all active stages of the cell cycle contain the nuclear nonhistone protein Ki-67.[11] Numerous research have looked into the proliferation biomarker Ki-67, which is also thought to be a predictive factor for breast cancer.[12,13]

A higher chance of developing breast cancer later on has been linked to Her-2/neu gene amplification and/or overexpression in benign breast disease.[14] The majority of commonly employed prognostic variables, such as hormone receptor status, have a lower predictive value than her-2 / neu amplification. The biological behavior and/or pathophysiology of human breast cancer may be influenced by this

gene.[15] In individuals with breast cancer, overexpression and amplification of the Her2/neu oncogene have been linked to early metastases initiation, resistance to hormone therapy, some types of chemotherapy, and a reduced survival time. [16]

Owing to their great incidence and the dearth of contemporary minimally invasive methods, some 500,000 fibroadenomas are still treated annually with surgical excision. The goals of surgical excision are to fully remove the fibroadenoma, leaving a rim of normal breast tissue in place, and to prevent any iatrogenic breast damage that may occur. This damage might potentially leave ugly scars or impede the development of the breast, leading to breast asymmetry.[17] Additionally, the current strategies for treating carcinoma use combinations of chemotherapy, hormone therapy, and radiation. One of the most important decisions a clinician must make is between hormone therapy, which has few side effects, and chemotherapy, which is known to have significant risks and morbidity. Consequently, it is essential that the pathologist and operating surgeon accurately and consistently evaluate the ER, PR HER2/neu, and Ki 67 status of breast tumors.[14,15]

In order to effectively use these criteria to prognosticate and treat breast cancer patients, the current study is being conducted to determine a correlation between ER and PR status, HER2/neu overexpression, proliferative activity, clinical characteristics, and tumour histology.

MATERIALS & METHODS

The present observational study was carried out on Fifty excisional/Trucut biopsy samples of breast tissues excised from 50 patients clinically and USG confirmed diagnosed Breast fibroadenoma patients and an equal number of normal adjacent mass was excised and further subjected to immunohistochemistry findings for the ER,PR, Her 2 Neu and Ki-67 markers. Girls below age of 15 years and diagnosed malignant breast diseases were excluded from the study.

The ALLRED scoring system was followed to score qualitatively the expression pattern of ER and PR after immune-histochemical staining of the tissue for ER and PR.

The intensity and proportion of the stained cells were assessed and then final results were calculated and reported as follows; 0–1 score as negative, 2-3 score as weak expression, 4-6 as moderate expression and 7–8 as strong expression of ER or PR proteins.

Ethical permission for conducting the research was taken from institutional ethical committee of the college and hospital before starting the research. Patients who are willing to participate was asked to sign a consent form before study commencement.The data was entered into the Microsoft excel sheet and was analysed using SYSTAT 13.2 Descriptive statistics was calculated in the form of percentages and frequency distribution keeping the value of significance p less than 0.05.

RESULTS AND OBSERVATIONS

AGE DISTRIBUTION

It was observed that, the mean age of the patients in our study was 24.7 ±5.76 years. Majority of the patients were in the age group of 21-25 years (36%)

CHIEF COMPLAINT

All the patients in our study had a chief complaint of presence of lump in the breast (74%). Associated pain was reported by 13 patients (26%)

BREAST SIDE INVOLVEMENT

In our study patients, right side breast was most commonly involved in 28 patients (56%) whereas left side was involved in 22 patients (44%)

DURATION OF CHIEF COMPLAINT

In our study , the mean duration of chief complaint was 16.68±22.01 months (Median :12 (0.2 -120) . In majority of the patients, the duration of chief complaint was 1 year (34%).

QUADRANT INVOLVEMENT

In our study , the most commonly involved quadrant was upper outer (68%) followed by upper inner quadrant (16%), Lower outer (6%) , Lower (2%) , lower inner (4%),upper (4%)

SIZE OF THE LESION

The mean size of the lesion was 3.22 ±1.66 (median :3 (1.4 – 9)] cms. In majority of the patients the size of the lesions was 1.4 – 3.4 cms (70%).

