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Original Research Article

Histopathological Study of the Architectural Patterns of in Situ Carcinoma in Cases of Invasive Breast Cancer

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Abstract

Context: In situ carcinoma in breast can be studied at two levels:

1. different morphologic patterns

2. by utilizing a prognostic grading system like the Van Nuys system. This study would provide information regarding the patterns, classification, prognostic grading, also predict the risk of recurrence after excision and assist in selecting treatment options.

Aims:

- To estimate the cases displaying different architectural patterns of in situ carcinoma in invasive breast cancers.
- Determination of prognostic index (Van Nuys) of in situ carcinoma based on these patterns.

Methods and Material: A Cross sectional study of 40 Modified Radical Mastectomy specimens collected for a period of 18 months in our Tertiary care hospital. For histopathology study, specimens were fixed in 10% formalin, processed, paraffin embedded, sections (3-5 ì thickness) taken, stained with Haematoxylin and Eosin and studied under light microscope.

Statistical analysis used: Continuous variables are expressed as mean ±SD whereas categorical variables are expressed as percentages. Data was analysed using SPSS version 20. P value < 0.0 was considered as statistically significant.

Results: All architectural patterns of DCIS either single or mixed were present in the cases of invasive breast carcinoma, with solid [9 (36%) cases]: most common single architectural pattern and Solid and comedo [7 (47%) cases]: the most common mixed architectural pattern. High grade ductal carcinoma in situ was seen in 18 patients (45% of cases), intermediate grade in 17 patients (43%) and low grade was seen in 5 patients (12%).

Conclusions: The current study provides evidence of the frequency of significant histologic heterogeneity of in situ carcinoma, with at least 2 different architectural patterns of ductal carcinoma in situ commonly present in individual lesions.

Keywords: Ductal Carcinoma; In Situ Component; Histological Grading.

Introduction

Carcinoma of the breast is the most common carcinoma in women (31%) and is the second most common cause for cancer-related mortality [1]. The number of women with breast cancer is expected to increase by a third in the next 20 years [1,2].

Breast carcinoma is a group of genetically distinct diseases with different behaviors. Outcomes are maximized when therapy is tailored to individual patient and disease characters.[3] Breast carcinoma emerges by a multistep process which can be broadly equated to transformation of normal cells via the steps of hyperplasia, premalignant change and in situ carcinoma [4,5].

In situ carcinoma can be studied at two levels either by using the different morphological patterns or by using a prognostic grading system like the Van Nuys system.

Few studies have demonstrated that coexisting DCIS may be associated with less aggressiveness but not in others [6,7]. This study was conducted to describe the different architectural patterns of DCIS in invasive breast cancer patients and to assess whether associated with aggressiveness of the coexisting invasive ductal carcinoma.

Materials and Methods

The study included consecutive cases of invasive breast cancers with an in situ component over the period of three years from January 2011 to July 2014. For the retrospective study cases archived in the Department of Pathology, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru between January 2011 and July 2012 were selected. For the prospective study, specimens and slides received by the Department of Pathology, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, from August 2012 to July 2014 were included. Those patients who had underwent trucut biopsies or lumpectomy without axillary clearance, cases of exclusive carcinoma in situ without an invasive component and improperly fixed tissues were excluded from the study.

The medical records of the patients were examined and data regarding age, menopausal state, location of the tumor with respect to site (right or left) and quadrant (inner, outer or centre), size of tumor assessed clinically by palpation and mammography reports were noted.

The modified radical mastectomy specimens received were examined grossly for size, shape, colour and consistency. Changes in the nipple and skin were also noted wherever relevant. The mastectomy specimens were cut serially at a distance of 2- 3 cm. Cut surfaces were noted for tumor, colour, size, extension, involvement of skin and secondary changes such necrosis, cystic degeneration, haemorrhage and fibrosis. The axillary tail was dissected and as many nodes as possible were isolated in fresh state and their number and size were noted.

