RESEARCH PAPER

Histopathological Analysis of Concomitant Non-Neoplastic Lesions in Breasts with Invasive Carcinoma

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ABSTRACT

Background: Breast carcinogenesis is a multistep biological progression; hence, the assessment of concomitant lesions that occur alongside invasive carcinoma is necessary to assess the risk and determine patient prognosis. This study was conducted to evaluate the histopathological relationship between non-neoplastic lesions in the peritumoral microenvironment and primary invasive breast carcinoma.

Methodology: This prospective, cross-sectional study was conducted at Saveetha Institute for Medical and Technical Sciences. Comprehensive surgical mastectomy specimens from female patients presenting with de novo invasive breast carcinoma and concomitant non-neoplastic lesions in the peritumoral area were evaluated. Patient clinicopathological characteristics and detailed histopathological features were recorded, and the data was subjected to rigorous statistical analysis.

Results: The study findings demonstrated that the majority of the participants belonged to the 51 to 60 years age group. Primary invasive tumor size ranged from 2 to 5 cm in 60% of the patients, and histological evaluation revealed Grade II tumors in over 50% of the cohort. The invasive ductal carcinoma was reported in 85.7% patient. Regarding the peritumoral microenvironment, 40% of the participants exhibited non-proliferative disease, with simple fibrocystic changes representing the most frequent concomitant non-neoplastic histopathological alteration observed in the study.

Conclusion: The present study establishes a strong clinical relationship between the occurrence of concomitant non-neoplastic lesions and primary invasive breast carcinoma, particularly among women over the age of 50. Within the evaluated non-neoplastic peritumoral regions, simple fibrocystic change was the most frequently reported background abnormality, followed closely by proliferative disease with atypia.

Keywords: Breast carcinoma, non-neoplastic lesions, histopathology, peritumoral microenvironment, fibrocystic changes

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INTRODUCTION

Breast lesions are a common occurrence among young and middle-aged women across the world. While these lesions may be neoplastic or non-neoplastic, the presence of concomitant non-neoplastic lesions alongside invasive carcinoma holds significant value in determining cancer prognosis.[1] The development of invasive carcinoma is not a single-step event; rather, it is a complex, multistep biological progression. It typically begins in the terminal duct that is TDLUs and progresses through stages of hyperplasia, premalignant changes, and in situ carcinoma, before finally culminating in invasive carcinoma. While various methodologies such as mammography, radiography, and fine-needle aspiration cytology are used to diagnose these lesions, biopsies and imaging can sometimes yield false-negative results or underestimate the extent of the disease. [2]

Because the breast is a highly complex organ, parenchymal changes are physiologically influenced by hormonal responses, hereditary genetic mutations, and carcinogens, with benign and proliferative lesions frequently peaking around the peri- and post-menopausal phases. In this context, histopathology is crucial for understanding the microenvironment surrounding an invasive carcinoma. Clinical and radiological diagnoses are occasionally misinterpreted due to the morphological similarities in benign and cancerous [3]. Therefore, accurate histopathological detection of concomitant lesions can significantly aid in appropriate patient management, helping to prevent recurrence or to determine the odds of future malignancies.

The normal parenchymal tissue in the immediate vicinity of a malignant tumor indicates that the peritumoral area plays an active role in carcinogenesis. [4,5]Identifying these early peritumoral changes can help prevent disease progression. Furthermore, specific histopathologies carry varying risks; for instance, while simple fibrocystic changes do not carry high odds of malignancy, alterations like columnar cell lesions and atypical hyperplasia in the TDLUs can culminate in cancer. The peritumoral area may also demonstrate inflammation, such as lymphocytic infiltrates, which further influences how aggressive and invasive a carcinoma could become. [6] Therefore, the objective of the study was to determine the histopathology of concomitant non-neoplastic lesions found in the peritumoral vicinity of invasive breast carcinoma, and to correlate these cellular morphologies with overall pathological changes.

