ORIGINAL ARTICLE

OESTROGEN AND PROGESTERONE RECEPTORS' EXPRESSION PATTERN IN FIBRO-ADENOMA OF THE FEMALE BREAST

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Background: Fibro-adenoma is the most common benign condition of the female breast comprising about 68% of all breast lumps. Fibroadenoma is an independent risk factor for the development of breast cancer. Complex fibroadenoma has a 2-3-fold increased risk ratio and simple fibroadenoma has 1.49 times increased risk ratio of developing cancer than the normal population over a period of 20 years. This study aimed to qualitatively check the frequency of oestrogen receptor-positive and progesterone receptor-positive cases of fibroadenoma in our region. **Methods:** This cross-sectional study was conducted in the pathology department of Ayub Medical College, Abbottabad from June 2020 to December 2021. Biopsy confirmed cases of fibroadenoma were examined using immune-histochemical stains to score qualitatively the expression pattern of ER and PR. Data was analyzed and assessed using SPSS version 25. A *p*-value of ≤0.05 was considered statistically significant. **Results:** The mean age of patients who presented with fibro-adenoma was 24.5±9.29 years with a median age of 21.5 years. In most cases, oestrogen receptor expression was mild 23 (54.76%) whereas progesterone receptor expression was severe 19 (45.23%). On chi-square test, the pattern of progesterone receptor expression for the category of hormone intake showed significant differences. Whereas, the pattern of oestrogen receptor expression for the categories of marital status, history of hormone intake, history of menstrual cycle and type of fibroadenoma showed no statistically significant difference. **Conclusion:** Further study into the pathogenesis of fibroadenoma is required to understand the role of ER and PR and explore the therapeutic potential of such drugs that affects these receptors. Cabling

Keywords: Fibro-adenoma breast; Oestrogen receptor expression; Progesterone receptor expression; immune-histochemical staining

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INTRODUCTION

Fibroadenoma a biphasic tumour, consists of intra-lobular stroma and epithelium lining the duct-lobular system of the breast.[1] It is the most common benign condition of the female breast comprising about 68% of all breast lumps.[2] Its gross histology shows a rubbery, greyish-white and well-encapsulated nodular mass.[1] It is an Aberration of Normal Development and Involution (ANDI) of breasts and not a malignant neoplasm as it arises from a whole lobule and is influenced by the hormones the same way as the normal breast tissue.[2] It enlarges during pregnancy and with the use of hormone therapy but regresses after menopause.[2] Fibroadenoma is a disease of young females with an average age of 15–25 years. The overall occurrence of FA is 2.2% in the general young population.[1,3]

Fibroadenoma has been classified into the following types: Simple fibroadenoma - smaller than 3 cm in size and accounts for more than 70% cases of FA[4], Complex fibroadenoma - occurs mostly in older patients, has any of the features such as sclerosing adenosis, calcifications or papillary apocrine change[1], Multi-centric fibroadenoma - when more than three fibroadenoma occurs in the same breast. This type accounts for 10–25% of cases[4], Giant Juvenile fibroadenoma - girls under 16 years of age can present with an enormously increased size of fibroadenoma of more than 5 cm and more than 500 grams weight and can occur with a frequency of about 0.5–2%[5].

Fibroadenoma is an independent risk factor for the development of breast cancer. Complex fibroadenoma has a 2-3 fold increased risk ratio and simple fibroadenoma has 1.49 times increased risk ratio of developing cancer than the normal population over a period of 20 years.[6,7] The overall risk of development of cancer in a fibroadenoma is about 0.002–0.125%.[3] The risk factors for the development of fibroadenoma as has been reported are high socioeconomic status, early menarche, and family history of breast cancer in the first-degree relative and use of hormonal contraceptive pills before 20 years of age.[7,8]

The diagnosis of fibroadenoma can be confidently made 99.9% of the time using the Triple

