Histopathological Patterns and Cytonuclear Grade of Ductal Carcinoma in situ Occurring Concurrent with Infiltrating Ductal Carcinoma of the Breast

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ABSTRACT

Introduction: The presence of ductal carcinoma in situ (DCIS) confers an improved prognosis for patients with infiltrating carcinoma. Different architectural patterns and cytonuclear grades of DCIS have different prognosis. A number of classification systems of DCIS have been developed, but there is a lack of uniformity in the diagnosis and prognostication of this disease. Therefore, in this study different architectural patterns of DCIS along with their cytonuclear grade were evaluated and further correlated with histological grades of infiltrating ductal carcinoma (IDC) in patients having concurrent DCIS with IDC.

Materials and Methods: The present study included 100 cases of DCIS occurring concurrent with IDC of the breast in a tertiary care hospital. Histopathological examination was done for studying the different architectural pattern and cytonuclear grades of DCIS along with the histological grades of IDC. The correlation of architectural patterns and nuclear grade of DCIS with histological grades of IDC was evaluated.

Results: The comedo pattern DCIS was significantly associated with grade III IDC, (p value 0.001) whereas the cribriform and micropapillary pattern were found to be associated with grade II and I IDC (p value=0.001). The association of the nuclear grade with histological grade of IDC was also found to be statistically significant (p value <0.0013).

Conclusion: Comedo pattern DCIS is usually associated with grade III IDC whereas cribriform and micropapillary patterns are usually associated with lower grade IDC. Similarly, high nuclear grade of DCIS usually results in high grade IDC. This knowledge can help in better timely management of the patients.

Keywords: Breast, Ductal Carcinoma In Situ, Infiltrating ductal carcinoma, comedo, histological grade

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women worldwide.[1] Ductal carcinoma in situ is a proliferation of malignant appearing cells of the ducts and terminal lobular units of the breast that have not yet breached the basement membrane. It represents an intermediate step between normal breast tissue and invasive breast cancer. It has been estimated by multiple mammography screening trials that the incidence of DCIS that will progress into invasive breast cancer if untreated is 100-270 per 100, 000.[2]

In the last several decades, the incidence of DCIS has increased dramatically, due largely to screening mammography. In developing countries like India, the rate of detection of DCIS remains low due to lack of screening programmes as well as lack of diagnostic facilities in the periphery. Most of the patients remain asymptomatic and usually present with an invasive form of breast cancer. So, the majority of DCIS occur in association with invasive carcinomas. Histopathological studies of invasive carcinoma with an associated in situ component have shown a close link between the grade of the in situ component and that of the invasive component. Patients having breast tumor with both DCIS and infiltrating ductal carcinoma have a different prognosis than patients with invasive carcinoma without DCIS.[3] The patients who present with concurrent DCIS have superior survival characteristics.[4]

Increased prevalence of DCIS has produced growing awareness of the importance of its diverse architectural patterns. These differences in pattern are clinically significant as they are important markers of prognosis. DCIS is generally categorized by architectural description into four groups - comedo, solid, cribriform, and micropapillary.[5] However, significant heterogeneity is observed between architectural patterns and mixed patterns can be seen in a single case.[6]

The appropriate classification of DCIS has provoked much debate; a number of classification systems have been developed, but there is a lack of uniformity in the diagnosis and prognostication of this disease. Most DCIS classification systems take into account architectural features only, however nuclear grade (high, intermediate and low) and absence or presence of necrosis are important prognostic markers.[7]

It is universally accepted that the nuclear grade is one of the most essential features and there exists an association between the nuclear grade and the architectural pattern.[8] Comedo type DCIS with a high nuclear grade is biologically more aggressive than other patterns of DCIS and more likely to progress rapidly to invasive carcinoma.[9] A positive correlation between the architectural pattern of DCIS and the grade of the invasive component has been noticed. In addition, significant association between nuclear grade of DCIS and

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histological grade of infiltrating carcinoma has also been observed.[10] However, there are variable reports in the literature and exact association is difficult to estimate from the present studies.