USG FINDING

The ultrasound features of fibroadenomas in our patients mainly distributed in three main categories,highlighted in Table 1

Table 1. Distribution of USG findings

USG Finding	N	%
Shape		
Round	3	6%
Oval	47	94%
Margin definition		
circumscribed	50	100%
Content		
Hypoechoic	46	92%
With heterogenic	4	8%

DISTRIBUTION OF IMMUNOHISTOCHEMICAL PARAMETERS

It was observed that in all the 50 patients the normal and fibroadenoma excised masses were ER and PR positive (100%)

In all the HER2 Neu was negative in normal and fibroadenoma tissue.(100%)

It was observed that presence of ki-67 values were significantly higher (10.55 ±0.06%) in excised masses with fibroadenoma than normal masses (5 ±0.03%).

No significant difference was observed between ER ,PR and HER-NEU values amongst normal and fibroadenoma tissues .

HORMONE RECEPTORS AND FIBROADENOMA

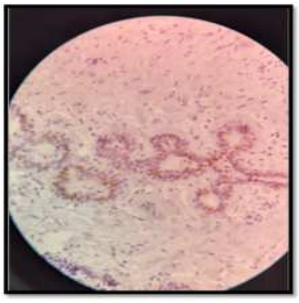


Figure 4. IHC ER - Strong nuclear positivity noted . (40 x) Allred score 7 = proportion score 4 + intensity score 3

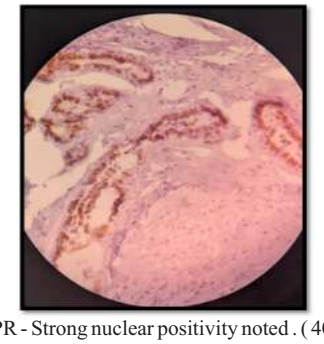


Figure 5.IHC PR - Strong nuclear positivity noted . (40 x) Allred score 8 = proportion score 5 + intensity score 3

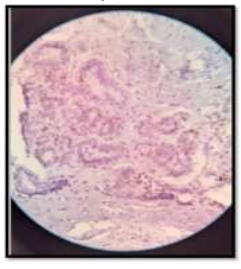


Figure 7. IHC Ki - 67- Nuclear staining in cells noted in less than 5 % of cells (40 x)

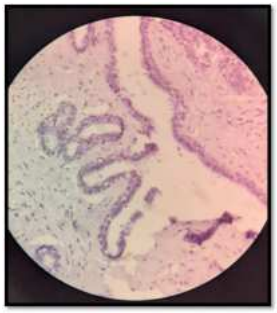


Figure 8. IHC Her 2 neu - Negative (40 x)

Age distribution and Immunohistochemical markers

It was observed that , the distribution of ER,PR and HER2 were comparable amongst the age groups .(Table 2)

		Normal			Fibroadenoma		
Age Group		ER	PR	HER 2 Neu	ER	PR	HER 2 Neu
16-20 (N=13)	Positive	13 (100%)	13 (100%)	0 0%	13 (100%)	13 (100%)	0 (0%)
	Negative	0 (0%)	0 (0%)	13 (100%)	0 (0%)	0 (0%)	13 (100%)
21-25 (N=18)	Positive	18 (100%)	18 (100%)	0 (0%)	18 (100%)	18 (100%)	0 (0%)
	Negative	0	0	18 (100%)	0	0 (0%)	18 (100%)
26-30 (N=11)	Positive	11 (100%)	11 (100%)	0 (0%)	11 (100%)	11 (100%)	0 (0%)
	Negative	0 (0%)	0 (0%)	11 (100%)	0 (0%)	0 (0%)	11 (100%)
31-35 (n=8)	Positive	8 (100%)	8 (100%)	0 (0%)	8 (100%)	8 (100%)	0 (0%)
	Negative	0 (0%)	0 (0%)	8 (100%)	0 (0%)	0 (0%)	8 (100%)

KI-67

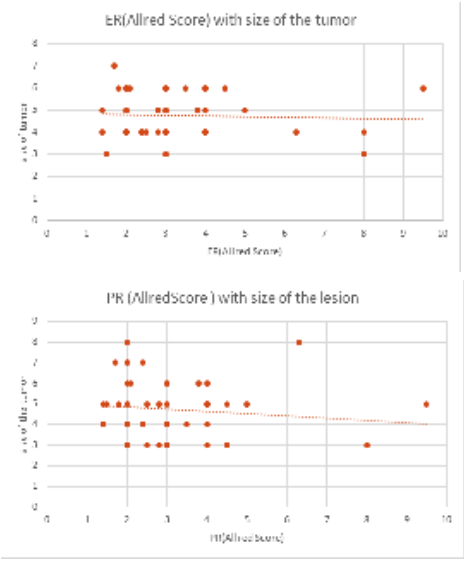
It was observed that the mean ±SD values of Ki-67 marker was comparable amongst all the age groups and amongst normal and fibroadenoma masses excised.(p>0.05)Table 3.