Assessment which includes a detailed history and clinical examination, imaging, and histopathology.[9] A prospective study on multi-centric fibroadenoma with a follow-up period of 10 years observed either a decrease or stability of size in 70% of cases of fibroadenoma over time. While a review article by Lee M *et al*. reported that fibroadenoma shows spontaneous regression in size in 10–40% of cases.[10, 4] Rangaswamy P *et al*. concluded that patients younger than 30 years of age having a simple fibroadenoma should be managed conservatively by the wait and follow-up protocol using ultrasonography every six months.[11] For the symptomatic case of fibroadenoma with size >3 cm, mastalgia, or from the dread of development of carcinoma, fibroadenoma can be surgically excised.[12]

At puberty, oestrogens prime the breast tissue by increasing progesterone receptors. Oestrogen not only causes ductal elongation and proliferation but also exerts permissive action on the powerful mitogenic effects of progesterone.[13] Talukdar MMI et al. studied the relationship of oestrogens, testosterone, and prolactin with Benign Breast Diseases and expressed that the cyclical variation of oestrogens and progesterone causes increased mitosis in the breast around day 22–24 of the menstrual cycle.[8,14] Therefore we want to qualitatively check the frequency of oestrogen receptor-positive and progesterone receptor-positive cases of fibroadenoma in our region and to assess the association of fibroadenoma with these hormone receptors.

MATERIAL AND METHODS

This cross-sectional study was conducted in the Pathology department of Ayub Medical College, Abbottabad from June 2020 till December 2021. A total of 42 patients who had biopsy proven fibroadenoma and had adequate biopsy specimens were enrolled after informed consent. Patients having co-existing breast pathologies such as fibroadenoma with usual ductal hyperplasia, carcinoma and those who did not consent were excluded from the study. Patients having true cut biopsies were also excluded due to non-availability of samples for Immuno-histochemical analysis. Data on the sociodemographic details and other parameters of the patient's health were collected on a self-developed proforma after a thorough history of the disease from the patient by a consultant pathologist. Consent for the use of tissue blocks (biopsy samples) to be utilized for further testing for the oestrogen receptors and progesterone receptors expression pattern analysis was taken from each patient. The paraffin embedded tissue blocks of biopsy confirmed cases of fibroadenoma were sent to health diagnostic services Islamabad for immune-histochemical studies. 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.

Data was analyzed and assessed using SPSS version 25. Post-stratification, the Chi-square test was applied to the pattern of ER and PR expression comparing it in the categories of marital status, history of hormone imbalance and hormone supplementation therapy. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The mean age of patients who presented with fibroadenoma was 24.5±9.29 years with a median age of 21.5 years. The youngest patient was 15 years old and the eldest one was 48 years of age.

Table-1 shows the general characteristics of the study population. The majority of the patients were unmarried 29/42 (69%), had not taken hormones supplement therapy for more than six months 24/42 (57.1%) and had irregular menstrual cycles 22/42 (52.4%).

Figure-1 shows the prevalence of each type of fibroadenoma in our population. The highest percentage of patients had simple fibroadenoma, i.e., 28/42 (66.7%) patients, followed by multi-centric fibroadenoma in 10/42 (23.8%) patients, and the number of patients who presented with Giant Juvenile fibroadenoma were 4/42 (9.52%) patients.

Figure-2 shows the pattern of oestrogen and progesterone receptors expression in the fibroadenoma of the studied population, shown by the bar charts. In most cases, mild oestrogen receptor expression was noted- 23/42 (54.76%) cases whereas severe progesterone receptor expression was noted in 19/42 (45.23%) cases.

Table 2 shows the pattern of oestrogen receptor expression for the categories of marital status, history of hormone intake for either contraception or dysfunctional uterine bleeding (either progestogens or both oestrogen and progestogen combined), history of menstrual cycle and type of fibroadenoma. No significant difference was found for either of the categories with respect to the oestrogen receptor expression pattern on the chi-square test.

