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COMPARATIVE STUDY OF HISTOPATHOLOGY IN CORRELATION WITH ESTROGEN RECEPTOR AND PROGESTERONE RECEPTOR IN CASE OF FIBROADENOMA

General Surgery

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ABSTRACT

INTRODUCTION: Fibroadenomas are the most common breast masses in adolescents. They may present a challenge for physicians as treatment guidelines are lacking in this population. Types of fibroadenoma include juvenile, cellular, or giant. Differentiation must be made between giant fibroadenoma and juvenile hypertrophy. Patients who present with breast masses should undergo a detailed evaluation to assess the mass, including an ultrasound. Surgical excision of fibroadenoma may be performed if the mass is symptomatic and/or rapidly growing. Hence the present study was done at our tertiary care centre to study the correlation, occurrence and recurrence of fibroadenoma with ER and PR status.

RESULTS: The mean age of the patients was 35.28 ± 10.25 years. 4 (8%) patients started menstruation at age of 12 years while 19 (38%) patients started menstruation at 13 years of age. 21 (42%) and 6 (12%) patients started menstruation at 15 and 16 years of age respectively. There was no significant association between Estrogen Receptor (ER) status and age, menopausal history, laterality and gross size of tumour of patients ($p>0.05$). Progesterone Receptor (PR) status and its intensity was seen to correlate with tumor size ($p<0.05$). On the other hand no significant association was noted between PR status and age, menopausal history, laterality and gross size of tumour of patients ($p>0.05$).

CONCLUSION: Immunohistochemical diagnosis for estrogen and progesterone receptors has proved to be advantageous and an aid in the diagnosis. Several cases of diagnostic dilemma such as invasion or pseudoinvasion, ductal or lobular type, and in situ or invasion can be reliably diagnosed by the use of immunohistochemical diagnosis of estrogen and progesterone receptors.

KEYWORDS

INTRODUCTION

Fibroadenomas are the most common breast masses in adolescents. Fibroadenomas generally present as 2 to 3 cm in size, but they may increase to > 10 cm and cause associated breast asymmetry and/or hypertrophy. Types of fibroadenoma include juvenile, cellular, or giant. Differentiation must be made between giant fibroadenoma and juvenile hypertrophy.

Fibroadenomas are common benign lesions of the breast that usually present as a single breast mass in young women. They are assumed to be aberrations of normal breast development or the product of hyperplastic processes, rather than true neoplasms. The clinician often faces the dilemma whether to remove the mass or to monitor it by means of periodic follow-up examinations. Although removal of these lesions is a definitive solution, surgery may involve unnecessary excisions of benign lesions and unbecoming cosmesis.

It may occur at any age after puberty but is most frequent in the third decade.[1]

Fibroadenoma presents as a painless, solitary, firm, slowly growing, mobile, well-defined nodule and less frequently it may appear in the form of multiple nodules. The admixture of stromal and epithelial proliferation gives rise to two distinct growth patterns of no clinical significance.[2] Both epithelial and stromal components can show a wide spectrum of changes typically occurring at certain age, such as apocrine and squamous metaplasia in the epithelial component or focal and diffuse hypercellularity, extensive myxoid change and hyalinization with dystrophic calcification, or ossification in the stromal component.[2]

Ductules vary in configuration; two classic patterns are described, intracanalicular when ductules are compressed by the stroma into clefts, and pericanalicular when the stroma appears to surround ductules in a circumferential fashion.[1]

In benign breast disease, the intensity of steroid hormones expression parallels the degree of hyperplasia. A progression is noted from fibrocystic disease (35%) to fibrosing adenosis (50%) to lobular and ductal hyperplasia (85%).[3] A positive relationship is seen between PR presence and fibroblastic or epithelial proliferation.[4] Fibroadenomas contain progesterone receptors almost universally, and estrogen receptors in approximately one fourth of the cases.[5] PR expression is also seen in benign phyllodes tumors at a very high level, almost as high as in malignant tumors.[6]