Age Group	Normal	Fibroadenoma	P value
16-20 (N=13)	7 ±0.02%	7±0.03%	0.486
21-25 (N=18)	6±0.02%	7 ±0.02%	0.239
26-30 (N=11)	7 ±0.01%	8±0.01%	0.174
31-35 (n=8)	6±0.01%	7 ±0.02%	0.415
P value	0.459	0.505	

CORELATION OF ALLRED SCORE FOR ER ,PR WITH SIZE OF THE LESION

We observed a statistically non significant weak correlation of Allred score for ER and size of the lesion .The pearson correlation coefficient of Allred score for ER with size of the lesion was 0.045 (p=0.756) .We observed a statistically non significant weak inverse correlation of Allred score for PR and size of the lesion .The pearson correlation coefficient of Allred score for ER with size of the lesion was 0.0139 (p=0.469) Table 4. Figure 2 & 3

Size	ER Mean Allred Score	PR Mean Allred Score
1-3 cm (N=36)	4.66±1.04	4.77±1.39
>3 - < 6cm (N=10)	5.3±0.82	4.07±1.07
≥6 cm -10 cm (N=4)	4.25±1.08	4.75±2.04
P value	0.080	0.4506



CORELATION OF KI -67 WITH SIZE OF THE LESION

The mean Ki-67 index score in patients with 1-3 cm of fibroadenoma mass was 7±0.3% , in patients with >3 - < 6cm , it was 9 ±0.2% while in those with ≥6 cm -10 cm , the ki-67 marker index score was 11±0.1% .We observed a significant strong positive corelation between values of ki-67 and size of the lesion (r= 0.933) (p <0.001)Figure 1.

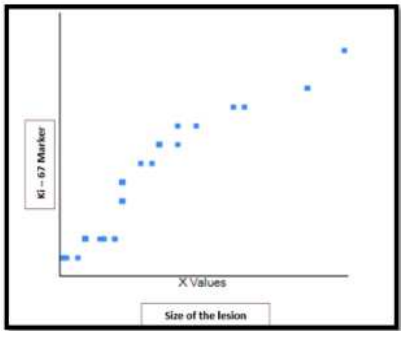


Figure 1 scatter plot showing linear relationship of Ki-67 marker with size of the lesion

CORELATION OF KI -67 WITH DURATION OF THE LESION

It was observed that the distribution of Ki-67 marker is comparable in normal and fibroadenoma mass in patients with less than 1 year, 1 year and > 1 year < 5 years of chief complaint (p>0.05) .However , in patients with more than 5 years of chief complaint , Ki-67 values were significantly higher in fibroadenoma mass (8±3%)as compared to normal mass(4±2%).

CORELATION OF ER ,PR AND HER2 NEU AND DURATION OF CHIEF COMPLAINT

It was observed that the distribution of ER ,PR and HER2 Neu were comparable between normal and fibroadenoma mass and does not differ significantly based on duration of chief complaint (p>0.05)

SIDE OF BREAST INVOLVED AND ER,PR,HER2 NEU

It was observed that the distribution of ER,PR .HER2 NEU values were comparable amongst the side of breast involved **.(p>0.05)**

KI -67 INDEX SCORE AND SIDE OF BREAST INVOLVED

It was observed that the Ki-67 index score was comparable amongst both the side of breast involved in normal and fibroadenoma mass (p >0.05)

DISCUSSION

Proliferating epithelial and connective tissue elements form benign fibroadenomas with marked histologic evidence of lobular origin. Fibroadenomas are biphasic epithelial and stromal tumours that develop from breast lobule glandular parenchyma. In axillary accessory breast tissue, they can arise. Fibroadenomas disturb breast

development and involution, although their cause is unknown. Fibroadenomas, however benign, raise breast cancer risk .[2,5,6] Even though women with complex fibroadenoma were more likely to have high-risk histological characteristics, Nassar et al. (2015)[18] found no independent association with breast cancer risk.Hence, this study examined fibroadenomas' immunohistochemistry markers.