Table-3 shows the pattern of progesterone receptor expression for the categories of marital status, history of hormone intake for more than six months, history of menstrual cycle and type of fibroadenoma. A significant difference was found only for the category of history of hormone intake (either progestogens or both oestrogen and progestogen

combined) with respect to progesterone receptor expression pattern on the chi-square test.

Figure-3 is an H&E-stained slide of the fibroadenoma of one of our study participants. It shows distorted slit-like glands with abundant fibro myxoid stroma.

Table-1: General characteristics of the studied population

Characteristics	Frequency	Percent
Married	13	31
Unmarried	29	69
Hormone therapy taken	18	29.9
Not taken	24	57.1
Regular Menstrual history	20	47.6
Irregular Menstrual history	22	52.4

Table-2: ER expression Pattern

Characteristics	Mild	Moderate	Severe	Chi-Square Test
Unmarried	13	13	3	0.126
Married	10	3	0	
Negative Hx of Hormone Intake	12	10	2	0.767
Positive Hx of Hormone Intake	11	6	1	
Regular Menstrual Cycle	12	7	1	0.766
Irregular Menstrual Cycles	11	9	2	
Simple fibroadenoma	15	10	3	0.777
Giant Juvenile fibroadenoma	2	2	0	
Multicenter fibroadenoma	6	4	0	

Table-3: Pattern of PR expression

Characteristics	Mild	Moderate	Severe	Chi-Square Test
Unmarried	9	9	11	0.206
Married	1	4	8	
Negative Hx of Hormone Intake	9	7	8	0.045
Positive Hx of Hormone Intake	1	6	11	
Regular Menstrual Cycle	7	6	7	0.234
Irregular Menstrual Cycles	3	7	12	
Simple fibroadenoma	5	7	16	0.153
Giant Juvenile fibroadenoma	1	1	2	
Multicenter fibroadenoma	4	5	1	