The determination of ER and PR on biopsies of invasive carcinomas prior to therapeutic manipulations has become a standard practice in the management of breast cancers because it provides information on response to hormonal therapy and prognosis. Tumors that contain estrogen receptors have a better prognosis and are more likely to respond to hormonal therapy than tumors that lack them. The presence of progesterone receptor in addition to ER increases the likelihood of response to hormonal therapy because its presence implies a functioning ER pathway.[7,8]

Adolescent patients who present with breast masses should undergo a detailed evaluation to assess the mass, including an ultrasound. If malignancy is ruled out, a fibroadenoma confirmed by imaging studies that is stable in size may be managed with careful observation and follow-up. Surgical excision of the fibroadenoma may be performed if the mass is symptomatic and/or rapidly growing.

Hence the present study was done at our tertiary care centre to study the correlation, occurrence and recurrence of fibroadenoma with ER and PR status.

MATERIAL AND METHODS

A tertiary hospital based prospective observational study was done among 50 patients to evaluate the correlation of fibroadenoma with estrogen receptor (ER) and progesterone receptor (PR) status over a period of 2 years

Study site-

Department of General Surgery, D Y Patil Medical College, Hospital And Research Centre, Pune, Maharashtra

INCLUSION CRITERIA:

1. Those patients who are given informed consent
2. Age between 15 to 60 years
3. Cases diagnosed as Fibroadenoma by FNAC

EXCLUSION CRITERIA:

1. Patients who did not give written consent
2. Immunocompromised patient
3. Patients having other pathology with Fibroadenoma

METHODOLOGY

Clinically diagnosed case of fibroadenoma
Excision of fibroadenoma and true cut biopsy taken from the specimen
Biopsy sent for ER and PR studies.

After tissue collection and processing selected blocks were used for IHC procedure. Pro forma designed to gather uniform necessary information was used for every case .

ER or PR was considered positive when more than 1% of tumor cell nuclei were immunoreactive. ER or PR were considered negative if <1% of tumor cell nuclei were immunoreactive in the presence of evidence that the sample can express ER or PR (positive intrinsic controls seen). Uninterpretable for ER or PR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining.

For interpretation of her2/neu staining, the following method was used:

- Score 0 (Negative): No staining is observed or membrane staining is observed in <10% of the tumor cells
- Score 1+ (Negative): A faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells. The cells are only stained in part of their membrane
- Score 2+ (weakly Positive): A weak to moderate complete membrane staining is observed in more than 10% of the tumor cells
- Score 3+ (Strongly Positive): A strong complete membrane staining is observed in more than 30% (formerly 10%) of the tumor cells
- Score 3 + was considered as positive immunostaining for her2 neu.

STATISTICAL ANALYSIS

Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student 't' test and Chi-Square test. 'p' value less than 0.05 is taken as significant**.**

Results were graphically represented where deemed necessary.
Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 will be used for statistical analysis. Graphical representation will be done in MS Excel 2010.

RESULTS

Majority of the patients (40%) were in the age group of 31-40 years followed by 32% in the age group of 21-30 years, 14% patients in the age group of 41-50 years, 10% patients in the age group of 51-60 years and 4% patients in the age group of 15-20 years. The mean age of the patients was 35.28 ± 10.25 years.

4 (8%) patients started menstruation at age of 12 years while 19 (38%) patients started menstruation at 13 years of age. 21 (42%) and 6 (12%) patients started menstruation at 15 and 16 years of age respectively.