In our study the age range was 15-35 years with a mean age of 24.7 ±5.76 years ,consistent with our findings , BUTT SJ et al[19] also reported mean age of 24.4+ 6.59 years and age range f 15-38 years. Similar findings were reported by Goldenberg et al (1968)[20], Haagensen (1971)[21], Matar et al (1998)[22] and Mima et al (2013)[23] who also noted that it is a most common cause of palpable breast mass in women younger than 30 years of age. The peak incidence of fibroadenoma ranged from the 2nd to the 3rd decade of life, which was consistent with the findings of other studies.

However, Levi et al (1994)[24] and Iua et al (1998)[25], in their studies observed that the median age was 37 years. This discrepancy in the median age between different studies might have risen because of geographical variations, hormonal factors, variable reproductive rates and socio-economic reasons.

All the patients in our study had a chief complaint of presence of lump in the breast (74%) . Associated pain was reported by 13 patients (26%) .Similarly,the presenting complaint was painless lump in 97.8% and painful lump in 2.2% in the study by Egwuonwu, et al 2016[26] ; Hebsur N.I et al 2018 [27], also reported painless lump in 67.5% and painful lump in 32.5% cases . A breast lump is any discrete mass noticed by the patient or by their physicians that prompts them to seek medical advice and treatment .[1] The presence of a lump in the breast is a great cause of anxiety and apprehension in females. The lump are usually small and can be managed conservatively; 0.5–2% of these lesions will grow rapidly. Public awareness has contributed largely to this and the consequence is a steady flow of frightened females attending outpatient clinics. Many of them have cyclical mastalgia, nodularity, or asymmetry but a small proportion will indeed present with breast lump.[2]

BREAST SIDE INVOLVEMENT

In our study patients , right side breast was most commonly involved in 28 patients (56%) whereas left side was involved in 22 patients (44%). Similarly, in the study by Hebsur N.I et al 2018[27] ,out of 40 patients, 24 cases were distributed in the right and 11 in left breast. . Most of the fibro-adenoma was found in right breast (50%) in the study by Purushothaman R et al ,2016.[28]. In contrast ,the left breast was involved in the majority of patients i.e. 58.8% in the study by Muhammad Kalim et al 2018[29].This finding was also noted by Isaac and colleagues[30]. Talpur et al[31] has also reported left side involvement more than the right side i.e. 53.33%.

DURATION OF CHIEF COMPLAINT

In our study , the mean duration of chief complaint was 16.68±22.01 months (Median :12 (0.2 -120) . In majority of the patients , the duration of chief complaint was 1 year (34%).In the study by Purushothaman R et al 2016[28] ,the duration of symptoms varied for months to 3 years with maximum 40 (50%) of them presenting within a year of symptoms.Similarly ,in the study by Egwuonwu, et al 2016[26] ,the duration between detection of lump and presentation was >12 months in 37.8%. patients. In the study by Hebsur N.I et al 2018[27] ,out of 40 patients More than three-fourth of them had symptoms between one month to one year and only 2.5% of the patients had symptoms between 5-6 years.

QUADRANT INVOLVEMENT

In our study , the most commonly involved quadrant was upper outer (68%) followed by upper inner quadrant (16%). In the study by Purushothaman R et al 2016[28] , Lower lateral quadrant was the main location of lumps 28 (35.0%) followed by upper lateral 22 (27.5%).

In the study by Santhosh Laxman, et al 2018[34], Maximum cases (34%) had upper lateral quadrant fibroadenoma. Minimum cases (8%) had lower medial quadrant fibroadenoma (26%), patients had fibroadenoma in lower lateral quadrant (20%), patients had fibroadenoma in upper medial quadrant (12%), patients had centrally located fibroadenoma.

In the study by Egwuonwu, et al 2016[26],The upper outer quadrant was affected mostly in 31.1%, followed by the upper inner quadrant in 28.9%.

