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STUDY OF STROMAL ELASTOSIS IN PREMALIGNANT AND MALIGNANT BREAST LESIONS AND ITS ASSOCIATION WITH HORMONE RECEPTORS STATUS IN MALIGNANCY

Pathology

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ABSTRACT

Background: The most prevalent cancer in women worldwide and the main cause of mortality is breast cancer. Elastosis is a common occurrence in female breast lesions that has been extensively researched. **Aims And Objective:** This study showed presence of stromal elastosis in premalignant and malignant breast lesions and its association with hormonal receptors status in malignant lesions of breast. **Materials And Method:** This study was conducted at Department of Pathology, Gandhi Medical College, Bhopal from January 2021 to June 2022. Total 100 breast lesions specimens were submitted for histopathological diagnosis. Out of 100 cases, 18 cases were premalignant lesions, while rest 88 were malignant lesions and out of these 88 malignant lesions, 19 were non invasive while 63 were invasive. **Results:** In the present study out of 18 premalignant lesions, 83.3% were reported as grade0 and 16.7% reported as grade1 of stromal elastosis. Out of 63 invasive lesions, reported grade0 in 28.6% of patients followed by grade1 (27%), grade2 (25.4%) and grade3 (19%) of stromal elastosis. Showing significant association between stromal elastosis with invasive lesion. Majority (43.8%) of subjects with ER/PR+, Her2+ reported elastosis grade2. Showing significant association between stromal elastosis with hormonal receptor status of tumor. **Conclusion:** Stromal changes like elastosis during progression of the breast cancer leads to the possible identification of new treatment targets for the breast cancer lesion. Mostly, cases were falling in group of luminal A were showing marked elastosis.

KEYWORDS

Breast Lesions, Elastosis, Hormonal receptors status.

INTRODUCTION:

The leading cause of cancer-related death in women worldwide is breast cancer. The developing low- and middleincome countries account for over 70% of deaths from breast cancer. [1]

Number of clinical, pathologic, and molecular characteristics, including the traditional prognostic variables of histologic type, grade, tumour size, and lymph node metastases, are connected to prognosis.[2] Estrogen and progesterone receptors (ER, PR) as well as, more recently, HER-2/neu, have a growing impact on treatment. [3]

The epithelium and the stroma are the two main components that build up the normal breast tissue. Extracellular matrix, specific mesenchymal cells, leukocytes, as well as the vasculature, are all parts of the tumour stroma.[4] The extracellular matrix (ECM) is a complex network mostly made up of fibronectin, elastin fibres, interstitial collagen, and other proteoglycans. In breast carcinoma, an excessive buildup of ECM components is seen. The stroma that surrounds the malignant cells in breast tumours, which offers support and a better environment for tumour cell growth. [5]

The prominent feature is the elastosis, or aggregation of elastin fibres in and around the tumour. The quantity of these fibrils varies depending on the kind of lesion; in benign breast lesions, present along with the number of dysplastic cells, whereas in malignant lesions, the quantity is significantly higher. [1]

The surrounding stroma undergoes neovascularization, inflammatory cell influx and extensive remodelling of extracellular matrix in the form of fibrosis and elastosis as a result of the basement membrane being penetrated through a process of degradation. [6]

Shivas and Douglas classified elastosis into four classes in 1972, with grade 0 denoting no elastosis and grade 3 denoting numerous dense clusters of elastic fibres. They discovered that female breast tumours with high levels of elastosis had a better prognosis. Hematoxylin-eosin stained sections show eosinophilic hyaline acellular regions as elastosis, while Verhoeff's VanGieson stained sections show a black colour. [7]

MATERIALS AND METHODS:

This study was conducted at Department of Pathology, Gandhi Medical College, Bhopal from January 2021 to June 2022. All the cases histologically diagnosed as breast lesions in female patients were included in the study. The clinical details like age, sex, laterality, duration of symptoms, size of the tumour, axillary lymph node status were recorded in each case. Total 100 breast specimens (mastectomy, lumpectomy and biopsy) were submitted and histopathological study of the specimens was done by Haematoxylin and Eosin staining as per standard protocol and elastosis grading using veroeff-van gieson stain for elastic tissue. IHC was done for ER, PR and HER2/neu expression only in Invasive malignant cases.

VERHOEFF-VAN GIESON STAINING:

5 um tissue sections were cut, de-paraffinize and hydrate slides to distilled water, stain in Verhoeff's solution for 10 mins. Tissue should be completely black then rinse in distilled water 2-3 times. Differentiate in 2% ferric chloride for 15seconds. Stop differentiation with several changes of tap water and check microscopically for black elastic fiber staining and gray background, then wash in running tap water for 5 minutes. Counterstain in Van Gieson's solution for 1-2 minutes. Sections were stained, mounted with DPX, and allowed to dry. The tissue cells showing dark black colour elastic fibrils under a 40X light microscope. [8]

Grading of elastosis according to Shivas and Douglas [9]

Grade 0:-No elastosis.
Grade 1:- Small deposits (single elastin fibrils or a thin rim of elastosis around ducts) were present.
Grade 2:- Thicker zones of elastosis were found.
Grade 3:- Large deposits dominated substantial areas of tumour.