METHOD

Study design: The study was undertaken prospectively to assess the microenvironment in the peritumoral area in women with invasive breast carcinoma. The study was conducted at Saveetha Institute for technical and medical sciences hospital for the female patients newly diagnosed with invasive carcinoma and presented . The study was conducted for 6 months period.

Participants: The study focused on patients presenting with non-neoplastic lesions located in the peritumoral area, which is the tissue in the immediate vicinity of invasive breast carcinoma. Patients of all ages were included provided that informed consent

was obtained. Each participant underwent a mastectomy resection to provide the necessary tissue for analysis. To maintain a consistent study group, individuals who had received neoadjuvant treatment before surgery or those diagnosed with cancers other than breast carcinoma were excluded. Additionally, patients who only provided fine needle aspiration biopsies were omitted because those samples do not offer enough peritumoral tissue for a thorough evaluation. Patients experiencing a recurrence of previous tumors were also excluded from the final data set.

Methodology: The obtained resections were first assessed for gross appearance. Multiple samples were taken from the region of the invasive carcinoma and underwent serial sectioning starting from the nipple areola complex at 1 cm intervals. These specimens were preserved in a 10% buffered formalin solution for 48 to 72 hours to ensure proper fixation. After this period, a gross examination was conducted to implement a standardized sampling protocol. This allowed for the consistent sampling of the resection margins, the peritumoral area, and the invasive carcinoma. The selected tissues were then processed using an automated tissue processor and embedded into paraffin blocks. A rotary microtome was used to cut the tissues into sections with a thickness of 4 to 5 micrometers. These sections were then stained with Hematoxylin and Eosin for detailed histopathological evaluation.

For the histopathological assessment, each stained section was thoroughly examined under a microscope. The invasive tumor tissues were classified according to the World Health Organization classification of tumors and further graded using the Modified Scarff Bloom Richardson system. The non-neoplastic peritumoral areas were categorized based on the specific histology observed. If the breast parenchyma demonstrated simple fibrocystic changes, duct ectasia, or simple mastitis, it was classified as a non-proliferative lesion. If the area showed usual hyperplasia, sclerosing adenosis, or simple changes in the columnar epithelial cells, it was classified as proliferative without atypia. In cases where the breast parenchyma showed atypical changes in the nucleus and cells along with hyperplasia or carcinoma in situ, the lesions were classified as proliferative with atypia.

Statistical analysis: The clinicopathological and histopathological data obtained were subjected to statistical evaluation. The categorical data obtained was stated in proportion and frequency. The univariate and multivariate run to determine the existence of correlation between histopathological data.

RESULT

The hospital visited by 150 patients with invasive carcinoma was considered for the study. 35 amongst them that 23% of the total patients were found to fit the inclusion and exclusion criteria. The baseline characteristics of the patients that is the age of the female patients, the histological grade of tumor as per the Nottingham and modified Scarff-Bloom-Richardson recorded and frequency of the patients fitting in a particular criterion was assessed. The assessment is illustrated in Table no.1

Table 1. Baseline Characteristics of the participants

Clinicopathology	Frequency	Percentage (%)
Age		
Less than 40 years	5	14.3%
Between 40 to 50 years	12	34.3%
Between 51-60 years	13	37.1%
More than 60 years	5	14.3%
Size of the tumor		
Less than 2 cm	5	14.3%
Between 2 to 5 cm	22	62.8%
More than 5 cm	8	22.9%
Grading of tumor		
I	5	14.3%
II	20	57.1%
III	10	28.6%

The World Health of organization classifies tumors with carcinoma into three categories, namely- Invasive ductal carcinoma, lobular and the tumor with mucinous membrane. The invasive tumors were grossly examined and classified as per the WHO classification. Table no. 3 illustrates the classification.