SIZE OF THE LESION

The mean size of the lesion was 3.22 ±1.66 (median :3 (1.4 – 9)] cms. In majority of the patients the size of the lesions was 1.4 – 3.4 cms (70%) .

In the study by Hebsur N.I et al 2018[27] , 45% of the cases had lump size of less than 3cm, 35% between 3 to 5 cm, 17.5% between 5 to 10 cm and 1 patient (2.5%) between 10-20 cm.The largest was measuring about 11x11cm and smallest being lxl cm.

Santhosh Laxman, et al 2018[34]in their study categorized into fibroadenoma less than 1 cm in size as small fibroadenomas. When the size ranged 1cm to 3cm, it was grouped as large fibroadenoma. Giant fibroadenomas as size more than 3cm. Maximum patients (58%) had large fibroadenomas. Minimum cases (14%) had giant fibroadenomas. A 28% patient had small fibroadenomas.

In the study by Purushothaman R et al 2016,[28] The size of tumours varied from 1 to 20 cms with 43 (53.75%) cases between 3-5 cms. Giant fibro-adenoma>5 cms were found in 15 (18.75%).

USG FINDING

There are three basic ultrasonography types of fibroadenomas in our patients. The masses were mostly spherical, with 2.2% oval. Margin definition showed 58% circumscribed. Of the cases, 22% had noncircumscribed masses. 18.2% had noncircumscribed margins. All BIRADS cases were 4b or 4c.

Ultrasound content examination showed 94% hypoechoic masses. Some instances had lobulated masses (28%). Spongy masses made up 8%, calcified masses 6%, and heterogenic masses 2%. According to Alireza Namazi et al., 2017[35], most masses were spherical and barely 4% oval. Circumscribed cases exceeded 50%. 20% of instances had noncircumscribed masses. Noncircumscribed margins were noted in 22% of 4b or 4c BIRADS cases. Ultrasound content examination showed 94% hypoechoic masses. Of the cases, 27% had lobulated masses. The masses were 12% spongy, 10% calcified, and 4% heterogenic.

IMMUNOHISTOCHEMICAL PARAMETERS

It was observed that in all the 50 patients, the normal tissue had ER and PR receptors positive . In Fibradenoma tissue, ER was positive in 48 patients (96%) while PR was positive in 46 patients (92%). No significant difference was observed between ER ,PR and HER-NEU values amongst normal and fibroadenoma tissues .

Umekita Y, Yoshida H,1998[36] reported that Fibroadenomas contain progesterone receptors almost in all cases, and estrogen receptors in approximately one fourth of the cases .

F. Kuttenn, & S Fournier, 1981[37] found that ER and PR in breast fibroadenomas and their changing levels during menstruation and hormonal treatment reveal the hormone reliance of the disease. As the follicular phase progressed, ERc and ERn levels spiked to their peak in the preovulatory phase. Luteal phase lowered them. In the follicular phase, PRc levels were high. PRn increased during the start of the luteal phase while PRc declined. PRC and PRn then dropped and stayed low during luteal phase. In fibroadenomas from estrogen-progestagen-treated patients, PRc and PRn levels were similar to those in untreated patients' luteal phase. PRn was significantly greater than PRc in deficient progesterone patients. During benign breast disease, steroid hormone levels increase with hyperplasia. The progression from fibrocystic disease (35%), fibrosing adenosis (50%), to lobular and ductal hyperplasia (85%) is noted. PR promotes fibroblastic or epithelial proliferation . In benign phyllodes tumours, PR expression is practically as high as in malignant tumours .[5]

The present investigation found HER2/Neu negative in normal and fibroadenoma tissue. Abdul-Aal (2009)[38] found no HER-2/neu overexpression in benign fibroadenoma breast tumours.

BUTT SJ, 2017[19] in their study ,testing for over-expression of Her-2 receptors on 25 cases of fibroadenoma exhibited 4 (16%) moderately stained cases in age group B (20-39 years). Kalogeraki et al [39]

observed that 6 (24%) out of 25 fibroadenomas cases were found to display moderate Her-2 / c-erb B2 over expression in the similar age range. However Zubor et al (2008)[40] are of the view that their results indicate that HER-2 over expression in their study might play some role in the etiology of breast fibroadenoma formation. Gown and Yaziji (2000)[41], are of the similar view and stated that Her-2 expression on benign breast epithelium never implies true over-expression of the protein but as existing immunohistochemistry methods are sensitive enough that they detect very low levels of protein expression .Little discrepancies in the results of these studies could stem from the sources of tissue fixation, antigen retrieval and variable antigenicity of oncoprotein receptors in breast tissue employing the present immunohistochemistry methods are quite sensitive and detect very low levels of protein expression. The significance of this susceptibility, however, will have to be verified by larger studies.

