Section: Pathology

Original Research Article

STROMAL EXPRESSION OF P53 AND KI67 IN FIBROADENOMA: A PROSPECTIVE EVALUATION STUDY

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Received : 02/11/2023
Received in revised form : 01/12/2023
Accepted : 13/12/2023

Keywords:
Fibroadenoma, Markers, Tumor, P53, KI67, Morphological, Immunohistochemistry.

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DOI: 10.47009/jamp.2023.5.6.161

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (6); 774-777

Abstract

Background: Fibroadenoma accounts for the vast majority of benign biphasic breast tumour. It mainly developed in younger women. The present study aimed to evaluate the stromal expression of p53 and ki67 in fibroadenoma. **Materials and Methods:** This study was conducted in the department of Pathology, Government Medical College, Thiruvanthapuram, Kerala. A total of 94 fibroadenoma cases were included in the study based on inclusion and exclusion criteria. All the patient's demographic data was collected and informed consent was obtained. The tissues were analyzed for expression of P53 and KI67 expression. The data was analyzed by Statistical Package for Social Sciences (20.0) version. **Result:** This study had 94 fibroadenoma. In this 89 was fibroadenoma and 5 are juvenile fibroadenoma. Maximum number of patients had age between 21-40 years. 47 patients had a tumor size between 2-5 cm diameter. Mitosis, increases stromal cellularity and stromal overgrowth were absent in all the samples of fibroadenoma. Less than 10 % stromal expression was observed for P53 and Ki-67 in all samples of fibroadenoma studied. **Conclusion:** The study concludes that stromal expression of p53 and KI67 markers cannot be used as diagnostic tool for the diagnosis fibroadenoma and differentiating it from phyllodes tumour.

INTRODUCTION

Fibroadenoma is a common benign proliferative breast lesion typically occurring in a younger age group (20-35 years).[1-3] It is well circumscribed, movable lesion and can be solitary or multiple, unilateral or bilateral. Histologically it is similar to phyllodes tumour, that is, both lesions have two components: Epithelial and stromal. Some studies suggest that phyllodes tumour and fibroadenoma arise as intralobular tumour and it is often difficult to distinguish phyllodes tumour from large fibroadenoma. Fibroadenoma often causes no pain. It ca feel smooth and rubbery.[4] The cause of fibroadenoma is not known. They might be related to hormonal changes in the body. They are mainly classified as follows complex fibroadenomas, giant fibroadenomas and phyllodes tumours.[5] Recent studies showed that mutations of p53 and KI67 gene are among the commonest detected in human malignancies. p53 is a tumour suppressor gene, i.e., its activity is to stop formation of tumour. It is located on chromosome 17p13.1, it encodes for a 53kDa nuclear phosphoproteins that is expressed in all normal cells at low levels.[6,7] Mutant p53 protein acquire oncogenic properties enabling them to promote invasion, metastasis, proliferation and cell survival.[8,9] KI67 is essential for formation of the peri chromosomal layer, a ribonucleoprotein sheath coating the condensed chromosomes.[10] In thus structure KI67 acts to prevent aggregation of mitotic chromosomes. With this background the present study aimed to evaluate the stromal expression of p53 and ki67 in fibroadenoma.

MATERIALS AND METHODS

Study Settings: The study was conducted in the department of pathology, Government Medical College, Thiruvanthapuram, Kerala.
Study period: This descriptive study was conducted for the period of 2 years.
Procedure: All fibroadenoma cases were included in the study during the study period. Gross features like size of the tumor, margin of the tumor was assessed. Representative formalin fixed paraffine embedded

ISSN (O): 2687-5365; ISSN (P): 2753-6556

sections of the tumour will be stained with H & E and microscopy was studied based on stromal cellularity, mitosis, stromal overgrowth, stromal atypia and histological typing was done according to WHO criteria. Sections were immunostained with IHC markers p53 and Ki67 antibodies to study their expression in each of the specimen. The p53 expression and Ki-67 antigen (MIB-1 index) were defined as the percentage of positive nuclear staining after counting five hundred neoplastic stromal cells. We separate the percentage of p53 and Ki-67 into four groups as follows: 0-10%, 11-30%, 31-50% and 51- 100%.

Statistical Analysis: The data was expressed in number, percentage, mean and standard deviation. Statistical Package for Social Sciences (SPSS 20.0) version used for analysis. Microsoft excel 2003 version used for analysis.

RESULTS

This study was included 94 fibroadenoma cases. [Table 1] In this 5 are juvenile fibroadenoma. 45 patients had age between 21-40 years, 34 had <20 age between in fibroadenoma. In juvenile fibroadenoma 5 patients had <20 years. 47 patients had 2-5 cm size a diameter in fibroadenoma and 4 had 5-10 cm in juvenile fibroadenoma. 89 in fibroadenoma and 5 juvenile fibroadenoma are absent with gross infiltration. Mitosis, microscopic infiltration, increased stromal cellularity and stromal overgrowth was absent in both fibroadenoma and juvenile fibroadenoma. [Table 2]. P53 and Ki-67 expression was expressed less than 10% in fibroadenoma and juvenile fibroadenoma [Table 3].