RESULTS:

In our study, total of 100 samples were examined. Most of cases were in the age group of more than 45 years. The age of the patients was ranged from 27 to 80 years. Mean age of cases in our study was 52.6 years. Mean age of menarche and menopause was 12.9 years and 45.3 years, respectively.

Table 1: Distribution Of Patients On The Basis Of Histopathological Findings

Sl. No	Histopathological finding	Frequency (n=100)	Percentage (%)
1	Premalignant		
A	Usual Ductal Hyperplasia (UDH)	7	7.0
B	Atypical Ductal Hyperplasia (ADH)	11	11.0
2	Non Invasive malignant		
A	Ductal Carcinoma in situ (DCIS)	15	15.0
B	Lobular carcinoma in situ (LCIS)	4	4.0
3	Invasive malignant		
A	Invasive ductal Carcinoma (IDC)	53	53.0

B	Mucinous Carcinoma	4	4.0
C	Medullary Carcinoma	3	3.0
D	Invasive lobular carcinoma (ILC)	2	2.0
E	Bilateral lobular Carcinoma	1	1.0
	Total	100	100

Histopathological examination revealed that Invasive ductal Carcinoma was the most common (53%) type of cancer which was followed by Ductal Carcinoma in situ (15%), Atypical Ductal Hyperplasia (11%), Usual Ductal Hyperplasia (7%), Lobular carcinoma in situ (4%), Mucinous Carcinoma (4%), Medullary Carcinoma (3%), Invasive lobular carcinoma (2%) and Bilateral lobular carcinoma (1%).

Table 2: Distribution Of Patients On The Basis Of Grade Of Stromal Elastosis

Sl.No	Stromal Elastosis	Frequency (n=100)	Percentage (%)
1	Grade 0	46	46.0
2	Grade 1	26	26.0
3	Grade 2	16	16.0
4	Grade 3	12	12.0
	Total	100	100

46% of cases reported as grade 0, which was followed by grade 1 (26%), grade 2 (16%) and grade 3 (12%)

Table 3 Distribution Of Patients On The Basis Of Subtypes Of Receptors (n=63)

Sl.No	Ssubtype	Frequency (n==63)	Percentage (%)
1	ER/PR+, Her2+	16	25.4
2	ER/PR+, Her2-	14	22.2
3	ER/PR-, Her2+	6	9.5
4	ER/PR-, Her2-	27	42.9
	Total	63	100

In invasive malignant cases only, subtype ER/PR+, Her2+ and ER/PR+, Her2- was observed in 25.4% and 22.2% of patients respectively. Subtype ER/PR-, Her2+ and ER/PR-, Her2- was observed in 9.5% and 42.9% of patient respectively

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Table 4 Comparison Of Grade Of Stromal Elastosis With Premalignant And Invasive Lesion

			Lesion type		Total	p value
			Premalignant	Invasive		
Stromal ealstosis	Grade 0	n	15	`18	33	0.0002
		%	83.3	28.6	40.7	
	Grade 1	n	3	17	20	
		%	16.7	27.9	24.7	
	Grade 2	n	0	16	16	
		%	0.0	25.4	19.8	
	Grade 3	n	0	12	12	
		%	0.0	19.0	14.8	
Total	n		18	63	81	
	%		100	100	100	

Premalignant lesions reported grade 0 (83.3%) and grade 1 (16.7%) of stromal elastosis. Although, invasive lesions, reported grade 0 in 28.6% of patients followed by grade 1 (27%), grade 2 (25.4%) and grade 3 (19%) of stromal elastosis. **P = 0.0002** indicates that there is **significant association between stromal elastosis with premalignant and invasive lesion.**

Table 5: Comparison Of Grade Of Stromal Elastosis With Non Invasive And Invasive Malignant Lesion

			Lesion type		Total	P value
			Non invasive	Invasive		
Stromal elastosis	Grade 0	N	13	18	31	0.008
		%	68.4	28.6	97.0	
	Grade 1	N	6	17	23	
		%	31.6	27.0	58.6	
	Grade 2	N	0	16	16	
		%	0.0	25.4	25.4	
	Grade 3	N	0	12	12	
		%	0.0	19.0	19.0	
Total		N	19	63	82	
		%	100	100	100	

Noninvasive lesions reported grade 0 (68.4%) followed by grade 1 (31.6%) of stromal elastosis. Although, invasive lesions, reported grade 0 in 28.6% of patients followed by grade 1 (27%), grade 2 (25.4%) and grade 3 (19%) of stromal elastosis. **P = 0.008** indicates that there is **statistically significant association between stromal elastosis with noninvasive and invasive lesion**