The specimen is then fixed in 10% formalin for 24- 48 hours. Several bits were taken from the tumor proper, its margins, nipple and lymph nodes. They were processed by the routine paraffin embedding technique and multiple sections were taken of 4- 6 microns thickness and stained with routine haematoxylin and eosin stain.

The in situ carcinoma cases are divided into pure and mixed patterns depending on the type of architectural pattern studied. If only a single pattern was present then it is termed 'pure' and if more than one pattern was noted then it is termed 'mixed'. Nuclear grading is based on the size of malignant cells nuclei in comparison to normal ductal epithelial cells. Grade 1, 2 and 3 were diagnosed when the nuclei of the malignant cells were between 1.5 and 2 times, 2 and 2.5 times and greater than 2.5 times that of normal ductal epithelial cells, respectively. The Van Nuys Prognostic Index (VNPI) combines three significant predictors of local recurrence: tumor size, margin width, and pathologic classification. Scores of 1 (best) to 3 (worst) were assigned for each of the 3 predictors and then totalled to give an overall VNPI score ranging from 3 to 9. [8]

Using the modified Bloom Richardson grading system, the resection specimens were classified into 3 grades based on the percentage of tubule formation, degree of nuclear pleomorphism and number of mitosis. Those with score 3-5, 6-7 and 8-9 were assigned a grade 1, 2 and 3 respectively. The digital images of the selected tissue preparations were photographed from the Olympus light microscope using a Sony Cybershot DSC-WX200/NCE32 digital camera.

Results

Forty patients who fulfilled the inclusion criteria were recruited for the study. The age of the study population was 46.4±11.7 years. Twenty patients (50%) were in the premenopausal and perimenopausal age group (< 47 years), ten patients (25%) were in the menopausal and postmenopausal age group each. In twenty five cases tumours were located in outer quadrants whereas in nine cases tumours were located in inner quadrants. In five cases tumour were located centrally whereas one case involved all the quadrants. Tumour size was smaller than 2 cm in seven (17.5%) patients, between 2 and 5 cm in 24 (60%) patients and larger than 5 cm in 9 (22.5%) patients. Twenty one tumours were classified as grade I, 13 tumours as grade II and 6 tumours as grade III on histology.

Various architectural patterns of ductal carcinoma in situ associated with 40 cases of invasive carcinoma are summarised in table 1 and representative photographs are depicted in figure 1. Pure patterns were observed in 24 patients whereas mixed forms were 16 patients. Solid pattern was the most common pure form whereas solid and comedo was the most common mixed pattern. None of the variables differed significantly between patients with pure form of DCIS and mixed forms (Table 2).

Necrosis was more commonly associated with comedo pattern (p=0.00021) and cribriform (p= 0.029) than solid patterns whereas it was more commonly associated with comedo pattern than micro papillary pattern (0.0047). Vascular invasion was more common in patients with solid pattern than those with comedo pattern (p=0.04) and cribriform pattern (p=0.017). Lymph node involvement stage 1 was more common in patients with solid pattern than those with other patterns (p= 0.015). Solid pattern was associated with lower histological grades than others. There were no significant differences with respect to any other variables (Table 3).

Necrosis was more commonly associated with solid and comedo pattern than micro papillary and cribriform pattern (p = 0.0233) and solid and cribriform pattern (p = 0.0112) whereas it was more commonly associated with

Table 1: Distribution of growth pattern in patients with invasive carcinoma

DCIS with a single growth pattern	**24 (60%)**
Micropapillary	1 (2.5%)
Cribriform	5 (12.5%)
Solid	11 (27.5%)
Comedo	7 (17.5%)
DCIS with a mixed growth pattern	**16 (40%)**
Solid and comedo	7 (17.5%)
Solid and cribriform	3 (7.5%)
Cribriform and micropapillary	2 (5%)
Solid, comedo and cribriform	3 (7.5%)
Solid, comedo and micropapillary	1 (2.5%)