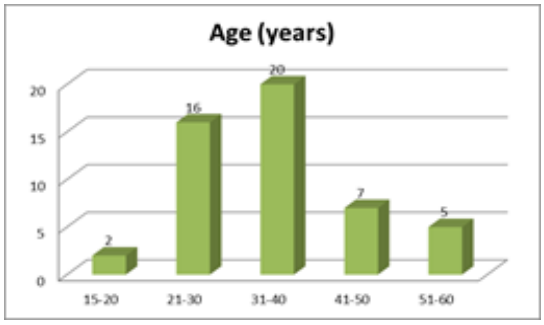

figure 1 : Distribution of patients according to age

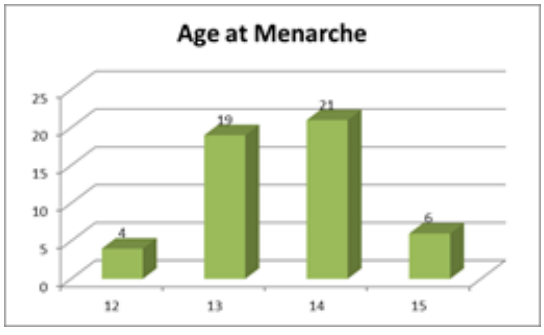

figure 2 : Distribution of patients according to age at menarche

Majority of women (82%) were premenopausal while 9 (18%) patients were postmenopausal.

It was observed that family history of fibroadenoma was present in 4 (8%) patients.

Upper outer quadrant (42%) was involved in most patients followed by central quadrant (30%), upper inner quadrant (18%), lower outer quadrant (8%) and lower inner quadrant (2%).

25 (50%) patients had tumor size between 2.1 to 5cm while 14 (28%) and 11 (22%) patients had tumour size >5 cm and ≤2 cm respectively.

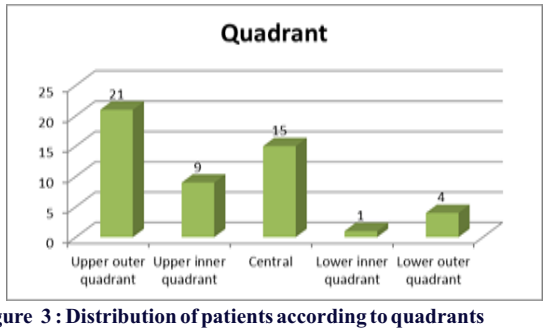

figure 3 : Distribution of patients according to quadrants

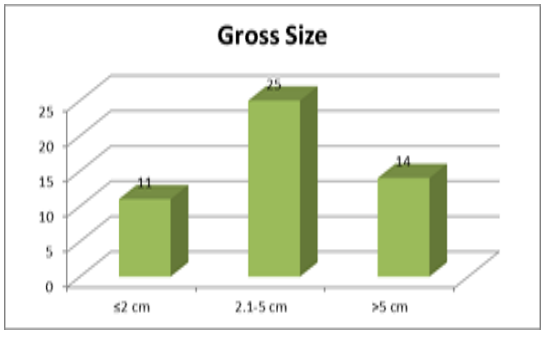

figure 4 : Distribution of patients according to lump size

The total number of Estrogen Receptor (ER) positive cases was 42% while there was 58% ER negative cases.

The total number of Progesterone Receptor (PR) positive cases was 36% while there was 64% PR negative cases.

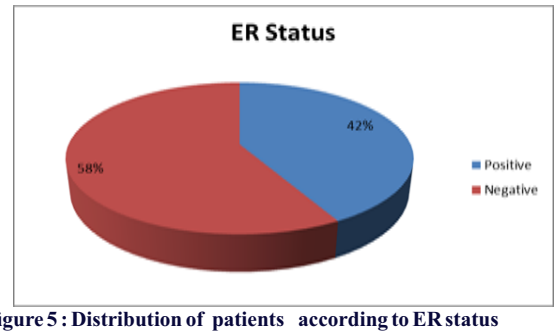

figure 5 : Distribution of patients according to ER status

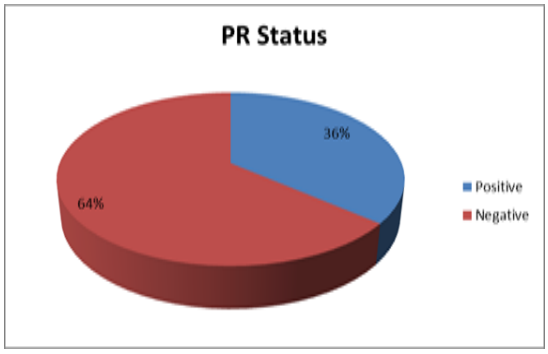

figure 6: Distribution of patients according to PR status

The patients in which both ER and PR markers showed similar results (i.e. either both positive or both negative) were considered to be concordant whereas patients with one marker positive and other negative or vice versa were taken as discordant.