In our study ,it was observed that presence of ki-67 values were significantly higher (9.50 ±0.06%) in excised masses with fibroadenoma than normal masses (7 ±0.03%). We observed a significant strong positive corelation between values of ki-67 and size of the lesion ($r= 0.933$) ($p <0.001$)

Similary ,in the study by Sasidharan S (2023)[42] the authors observed less than 10 % stromal expression for P53 and Ki-67 in 94 samples of fibroadenoma studied.

In the study by Zhang L et al 2020[43], Ki-67 showed lowest proliferative index in fibroadenomas (median 2.0%, mean 2.5%, range 1 to 10%).

Rego MF et al 2009[44] did not observed significant relationship between proliferative activity [Ki-67]and average diameter of the tumour . Concerning cell proliferation indices for Ki-67 antigen in the epithelium of the fibroadenomas, average values for stained nuclei (per thousand counted epithelial cells) were 27.88 ±27.52 in group 1 (follicular phase) and 37.88 ±31.08) in group 2 (luteal phase). Although the average value found for the cell proliferation index in group 2 is higher than in group 1.

The antigen protein, Ki-67, is localized to the nucleus, possibly associated either to the nucleolus or to fibrillar components, being present in the active phases of the cellular cycle (G_1, S, G_2 and M) and absent in G_0 .Its expression is linked to cell proliferation. It is well established that distribution of Ki-67 antigen is not constant, undergoing marked changes during the cycle, yet being associated to the nucleoli of proliferating cells and to chromosomes during mitosis .[42,44]

CONCLUSION

Acknowledging the findings of the study , it can be concluded that, It was observed that presence of ki-67 values were significantly higher in excised masses with fibroadenoma.

No significant difference was observed between ER ,PR and HER-NEU values amongst normal and fibroadenoma tissues .There exist significant strong positive corelation between values of ki-67 and size of the lesion.

In Fibroadenoma , ER and PR was present in all the patients. Therefore it can be suggested that patients with fibroadenoma could be benefitted by Anti-hormone therapy using drugs like Tamoxifen and Centchroman which could avoid unwarranted surgical management which could result in scar formation and affect the quality of life of young women due to unpleasant appearance.

HER2 Neu was negative in fibroadenoma tissue.Hence, its role in benign tumor is unclear.