Table 2: Comparison of variables between patients with single and mixed ductal carcinoma in situ patterns

	Single (24)	Mixed (16)	P value
Age (years)	47.46±11.38	46.56±11.46	0.809
Tumour size (cm3)	56.30±98.11	31.22±38.07	0.337
Maximum tumor dimension (cm)	3.79±2.30	4.66±2.50	0.267
Quadrants - Outer: inner: central: all	15: 4: 4:1	13: 1: 2: 0	0.285
VNIP score	6.04±1.46	6.12±1.14	0.849
Tubule formation (%)	15.08±10.09	15.00±10.32	0.980
Mitotic figure/hpf	7.67±6.15	6.25±7.61	0.520
Nuclear grade	2: 10: 12	2: 7: 7	0.89
Paget's disease of the nipple – Yes/No	1:23	0:16	0.6
Skin discolouration – Yes/No	12:12	9:7	0.475
Necrosis – Yes/No	11:13	10:6	0.239
Calcification – Yes/No	11:13	5:11	0.278
Lymphatic invasion – Yes/No	9:15	3:13	0.181
Perineural invasion – Yes/No	1:23	1:15	0.646
Vascular invasion – Yes/No	8:16	4:12	0.420
Lymphnode involvement – 0: 1: 2: 3	2: 11: 9: 2	0: 7: 7: 2	0.659
Histological grade – 1:2:3	15: 5: 4	7: 7: 2	0.300

Table 3: Comparison of variables among patients with different forms of single ductal carcinoma in situ

	Comedo (n=7)	Cribriform (n=5)	Micro Papillary (n=1)	Solid (n=11)	P value
Age (years)	48.00±7.72	37.00±4.00	45	52.09±13.29	0.097
Tumour size (cm3)	82.49±134.32	59.30±120.61	1.5	43.26±67.25	0.821
Maximum tumor dimension (cm)	4.52±2.850	4.26±3.26	2.0	3.28±1.40	0.588
Quadrants - Outer: inner: central: all	3: 1: 2: 1	2: 2: 1: 0	1: 0: 0: 0	7: 3: 1: 0	0.782
VNIP score	6.85±1.06	5.40±1.51	4	6.00±1.48	0.161
Tubule formation (%)	12.85±9.06	10.40±7.30	20	18.18±11.67	0.467
Mitotic figure/hpf	10.71±7.95	3.80±2.77	3	7.90±5.46	0.239
Nuclear grade- low: intermediate: high	1: 2: 4	1: 3: 1	0: 0: 1	2: 5: 6	0. 349
Paget's disease of the nipple – Yes/No	1: 6	0: 5	0: 1	0:11	0.469
Skin discolouration – Yes/No	3: 4	3: 2	1: 0	6: 5	0.698
Necrosis – Yes/No	7: 0	3: 2	0: 1	1: 10	0.001
Calcification – Yes/No	2: 5	1: 4	0: 1	8: 3	0.101
Lymphatic invasion – Yes/No	5: 2	0: 5	0: 1	4: 7	0.071
Perineural invasion – Yes/No	1: 6	0: 5	0: 1	0: 11	0.469
Vascular invasion – Yes/No	1: 6	0: 5	0: 1	7: 4	0.034
Lymphnode involvement – 0: 1: 2: 3	1: 3: 2: 1	0: 1: 3: 1	1: 0: 0: 0	0: 7: 4: 0	0.049
Histological grade – 1:2:3	3: 0: 4	3: 2: 0	1: 0: 0	8: 3: 0	0.038

solid, comedo and cribriform pattern than solid, comedo and micro papillary (p = 0.0143) and micro papillary and cribriform (p = 0.0253). There were no significant differences with respect to any other variables (table 4).

Necrosis was more common with any comedo group than cribriform (p = 0.0024), micro papillary (p = 0.0011) and solid patterns (p = 0.0006).