43 (86%) patients showed concordant results, of which 16 (32%) patients showed both ER and PR positivity and 27 (54%) patients showed both markers as negative. 7 (14%) patients showed discordant results of which 5 (10%) patients showed ER positive and PR negative while 2 (4%) patients showed ER negative and PR positive.

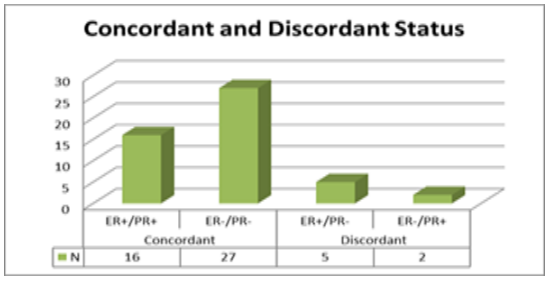

figure 7 : Distribution of patients according to concordant and discordant status

There was no significant association between Estrogen Receptor (ER) status and age, menopausal history, laterality and gross size of tumour of patients ($p>0.05$).

Progesterone Receptor (PR) status and its intensity was seen to correlate with tumor size ($p<0.05$). On the other hand no significant association was noted between PR status and age, menopausal history, laterality and gross size of tumour of patients ($p>0.05$).

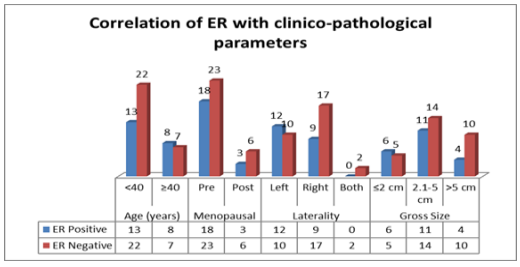

figure 8: correlation of ER status with clinic-pathological parameters

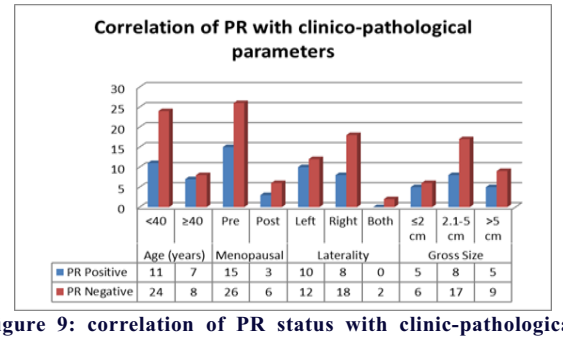

figure 9: correlation of PR status with clinic-pathological parameters

DISCUSSION

A hospital based prospective observational study was done among 50 patients to evaluate the correlation of fibroadenoma with estrogen receptor (ER) and progesterone receptor (PR) status.

The benign mammary lesions occur in the context of a hormonal imbalance, which, in the long run runs the risk of developing a mammary carcinoma. The activation of α estrogen receptor (ER-α) raises the sensitiveness of the target tissue for the action of circulatory estrogens, stimulating the DNA synthesis, cell division, active biological protein production, including pS2, TGF-α (transforming growth factor), EGF (epidermal growth factor), which influences the cellular growth and differentiation[9].