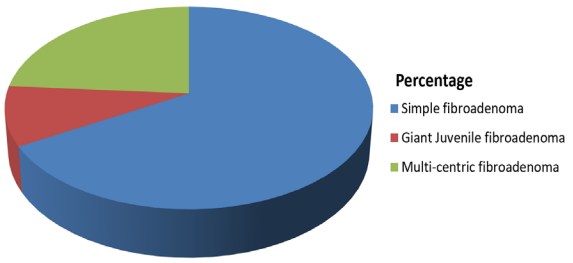

Figure-1: Prevalence of each type of Fibroadenoma

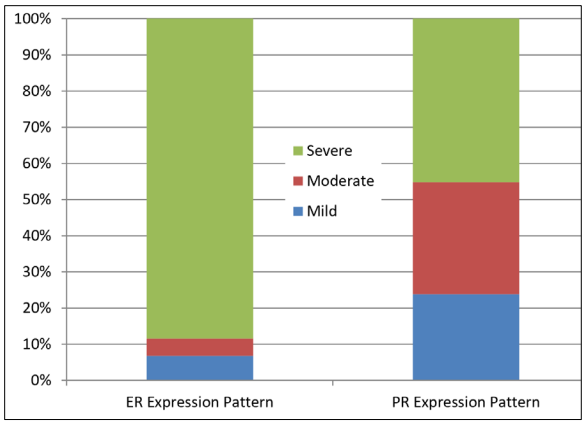

Figure-2: ER and PR Expression Pattern

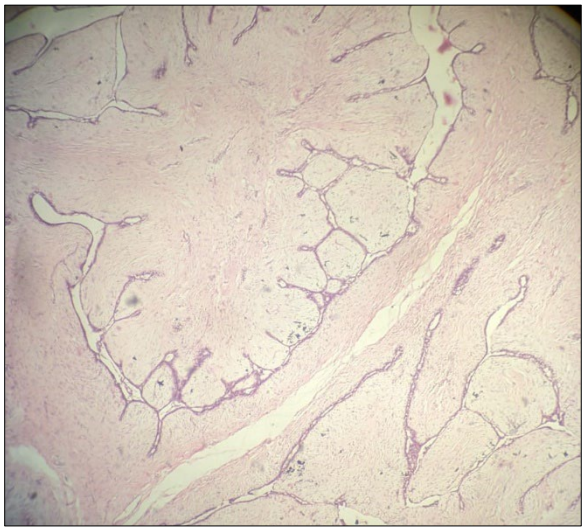

Figure-3: Picture of Fibro-adenoma

DISCUSSION

Morphologically, the fibroadenoma is a firm to hard, greyish-white, encapsulated mass lesion with a white surface on the cut section.[17] fibroadenoma can occur at a very young age causing extreme distress for the patients and the parents.[18] A study discussed the association of fibroadenoma with the age at menarche and family history showing a significantly increased risk with a positive family history and early age at menarche.[19] In this study, the mean age of the 42 patients included in the study was calculated to be 24.5±9.29 years. This finding correlates with international data where most researchers have reported the mean age for the occurrence of fibroadenoma in the 3rd decade of life.[11,14,17]

The lifetime risk of women for fibroadenoma is approximately 10%.[17] Studies suggest that it is difficult for the FNAC alone to diagnose and differentiate fibroadenoma from Phyllodes tumour; therefore, they suggest a biopsy and histopathology examination of the tissue under the light microscope

for proper diagnosis and typing of the fibroadenoma.[20] The most common type of fibroadenoma in our patients was simple fibroadenoma 66.7% of cases, followed by multicenter fibroadenoma in 23.8% of cases and Giant juvenile fibroadenoma in 9.52% of cases. Studies show the highest percentage of prevalence for simple fibroadenoma followed by multi-centric fibroadenoma and a rare occurrence of Giant Juvenile fibroadenoma.[20,21] Among all fibroadenomas, multi-centric fibroadenomas account for 10–25% of cases.[2,22]

The immuno-histochemical analysis showed the progesterone receptor expression pattern to be more severe compared to the estrogenic receptor expression pattern. It means that cases of fibroadenoma showed a greater amount of progesterone receptors than oestrogen receptors. Researchers have reported the expression of both oestrogen and progesterone receptors by fibroadenoma.[23] Grouthier V *et al* has reported a positive impact of progestogens particularly lynestrenol, on the evolution of fibroadenoma.[10] Branchini G. *et al*. observed higher levels of progesterone receptor A and B expression in fibroadenoma as compared to normal breast tissue.[15] Cericatto R *et al*. reported an exaggerated expression of oestrogen receptor alpha in the fibroadenoma as compared to the normal tissue.[16] These studies provide evidence of the role of oestrogen and progesterone in the pathogenesis of fibroadenoma.

Stratification was done for the oestrogen and progesterone receptors expression for the categories of marital status, history of hormone intake, history of menstrual cycle and type of fibroadenoma. Other than the category of history of hormone intake with respect to progesterone receptor expression pattern, no significant association was found for any other category with either the oestrogen or progesterone receptors. The patients who had no previous history of hormone intake had more mild expression pattern for progesterone receptors where as those who had a history of hormone therapy had a pattern of severe expression of progesterone receptors. Researchers are exploring the non-surgical therapeutic alternatives by targeting the anti-estrogenic/ anti-progestogenic and anti-proliferative properties of such drugs to suppress the growth and proliferation of fibroadenoma.[24]

CONCLUSION

Fibroadenoma is a benign disease of adolescent and young adult females causing distress and anxiety in the patients due to disfigurement. So, for aesthetic purposes, surgical options are often opted by the patient that does carry the potential of scarring. Further study into the pathogenesis of fibroadenoma is required to understand the role of ER and PR and explore the therapeutic potential of such drugs that affects these receptors.

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AUTHORS' CONTRIBUTION

SN, OK, EAKA: Literature search. SN, SN, HS: Conceptualization of study design, data collection, data interpretation, write-up. SN, HS, KA: Proofreading.

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