Discussion

In this study invasive carcinomas along with an in situ component were studied and the architectural pattern of in situ component was compared with the macroscopic and histopathologic features of coexisting invasive carcinoma. This is one of the very few studies that have

Table 4: Comparison of variables among patients with different forms of mixed ductal carcinoma in situ

	Micropapillary + cribriform (n=2)	Solid + comedo (n=7)	Solid + cribriform (n=3)	Solid + comedo + cribriform (n=3)	Solid + comedo + micropapillary (n=1)	
Age (years)	54.00±26.87	47.57±10.82	51.33±3.05	37.66±2.51	37	0.461
Tumour size (cm3)	54.75±41.36	23.43±35.79	13.05±15.26	61.33±54.01	2.88	0.422
Maximum tumor dimension (cm)	7.25±1.76	3.60±2.23	4.16±0.76	6.66±3.21	2.4	0.170
Quadrants - Outer: inner: central: all	2: 0: 0: 0	7: 0: 0: 0	1: 1: 1: 0	2: 0: 1: 0	1: 0: 0: 0	0.340
VNIP score	6.00±1.41	6.71±1.11	5.00±1.00	6.33±0.57	5	0.211
Tubule formation (%)	27.50±17.67	15.00±7.63	20.00±8.66	5.00±0.00	5	0.089
Mitotic figure/hpf	3.50±0.71	8.42±10.99	2.66±1.52	5.33±4.16	10	0.824
Paget's disease of the nipple – Yes/No	0: 2	0:7	0: 3	0: 3	0: 1	-----
Skin discolouration – Yes/No	1: 1	5: 2	0: 3	1: 2	0: 1	0.244
Necrosis – Yes/No	0: 2	6: 1	0: 3	3: 0	1: 0	0.015
Calcification – Yes/No	1: 1	3: 4	1: 2	0: 3	0: 1	0.629
Lymphatic invasion – Yes/No	1: 1	1: 6	0: 3	1: 2	0: 1	0.607
Perineural invasion – Yes/No	0: 2	1: 6	0: 3	0: 3	0: 1	0.849
Vascular invasion – Yes/No	1: 1	2: 5	0: 3	0: 3	1: 0	0.222
Lymphnode involvement – 0: 1: 2: 3	0: 2: 0: 0	0: 2: 4: 1	0: 0: 2: 1	0: 2: 1: 0	0: 1: 0: 0	0.428
Histological grade – 1:2:3	2: 0: 0	2: 4: 1	2: 1: 0	1: 1: 1	0: 1: 0	0.588

Table 5: Comparison of variables among ductal carcinoma in situ patients with a pattern in any combination

	Any comedo (n=18)	Any cribriform (n=13)	Any micropapillary (n=4)	Any solid (n=25)	P value
Age (years)	45.50±9.08	43.07±11.30	47.50±17.54	48.40±11.47	0.557
Tumour size (cm3)	51.57±89.66	48.39±76.98	28.47±38.62	34.63±52.22	0.835
Maximum tumor dimension (cm)	4.40±2.69	5.25±2.739	4.72±3.09	3.84±2.057	0.423
Quadrants - Outer: inner: central: all	13: 1: 3: 1	7: 3: 3: 0	4: 0: 0: 0	18: 4: 3: 0	0.625
VNIP score	6.61±1.03	5.61±1.19	5.25±1.25	6.08±1.28	0.070
Tubule formation (%)	11.94±8.06	14.00±11.01	20.00±14.71	15.40±10.09	0.467
Mitotic figure/hpf	8.88±8.41	3.84±2.60	5.00±3.36	7.20±6.95	0.206
Nuclear grade	0: 2: 2				
Paget's disease of the nipple – Yes/No	1: 17	0: 13	0: 4	0: 25	0.499
Skin discolouration – Yes/No	9: 9	4: 9	2: 2	12: 13	0.711
Necrosis – Yes/No	17: 1	6: 7	1: 3	11: 14	0.002
Calcification – Yes/No	5: 13	3: 10	1: 3	12: 13	0.354
Lymphatic invasion – Yes/No	7: 11	2: 11	1: 3	6: 19	0.509
Perineural invasion – Yes/No	2: 16	0: 13	0: 4	1: 24	0.501
Vascular invasion – Yes/No	4: 14	1: 12	2: 2	10: 15	0.129
Lymphnode involvement – 0: 1: 2: 3	1: 8: 7: 2	0: 5: 6: 2	1: 3: 0: 0	0: 12: 11: 2	0.290
Histological grade – 1:2:3	6: 6: 6	8: 4: 1	3: 1: 0	13: 10: 2	0.227