The cumulative exposure to estrogens contributes to the mammary carcinogenesis by means of stimulating a premalignant cells clone or the augmentation of spontaneous mutation percentage. The estrogens may also decrease the transition time in the cellular cycle, so that the spontaneous mutations become defined before the reparatory mechanism intervention. Another mechanism could be the toxic genetic effect of estrogens. It can be explained by the loss of the suppressing gene effect, whose function is to prevent the excessive proliferation of ER positive cells in the rich estrogens environment, especially in premenopausal women[10].

The allelic disequilibrium was proven in some intra-ductal and intralobular proliferation and is significantly increased into in situ carcinomas and atypical hyperplasia, compared with usual hyperplasia[11]. Increased hormonal contents, as those observed in the case of premenopausal women or those breastfeeding are associated with a reduced number of ER+ epithelial cells, while the reduced circulatory concentrations of estrogens, as those observed in the case of postmenopausal women, are associated with an increased number of positive ER cells.

In normal mammary tissue, the percentage of positive ER cells grows with the age, correlated with the diminished plasmatic concentration of the circulatory steroid hormones. In the case of premalignant proliferative lesions, as well as in the case of the in situ carcinomas, this negative association is lost, being a display of the early molecular changes that appear in the neoplastic transformation[12].

The relatively elevated risk of developing a carcinoma was associated with the sclerosing adenosis lesions, intraductal florid papiloma, fibroadenoma, phyllodes tumor, fibrocystic disease with proliferative lesions adenosis-type and ductal hyperplasia. Some histopathological changes, such as apocrine metaplasia and ductal ectasia were not associated with an increased risk of developing mammary cancer.

A correlation between the presence of hormone receptors in the tumor and response to hormonal therapy and chemotherapy is a significant development in the breast carcinoma management. At present, ER status is regarded as the most powerful predictive marker in the treatment of breast cancer even though ER and PR are codependent variables[1,13].

Hormone receptors were initially measured by binding assay on tissue cytosol, but this has been effectively taken over by IHC. They can also be assessed by in situ hybridization and polymerase chain reaction. IHC has the advantages that it does not require fresh tissue, can be performed even on minute quantities of tissues, and is a relatively easy technique. ER is a thermolabile unstable protein, water soluble with a

short half-life after surgical resection, so it is very important to ensure rapid fixation of specimen to obtain appropriate results.

Several authors have attempted to standardize the technique and method of reporting to bring some semi-quantitation to the reporting of IHC. Scoring systems have been devised to express the results incorporating two features: number of tumor cell nuclei which are stained and the intensity of staining[1,13].

Hormone receptor expression has not been found to correlate well with histological type of breast carcinoma (ductal vs. lobular, no significant association). However, breast cancers with negative ER generally have pushing margins, Grade 3 histology, comedo type necrosis, lymphoid stroma, and central necrosis/fibrosis[14]. ER concentrations are usually lower in tumors in premenopausal women compared to postmenopausal[15].

In the present study, majority of the patients (40%) were in the age group of 31-40 years followed by 32% in the age group of 21-30 years, 14% patients in the age group of 41-50 years, 10% patients in the age group of 51-60 years and 4% patients in the age group of 15-20 years. The mean age of the patients was 35.28 ± 10.25 years. 4 (8%) patients started menstruation at age of 12 years while 19 (38%) patients started menstruation at 13 years of age. 21 (42%) and 6 (12%) patients started menstruation at 15 and 16 years of age respectively. This is similar to the studies of Thakral A et al[16] and Bansal C et al[17].

In our study, majority of women (82%) were premenopausal while 9 (18%) patients were postmenopausal. Family history of fibroadenoma was present in 4 (8%) patients. Upper outer quadrant (42%) was involved in most patients followed by central quadrant (30%), upper inner quadrant (18%), lower outer quadrant (8%) and lower inner quadrant (2%). 25 (50%) patients had tumor size between 2.1 to 5cm while 14 (28%) and 11 (22%) patients had tumour size >5 cm and ≤2 cm respectively. This is comparable to the study of Bansal C et al[17] observed most of the cases (56.2%) belonged to intermediate group with tumor size of 2–5 cm. The most commonly encountered histologic type was infiltrating duct carcinoma, not otherwise categorized (invasive ductal carcinoma [IDC], NOC). Most of the tumors (64%) belonged to modified Richardson–Bloom (MRB) Grade 2.