Table 1: Distribution of tumors

Type	Number	Percentage (%)
Fibroadenoma	89	94.6
Juvenile fibroadenoma	5	5.4
Total	94	100

Table 2: Demographic data

Observations		Fibroadenoma		Juvenile fibroadenoma	
		N	%	n	%
Age (Years)	<20	34	38.20	5	100.00
	21-40	45	50.60	0	0.00
	41-60	9	10.10	0	0.00
	>60	1	1.10	0	0.00
Size in diameters (cm)	<2	40	44.90	0	0.00
	2-5	47	52.80	1	20.00
	5-10	2	2.30	4	80.00
	>10	0	0.00	0	0.00
Gross infiltration	Present	0	0.00	0	0.00
	Absent	89	100.00	5	100.00
Mitosis	Absent	89	100.00	5	100.00
	1-5/10hpf	0	0.00	0	0.00
	5-9/10hpf	0	0.00	0	0.00
	>10/10hps	0	0.00	0	0.00
Microscopic infiltration	Present	0	0.00	0	0.00
	Absent	89	100.00	5	100.00
Increased stromal cellularity	Present	0	0.00	5	1000.00
	Absent	89	100.00	0	0.00
Stromal overgrowth	Present	0	0.00	0	0.00
	Absent	89	100.00	5	100.00

Table 3: Gross morphology of fibroadenoma

Observations		Fibroadenoma		Juvenile fibroadenoma	
		n	%	n	%
P53 expression	<10%	89	100.00	5	100.00
	11-30%	0	0.00	0	0.00
	31-50%	0	0.00	0	0.00
	51-100%	0	0.00	0	0.00
Ki-67 expression	<10%	89	100.00	5	100.00
	11-30%	0	0.00	0	0.00
	31-50%	0	0.00	0	0.00
	51-100%	0	0.00	0	0.00

DISCUSSION

Fibroadenoma accounts for the vast majority of benign biphasic breast tumours. It is a circumscribed breast neoplasm arising from terminal duct lobular unit with both epithelial and stromal proliferation. Fibroadenomas occur usually in younger women, ages 20 to 30 years, but may also be seen in postmenopausal age groups. An increased likelihood of developing fibroadenoma has been observed in female transplant recipients treated with cyclosporine

ISSN (O): 2687-5365; ISSN (P): 2753-6556

with arrest in progression by changing the immunosuppressant. They are slow-growing tumours, with a size of less than 3 cm, except in the case rare giant fibroadenomas.[11] They present as solitary painless, firm, slow growing, mobile, well-defined nodule of up to 3 cm in diameter. Rarely present as multiple nodule which arise synchronously or metachronously in both or same breast. It can also present as very large mass (up to 20cm), mainly in adolescents. Grossly they are ovoid and well circumscribed cut surface being grey or white, solid, rubbery, bulging with faint lobulations and slit like spaces. Calcification and myxoid areas can occur. Microscopically, fibroadenomas show biphasic growth with epithelial and stromal proliferation with stroma showing latter may show a predominant intracanalicular or pericanalicular growth pattern with varying degrees of cellularity, but neither pattern is prognostically important. Intracanicular pattern is caused by compression of ducts into clefts by proliferating stromal cells. Stroma may sometimes show focal or diffuse cellularity (especially in young women < 20 years), bizarre multinucleated giant cells, extensive myxoid changes or hyalinization with dystrophic calcification and rarely ossification (especially in postmenopausal women). Myxoid fibroadenomas resemble myxomas.[12] Foci of lipomatous, smooth muscle, and osteochonroid metaplasia can rarely occur. Less frequently, foci of smooth muscle differentiation and foci of pseudoangiomatous stromal hyperplasia may be seen in fibroadenoma 1 Mitotic figures are uncommon but may be present in young or pregnant women. Cellular fibroadenoma shows prominent cellular stroma and shows features that overlap with those of phyllodes tumour and both fall into same spectrum of benign fibroepithelial tumours and possess low potential for local recurrence.[13] Complex fibroadenoma contains cysts > 3mm size, sclerosing adenosis, epithelial calcification, papillary apocrine hyperplasia and is reported to be having higher risk for the development of breast cancer and occur commonly in older age group, Juvenile fibroadenoma is seen mainly in adolescents and is characterised by increased stromal cellularity with fascicular stromal arrangement, pericanalicular epithelial growth pattern and usual ductal hyperplasia. Giant fibroadenomas are fibroadenomas with large size often more than 5 cm13 Being a benign tumour if conservative management of fibroadenoma is to be advocated, physical examination, sonography, and FNA should all be performed, and their results should be compatible with fibroadenoma. This is because, 30% of breast tumours that are diagnosed as fibroadenomas are found post surgically to be other types of benign lesions. In women older than 35 years, mammography should also be carried out due to increased risk of carcinoma breast. Because there is an increased incidence of carcinoma in older women, it is recommended that two different treatment approaches for fibroadenomas in women younger and older than 35. Women for whom fibroadenoma is diagnosed before the age of 35, it is recommended that a conservative management with a protocol of follow-up every 6 months in order to detect any changes of the lesion. In cases of regression, the follow-up should continue until there is complete regression. Fibroadenomas that either do not completely regress, or which remain unchanged by the age of 35, should be excised surgically. Fibroadenomas that become larger excision should be done without delay. If the patient is having a family history of breast cancer, or known changes of complex fibroadenoma, excisional biopsy is recommended shortly after diagnosis has been established. When detected in a woman older than 35 years of age, and all the findings of diagnostic modalities (including mammography) support diagnosis as fibroadenoma, a short follow-up period of 6-12 months is justified because other benign changes may resolve and an operation can be obviated). After 12 months, if there is any persistent fibroadenoma should be excised. Woman with multiple fibroadenomas can be treated in the same way as in the same manner as a woman with a single lesion.[14] Katie T et.al. study aimed to use DNA promoter methylation profiling selected genes to learn more about the biology of fibroadenoma.[15] Expression of genes are very low in the fibroadenoma.

CONCLUSION

The present study concluded that stromal expression of p53 and KI67 cannot be considered as effective markers for the diagnosis of fibroadenoma and it does not have role in distinguishing fibroadenoma from phyllodes tumour. Histopathological assessment remains the practical gold standard in diagnosing and discriminating fibroadenoma and phyllodes tumour.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556