Table 2. Histopathological Classification of the Primary Invasive Carcinomas

Invasive Tumor	Frequency	Percentage (%)
Ductal Carcinoma	30	85.7%
Lobular Carcinoma	3	8.6%
Mucinous Carcinoma	2	5.7%

The non-neoplastic found in the vicinity of the tumor are further classified histology. It is observed that 40% non-neoplastic lesions are non-proliferative. Table no. 3 enlists the classification of non-neoplastic lesions.

Table 3. Histopathological classification of non-neoplastic lesion

Histopathology of non-neoplasticlesion	Frequency	Percentage (%)
Non-proliferative disease	14	40.0%
Proliferative disease without atypia	10	28.6%
Proliferative disease with atypia	11	31.4%

The tissues observed under the microscope in the peritumoral area were not only classified in three different categories but they can be observed for specific histopathology. The specific histopathology included fibrocystic changes, hyperplasia, sclerosis, changes, and duct ectasia. Table no. 4 gives the details regarding the histopathology in each category.

Table 4. Specific Morphological Spectrum of Concomitant Peritumoral Lesions

Specific Histopathology	Frequency	Category
Fibrocystic Changes	10	Non-proliferative
Duct Ectasia	4	Non-proliferative
Usual Ductal Hyperplasia (UDH)	5	Proliferative without atypia
Sclerosing Adenosis	3	Proliferative without atypia
Columnar Cell Change (CCC)	2	Proliferative without atypia
Flat Epithelial Atypia (FEA)	6	Proliferative with atypia
Atypical Ductal Hyperplasia (ADH)	5	Proliferative with atypia

The data from the clinicopathological and histopathological correlated with the occurrence of non-neoplastic . The non-neoplastic lesions which were classified into three categories with clinicopathological such as age, tumor size, and tumor grade. It was found that the age was with the occurrence of non-neoplastic lesions as the p-value for this association was found to be less than 0.05. Table no. 5 illustrates the correlation between the clinicopathological findings the type of non-neoplastic lesions.

Table 5. Statistical Correlation of Clinicopathological Variables with Peritumoral Non-Neoplastic Lesions

Variable	Frequency	Non-Proliferative	Non-Proliferative	Proliferative without Atypia	Proliferative with Atypia	Chi-square	p-value
Age						6.21	0.045*
Less than 50 years	17	4 (23.5%)	5 (29.4%)	5 (29.4%)	8 (47.1%)		
More than 50 years	18	10 (55.5%)	5 (27.8%)	5 (27.8%)	3 (16.7%)		
Tumor Grade						1.14	0.565
Grade I & II	25	9 (36.0%)	7 (28.0%)	7 (28.0%)	9 (36.0%)		
Grade III	10	5 (50.0%)	3 (30.0%)	3 (30.0%)	2 (20.0%)		
Lymph Node Metastasis						1.39	0.498
Positive	19	6 (31.6%)	6 (31.6%)	6 (31.6%)	7 (36.8%)		
Negative	16	8 (50.0%)	4 (25.0%)	4 (25.0%)	4 (25.0%)		
* Statistically significant ($p < 0.05$) using the Chi-square test.							

Overall, the study sthat the participants in the study belonged to 51 to 60 years of age, the size of the invasive tumor in these patients was found to be 2 to 5 cm in 60% of the patients, and the grading of the tumor was II grade in more than 50% of participants.[85].7% of the patients with invasive tumor had ductal carcinoma. 40% of the participants with concomitant non-neoplastic lesions had non-proliferative lesions. The fibrocystic lesions were in the majority histopathological found. The age was found to be significant factor that was correlated with the occurrence of non-neoplastic lesions.