REFERENCES

1. Guirguis MS, Adrada B, Santiago L, Candelaria R, Arribas E. Mimickers of breast malignancy: imaging findings, pathologic concordance and clinical management. Insights Imaging. 2021;12:53.
2. Ajmal M, Khan M, Van Fossen K. Breast Fibroadenoma StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; 2023.
3. Stachs A, Stubert J, Reimer T, Hartmann S.Benign breast disease in women. Dtsch Arztebl Int. 2019;116:565–574
4. Management of breast fibroadenomas. Greenberg R, Skornick Y, Kaplan O. J Gen Intern Med. 1998;13:640–645.
5. Deschênes L, Jacob S, Fabia J, Christen A. Beware of breast fibroadenomas in middle-aged women. Can J Surg. 1985;28:372–374.
6. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD, Jr, Rados MS, Schuyler PA. Long-term risk of breast cancer in women with fibroadenoma. N Engl J Med. 1994;331:10–15.
7. Buzanowski-Konakry K, Harrison EG, Jr, Payne WS. Lobular carcinoma arising in fibroadenoma of the breast. Cancer. 1975;35:450–456.
8. Fukuda M, Nagao K, Nishimura R, Matsuda M, Baba K, Ueno Y, Morinaga H, Omachi H, Hamada T. Carcinoma arising in fibroadenoma of the breast–a case report and review of the literature. Jpn J Surg. 1989;19:593–596. doi: 10.1007/BF02471669.
9. Giani C, D'Amore E, Delarue JC, Mouriesse H, May-Levin F, Sancho-Garnier H, et al. Estrogen and progesterone receptors in benign breast tumor s and lesions: relationship with histological and cytological features. Int J Cancer. 1986;37(1):7–10.
10. Umekita Y, Yoshida H. Immunohistochemical study of hormone receptor and hormone-regulated protein expression in phyllodes tumor: comparison with fibroadenoma. Virchows Arch. 1998;433(4):311–4
11. Nishimura R, Osako T, Okumura Y, Hayashi M, Toyozumi Y, Arima N. Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. Exp Ther Med. 2010;1:747–54.
12. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol. 2010;11:174–83.
13. de Azambuja E, Cardoso F, de Castro G Jr, Colozza M, Mano MS, Durbecq V, et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12 155 patients. Br J Cancer. 2007;96:1504–13
14. Stark A, Hulka BS, Joens S, Novotny D, Thor AD, Wold LE, Schell MJ, Melton III LJ, Liu ET, Conway K. HER-2/neu amplification in benign breast disease and the risk of subsequent breast cancer. Journal of clinical oncology. 2000 Jan 1;18(2):267-.
15. El Hadi H, Abdellaoui-Maane I, Kottwitz D, El Amrani M, Bouchoutrouch N, Qmichou Z, Karkouri M, ElAttar H, Errihani H, Fernandez PL, Bakri Y, Sefrioui H, Moumen A. Development and evaluation of a novel RT-qPCR based test for the quantification of HER2 gene expression in breast cancer.Gene. 2017 Mar 20;605:114-122.
16. Ding L, Zhang Z, Xu Y, Zhang Y; Comparative study of Her-2, p53, Ki-67 expression and clinicopathological characteristics of breast cancer in a cohort of northern China female patients. Bioengineered. 2017 Jan 11:110.
17. Salati S: Breast fibroadenomas: a review in the light of current literature. Pol Przegl Chir 2021; 93(1): 40-48.
18. Nassar A, Visscher DW, Degnim AC, Frank RD, Vierkant RA, Frost M, Radisky DC, Vachon CM, Kraft RA, Hartmann LC, Ghosh K. Complex fibroadenoma and breast cancer risk: a Mayo Clinic benign breast disease cohort study. Breast cancer research and treatment. 2015 Sep;153:397-405.
19. Butt SJ, Alam M, Muhammad A. Her-2/c-erb B 2 receptors Expression in Benign Fibroepithelial Lesions–Fibroadenomas; with Realtion to age of patients. PAKISTAN JOURNAL OF MEDICAL & HEALTH SCIENCES. 2017 Oct 1;11(4):1287-90.
20. Naeem S, Naz S, Amanullah K, Javed H, Khan O, Afridi EA, Ahmed S. OESTROGEN AND PROGESTERONE RECEPTORS'EXPRESSION PATTERN IN FIBRO-ADENOMA OF THE FEMALE BREAST. Journal of Ayub Medical College Abbottabad-Pakistan. 2023 Jul 1;35(3).
21. Yuan M, Saeki H, Horimoto Y, Ishizuka Y, Onagi H, Saito M, Hayashi T, Arakawa A, Yao T. Stromal Ki67 expression might be a useful marker for distinguishing fibroadenoma from benign phyllodes tumor of the breast. International Journal of Surgical Pathology. 2024 Apr;32(2):223-9.