It was observed in the present study that the total number of Estrogen Receptor (ER) positive cases was 42% while there was 58% ER negative cases. The total number of Progesterone Receptor (PR) positive cases was 36% while there was 64% PR negative cases. This is concordant to the studies of Thakral A et al[16], Bansal C et al[17], Verma D et al[18], Ambroise M et al[19], Doval DC et al[20] and Ali EM et al[21].

In our study, the patients in which both ER and PR markers showed similar results (i.e. either both positive or both negative) were considered to be concordant whereas patients with one marker positive and other negative or vice versa were taken as discordant. 43 (86%) patients showed concordant results, of which 16 (32%) patients showed both ER and PR positivity and 27 (54%) patients showed both markers as negative. 7 (14%) patients showed discordant results of which 5 (10%) patients showed ER positive and PR negative while 2 (4%) patients showed ER negative and PR positive. These findings were consistent with the studies of Bansal C et al[17], Moise M et al[22] and Thakral A et al[16].

In the present study, there was no significant association between Estrogen Receptor (ER) status and age, menopausal history, laterality and gross size of tumour of patients ($p>0.05$). Similar observations were reported in a study done by Bansal C et al[17] which noted no significant relation between ER positivity and tumor size.

It was observed in our study that Progesterone Receptor (PR) status and its intensity was seen to correlate with tumor size ($p<0.05$). On the other hand no significant association was noted between PR status and age, menopausal history, laterality and gross size of tumour of patients ($p>0.05$). Similar observations were noted in the studies of Bansal C et al[17], Sadaka E et al[23] and Gupta D et al[24].

Bansal C et al[17] observational study reported no significant association between ER and PR expression or triple negative cases and tumor stage. Regarding PR positivity, it had a significant association with only tumor grade while with all other clinicopathologic parameters such as age, menopausal status, tumor size, and lymph node status, no significant relation was noted.

Sadaka E et al[23] retrospective study reported CD 10 expression was significantly correlated with N stage ($p<0.001$), ER status ($p<0.001$), PR status ($p<0.001$) tumor grade ($p<0.001$), lymphovascular invasion ($p<0.001$) and HER-2 expression ($p<0.001$). While, there was no significant correlation with tumor size ($p=0.113$), age ($p=0.99$) and menstrual status ($p=0.99$). The 5-years disease free survival (DFS) was 88.7% for negative CD10 expression and 20% for positive expression ($p<0.001$). Multivariate analysis revealed that there was significant 5-years OS rate with CD 10 expression ($p=0.003$). Meanwhile, there were significant 5-years DFS rate with CD 10 expression ($p<0.001$), tumor size ($p=0.01$) and lymphovascular invasion ($p=0.006$).

Gupta D et al[24] prospective study reported scoring of steroid receptors paralleled intensity of hyperplasia in benign breast diseases but in breast carcinoma, it was inversely correlated with grade of tumor, NPI, HER2/neu status, tumor necrosis, lymphomononuclear infiltrate and elastosis and no relationship with tumor size, lymph node status or age. Assessment of hormone receptors for clinical management of breast cancer patients was strongly advocated to provide prognostic information and best therapeutic options.

CONCLUSION

Fibroadenoma of the breast is benign tumors characterized by an admixture of stromal and epithelial tissue. Microscopy has always been the mainstay of histological diagnosis in breast pathology. However, the immunohistochemical diagnosis for estrogen and progesterone receptors has proved to be advantageous and an aid in the diagnosis. Several cases of diagnostic dilemma such as invasion or pseudoinvasion, ductal or lobular type, and in situ or invasion can be reliably diagnosed by the use of immunohistochemical diagnosis of estrogen and progesterone receptors.

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