Table 6: Association of ER/PR/Her2neu Subtype Status With Stromal Elastosis

			Molecular subtype				Total	P value
			ER/PR+, Hre2+	ER/PR+, Her2-	ER/PR-, Her2+	ER/PR-, Her2-		
Stromal elastosis (Grade)	0	N	3	0	2	12	17	< 0.001
		%	18.8	0.0	33.3	44.4	27.0	
	1	N	2	0	4	12	18	
		%	12.5	0.0	66.7	44.4	28.6	
	2	N	7	7	0	2	16	
		%	43.8	50.0	0.0	7.4	25.4	
	3	n	4	7	0	1	12	
		%	25.0	50.0	0.0	3.7	19.0	
Total		n	16	14	6	27	63	
		%	100.	100.0	100.0	100.0	100.0	

P value of **<0.001** indicates that there is highly significant association between stromal elastosis with tumor subtypes. Majority (43.8%) of subjects with ER/PR+, Her2+ reported elastosis grade 2. 50% of subjects with ER/PR+, Her2- found grade 2 and grade 3 each. 66.7% of subjects with ER/PR-, Her2+ had grade 1 followed by grade 0 (33.3%). Around 88.8% of subjects with ER/PR-, Her2- had grade 1 and 2.

DISCUSSION:

The clinical spectrum of breast cancer is broad. Despite having similar histologic presentations at the time of disease diagnosis, it is impossible to conclude how long it will take for the disease to proceed and spread.

The existence of the hormone receptors ER and PR as well as the overexpression of the human EGFR-2 (HER-2) are crucial factors in determining the best course of treatment for breast cancer patients.

ELASTOSIS AND TYPE OF LESION

Table 7: Association Of Stromal Elastosis With Histological Type Of Lesions

Studies	Sample size	Observation
Toprak et al., (2022)	167	10 167 High elastic fiber score was more common (p = 0.001) in malignant lesions
Elasbali et al., (2018)	50	Elastic fibers in breast carcinoma are increased (P < 0.05).
Bindu et al., (2016)	90	Grade II malignant lesion having moderate to marked degree of elastosis.
Present Study	100	Present Study 100 Higher elastosis grades were associated with invasive lesions (p=0.008)

In present study, relation of elastosis grades with premalignant and malignant breast lesions. Stromal elastosis grade 0 was observed in 83.3% and grade 1 in 16.7% of total premalignant cases. No grade 2 or grade 3 observed in premalignant lesions. Out of total noninvasive lesions reported, 68.4% had grade 0 and 31.6% had grade 1 of stromal elastosis. Although, invasive lesions, reported grade 0 in 28.6% of patients followed by grade 1 (27%), grade 2 (25.4%) and grade 3 (19%) of stromal elastosis. Higher elastosis grades were present significantly more in invasive lesions than premalignant lesions (p = 0.0002). On comparing non invasive with invasive lesions with respect to elastosis grades, noninvasive lesions reported grade 0 (68.4%) followed by grade 1 (31.6%) of stromal elastosis. Although, invasive lesions, reported grade 0 in 28.6% of patients followed by grade 1 (27%), grade 2 (25.4%) and grade 3 (19%) of stromal elastosis. Higher elastosis grades were significantly associated with invasive lesions (p=0.008).

ELASTOSIS AND HORMOMAL RECEPTOR STATUS

Table 8: Association of stromal elastosis with hormonal receptors status

Studies	Observation
Abri et al.,1 (2021)	High elastosis and ER positivity was observed (p = 0.015)
Rasmussen et al, (1985)	Large amount of elastin is associated with intense estrogen positivity.
Present Study	High elastosis was found with ER/PR + cases (p < 0.001).

In present study, subjects with ER/PR+, Her2+ reported elastosis grade 2 (43.8%) followed by grade 3 (25%). 50% of subjects with ER/PR+, Her2- found grade 2 and grade 3 each. 66.7% of subjects with ER/PR, Her2+ had grade 1 followed by grade 0 (33.3%). Around 88.8% of subjects with ER/PR-, Her2- had grade 1 and 2. We noticed significant association of higher elastosis grade with ER/PR + cases (p < 0.001).

ASSOCIATION OF SBR GRADING WITH MOLECULAR CLASSIFICTION OF BREASTCARCINOMA

We found that subjects with ER/PR+, Her2+ were mostly had SBR grade II (56.3%) while subjects with ER/PR+, Her2- were mostly had grade III (64.3%). Most of the subjects with ER/PR-, Her2+ had grade II (66.7%) and those with ER/PR-, Her2- were mostly had grade II (48.1%) and III (37%). However, we didn't find any significant difference between them (p= 0.665).

CONCLUSION:

Important role of the stromal changes like elastosis during progression of the breast cancer leads to the possible identification of new treatment targets for the initial breast cancer lesion as well as prevention of its recurrence. In all cases of noninvasive and invasive malignant lesions of breast, elastosis should be carefully examined and considered for predicting the final outcome along with histological types to get the better results. We also arrived at the conclusion that most of the cases were falling in group of luminal A were found to have marked elastosis, indicating a link between hormone receptor expression and synthesis of elastin precursor.

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