studied the effect of various patterns of DCIS on histological aggressiveness of the coexisting invasive ductal carcinoma.

Only a small proportion of DCIS exist as pure whereas the remaining coexist with invasive cancer. In a study by Scripcaru et al.,[5],265 of the 289 DCIS cases coexisted with invasive cancer. The single pattern (79/133) was most common whereas mixed form accounted for the rest (54/133) of the DCIS associated with invasive carcinoma. Similar findings were also found in our study with slight predominance of single pattern (24/40). In the Scripcaru et al, study solid pattern (54/97) was the most common whereas micro papillary (4/97) was the least common [5]. Similarly, in our study solid pattern (11/24) was the most common whereas the micro papillary was the least common (1/24).

The significance of nuclear grade as a criterion for classifying DCIS into high and low nuclear grade of malignancy has been well-emphasized [9]. In the series by Lennington et al., the mixed DCIS were more frequently of intermediate grade whereas in Scripcaru et al., 12%, 45% and 43% had low, intermediate and high nuclear grades respectively. Similarly in our study 12.5%, 43.7% and 43.7% cases had low, intermediate and high nuclear grades respectively [5,10]. Although, few studies have reported lower nuclear grades with solid pattern, there were no significant differences in nuclear grades of various single patterns. Similar results are also reported by Scripcaruet al [5]. Even, the VNPI which has been considered as an important prognostic marker of DCIS was also not significantly different among various patterns.

Presence of necrosis has been demonstrated as an independent poor prognostic factor in patients with carcinoma breast [11]. In our study necrosis was more commonly associated with comedo and cribriform patterns than solid pattern whereas comedo pattern more frequently had necrosis than micro papillary pattern. Among the mixed patterns, combinations of solid and comedo patterns, and solid, comedo and cribriform patterns had more frequent necrosis than other combinations.

Presence of lympho-vascular invasion is also an independent predictor of prognosis in breast carcinoma patients [12]. Different patterns of DCIS did not differ with respect to lymphatic and perineural invasion. Vascular invasion was more commonly associated with solid pattern suggesting solid pattern may be more aggressive. However, lymph node involvement was less aggressive with solid pattern suggesting the contrary. In line with this solid pattern was associated with lower histological grades of coexisting invasive cancer. However, the data on association of DCIS pattern with grade of coexisting invasive cancer is extremely limited.

The study had few limitations. Firstly, the study was characterised by a small sample size. Secondly, the study included only the architectural patterns of DCIS andthere were no cases of lobular carcinoma or an associated lobular in situ component. Thirdly, the histological features of invasive ductal carcinoma with or without DCIS were not compared. Lastly, the effect of DCIS pattern on the long term outcome was not studied.

Conclusion

All architectural patterns of DCIS can coexist either in single or mixed variety with invasive breast carcinomas. The comedo DCIS pattern either in pure or mixed form is associated with necrosis whereas pure solid pattern is associated with histologically less aggressive tumours. The study suggests that patterns of DCIS coexisting with invasive carcinoma may have a prognostic role in the assessment of prognosis in breast carcinoma patients. However, larger follow-up studies are required to confirm this issue.

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NIL

Conflict of Interest

NIL

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