22. Nassar A, Visscher DW, Degnim AC, Frank RD, Vierkant RA, Frost M, Radisky DC, Vachon CM, Kraft RA, Hartmann LC, Ghosh K. Complex fibroadenoma and breast cancer risk: a Mayo Clinic benign breast disease cohort study. Breast cancer research and treatment. 2015 Sep;153:397-405.
23. Goldenberg VE, Wiegenstein L, Mottet NK. Florid breast fibroadenomas in patients taking hormonal oral contraceptives. Am J Clin Pathol 1968; 49-52
24. Haagensen CD, editor. Diseases of the breast. 2nd Ed. Philadelphia: WB Saunders; 1971.
25. Matar N, Soumani A, Noun M, Chraibi T, Himmi A, el Mansour et al. Phyllodes tumour of breast. Aust NZJ Surg 1998; 68: 19 -22
26. . Mima B. Maychet Sangma, Kishori Panda, and Simon Dasiah. A Clinico-Pathological Study on Benign Breast Diseases. J Clin Diagn Res. 2013 Mar; 7(3): 503–506.
27. Levi F, Randimbison L, TeVc, La Vecchia C. Incidence of breast cancer in women with fibroadenoma. Int J Cancer 1994; 57: 681-3.
28. Iau PT, Lim TC, Png DJ, Tan WT. Phyllodes tumour: an update of 40 cases. Ann Acad Med Singapore 1998; 27: 200-3.
29. Hebsur NI, Mulkipatil SY, Narayanaswamy RR. A clinico pathological study of fibroadenoma of the breast.
30. Rangaswamy P, Rubby SA. Clinical study on fibroadenoma of the breast. International Surgery Journal. 2016 Dec 10;3(4):1916-9.
31. Kalim M, Ullah H, Ahmad S, Shah FO, Yosaf M. Frequency of fibroadenoma in patients presenting with breast lump. Journal of Postgraduate Medical Institute. 2018 Mar 23;32(1).
32. Isaac U, Memon F, Zohra N. Frequency of Breast diseases at a tertiary hospital of Karachi. J Liaquat Uni Med Health Sci 2005; 4:6-9.
33. Talpur KAH, Laghari AA, Malik AM, Memon A. Clinicopathological profile of patients with breast diseases at University Hospital, Jamshoro. J Liaquat Uni Med Health Sci 2006; 5:71-5.
34. Laxman S, Sangolgi P, Jabshetty S, Bhavikatti A, Uttam A. Clinical profile of patients with fibroadenoma of breast. International Surgery Journal. 2018 Feb 26;5(3):1057-61.
35. Namazi A, Adibi A, Haghighi M, Hashemi M. An evaluation of ultrasound features of breast fibroadenoma. Advanced biomedical research. 2017 Jan 1;6(1):153.
36. Umekita Y, Yoshida H. Immunohistochemical study of hormone receptor and hormone-regulated protein expression in phyllodes tumour: comparison with fibroadenoma. Virchows Arch. 1998 Oct;433(4):311-4.
37. Kuttenn F, Fournier S, Durand JC, Mauvais-Jarvis P, Baudot N, Doukani A. Estradiol and progesterone receptors in human breast fibroadenomas. The Journal of Clinical Endocrinology & Metabolism. 1981 Jun 1;52(6):1225-9.
38. Abdul-Aal E, Kufa PO. The mean AgNOR values in relation to HER-2/neu overexpression In a series of Iraqi women with breast cancer.
39. Kalogeraki A, Tzardi M, Datseris G, Kanavaros P, Karvelas C, Chalkiadakis G, Tsiftsis D, Delides G. C-erbB-2: expression in patients with breast carcinoma in comparison to patients with benign breast diseases. Anticancer research. 1996 Mar 1;16(2):765-71.
40. Zubor P, Kajo K, Stanclova A, Szunyogh N, Galo S, Dussan CA, Minarik G, Visnovsky J, Danko J. Human epithelial growth factor receptor 2[Ile655Val] polymorphism and risk of breast fibroadenoma; Eur J Cancer Prev. 2008 Feb;17(1):33-8.
41. Gown AM, Yaziji H. Detection of HER-2/neu alterations in breast cancer: Facts and pitfalls. Phenopath Labs – Illustrated guide; 2000: 1-15.
42. Sasidharan S , Cerin AA , Sithalakshmi M , Joseph AM. STROMAL EXPRESSION OF P53 AND KI67 IN FIBROADENOMA: A PROSPECTIVE EVALUATION STUDY. Int J Acad Med Pharm 2023; 5 (6); 774-777
43. Zhang L, Yang C, Pfeifer JD, Caprioli RM, Judd AM, Patterson NH, Reyzer ML, Norris JL, Maluf HM. Histopathologic, immunophenotypic, and proteomics characteristics of low-grade phyllodes tumor and fibroadenoma: more similarities than differences. NPJ breast cancer. 2020 Jun 26;6(1):27.
44. Rego MF, Navarrete MA, Facina G, Falzoni R, Silva R, Baracat EC, Nazario AC. Analysis of human mammary fibroadenoma by Ki-67 index in the follicular and luteal phases of menstrual cycle. Cell Proliferation. 2009 Apr;42(2):241-7.