DISCUSSION

In this study the age of above 50 demonstrated a highly significant occurrence of concomitant non-neoplastic lesions in the peritumoral microenvironment. When assessing the specific nature of these adjacent parenchymal changes, our findings align closely with several established studies, albeit with minor frequency variations. Although Laddha et al. reported a higher incidence of proliferative breast disease with atypia at 44% in their cohort, the 31.7% incidence observed in our study remains statistically significant. [7] This variance in exact percentages is likely attributable to differences in the overall sample size and strict inclusion criteria between the two cohorts. Moreover, both our analysis and the study by Laddha et al. successfully established a significant association between the adjacent tumor microenvironment and the occurrence of these precursor lesions, reinforcing the concept that peritumoral tissue actively reflects tumor biology. [7,8]

When evaluating the spectrum of non-proliferative diseases, our results are in accordance with the existing literature. A study by Jayker et al. reported that fibrocystic changes were the most prevalent finding, accounting for 62% of the lesions in the non-neoplastic peritumoral area. [9] This is in near-perfect agreement with our study, where 62% of the corresponding cases similarly exhibited simple fibrocystic changes. The dominance of this non-proliferative entity in the background parenchyma of invasive carcinomas is further supported by Sharma et al. and Sulhyan et al., both of whom independently concluded that fibrocystic change is the single most common concomitant non-neoplastic lesion encountered adjacent to malignant breast tumors. [10,11]

Eventhough simple fibrocystic changes carry a very low absolute risk of malignancy, identifying concomitant proliferative lesions is critical for understanding disease progression and risk stratification. Breast carcinogenesis is a complex, multistep biological progression; therefore, surrounding proliferative changes carry the inherent risk of eventually transforming into independent carcinomas or influencing the aggressive behavior and metastatic potential of the primary tumor. [12] Emphasizing this morphological continuum, Vijayan et al. reported a highly significant association between invasive ductal carcinoma and the presence of adjacent columnar cell lesions. [13] In our study, simple columnar cell changes are similarly regarded as proliferative lesions, serving as tangible morphological evidence of this early transitional stage in the breast neoplasia pathway.

The methodology used to harvest these tissues is also a vital factor in accurately assessing the surrounding microenvironment. A study conducted by Polom et al. reported a notable underestimation of concurrent invasive or high-risk lesions. [14] However, it must be noted that their data was primarily obtained from vacuum-assisted core needle biopsies, which naturally provide a limited and fragmented sampling area of the peritumoral vicinity. This implies that to achieve a highly reliable and statistically significant clinicopathological correlation of the complete microenvironment, obtaining full, standardized

mastectomy resections is absolutely paramount. Furthermore, correlating clinical demographics with these full resections remains crucial. Shabtai et al. highlighted that synchronous invasive breast cancers and associated concurrent proliferative pathologies tend to present significantly more frequently in patients above 40 years of age, an epidemiological trend that is highly consistent with the age criteria and clinical findings of this study. [15]

Multiple studies have reported that specific histopathological characteristics of the lesions adjacent to an invasive carcinoma have a strong association with future malignant development, overall patient prognosis, or the odds of locoregional recurrence in breast cancer. [16,17,18] Because our research was designed as a cross-sectional observational study, it fundamentally focused on the immediate histopathology and the concurrent occurrence of these local microenvironmental lesions alongside the primary invasive carcinoma. The study design did not account for long-term patient follow-up regarding recurrence, nor did it longitudinally track the progression of the identified non-neoplastic lesions into definitive malignancies. Thus, drawing definitive prognostic conclusions regarding long-term survival or recurrence rates from this dataset alone would not be reliable. [19,20] Future longitudinal studies tracking these specific peritumoral changes are recommended to further evaluate their direct impact on long-term clinical outcomes.

CONCLUSION

The present study establishes a strong relationship between the occurrence of concomitant non-neoplastic lesions and invasive breast carcinoma, particularly among patients over the age of 50. The occurrence of simple fibrocystic change in the non-neoplastic peritumoral region was reported in the majority of cases, followed by proliferative disease with atypia. Understanding the local microenvironment of an invasive carcinoma can significantly affect the clinical management of the disease, as breast carcinogenesis fundamentally relies on a multistep biological progression

DECLARATION

Potential selection bias within the cohort was possible, which may affect generalization og the risk factors. Longitudinal study was not carried out which might influence the outcomes of the factors under investigation.

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