The study was planned to determine the various histomorphological patterns of DCIS occurring concurrent with infiltrating ductal carcinoma of breast using architectural and cytonuclear grade and further to correlate the architectural patterns and nuclear grade of DCIS with histological grade of infiltrating carcinoma.

MATERIALS AND METHODS

The present study included 100 cases of DCIS occurring concurrent with infiltrating ductal carcinoma of the breast in a tertiary care hospital. Mastectomy and lumpectomy specimen that didn't contain DCIS, known and treated cases of invasive carcinoma that had received neoadjuvant chemotherapy and were showing chemotherapy induced changes were excluded from the study. The mastectomy and lumpectomy specimens were fixed in 10% formalin. Multiple sections were taken from the representative sites and after processing, paraffin blocks were prepared. Sections from paraffin blocks were stained with Haematoxylin and Eosin stain. On the basis of architectural pattern DCIS was classified into four major patterns, namely comedo, solid, micropapillary and cribriform. Architecturally, DCIS was divided into single or pure when only one pattern was seen and as mixed when more than one pattern was present. Based upon Consensus Conference Committee recommendations for nuclear grading of intraductal carcinoma DCIS was graded into high grade (nuclear diameter - >2.5X RBC, significant pleomorphism, vesicular chromatin, prominent nucleoli, conspicuous mitosis), intermediate grade (nuclear diameter - 2-2.5X RBC, mild pleomorphism, coarse chromatin, inconspiuous nucleoli, infrequent mitosis) and low grade (nuclear diameter - <2X RBC, no pleomorphism, diffuse chromatin, absent nucleoli, occasional mitosis). Infiltrating ductal carcinoma was graded according to Nottingham modification of Bloom and Richardson system which takes into account tubule formation, mitotic activity and nuclear pleomorphism. The statistical correlation between architectural patterns and cytonuclear grade of DCIS with the histological grade of IDC was evaluated with the help of Chi-square test and SPSS computer software.

RESULTS

Age range of the patients was 31-78 years with a mean age of 53 years. On analyzing the architectural patterns of DCIS 69 cases (69%) displayed single growth pattern and 31 cases (31%) showed a mixed growth pattern. Out of the 69 cases of single pattern DCIS, comedo pattern (Fig 1) was seen in 35 cases (51%), whereas solid, cribriform and micropapillary patterns were seen in 24 cases (35%), 8 cases (11%) and 2 cases (3%) respectively. In the mixed type DCIS, solid with comedo mixed pattern was present in 14/31 cases (45.3%), solid with cribriform mixed pattern was identified in 13/31 cases (41.9%), solid with micropapillary mixed pattern DCIS was seen in 3/31 cases (9.6%) and solid with micropapillary and comedo mixed pattern was seen in 1/31 cases (3.2%). The nuclear grading was done in all the cases; low nuclear grade was recognized in 11 cases (11%), intermediate nuclear grade in 43 cases (43%) and high nuclear grade in 46 cases (46%). Low grade was present in 9/69 cases (13.1%) of DCIS with a single architectural pattern, whereas 24/69 cases (34.8%) and 36/69 cases (52.1%) were having intermediate and high grade respectively. In the mixed architectural pattern DCIS, low grade was observed in 2/31 cases (6.4%), intermediate grade in 19/31 cases (61.4%) and high nuclear grade in 10/31 (32.2%) cases. 68.6% of comedo DCIS had grade nuclei and 31.4% had intermediate grade nucei whereas none of the comedo DCIS revealed low grade nuclei. 50% of the solid DCIS cases were showing high grade nuclei and each of the intermediate and low grade nuclei were seen in 25% cases. Most of the cribriform DCIS cases (75%) were seen to have intermediate grade nuclei and rest of the 25% cases had low grade nuclei (Fig. 2). Micropapillary DCIS had low (50%) to intermediate (50%) grade nuclei. It was interesting to note that none of the micropapillary and cribriform DCIS cases had high grade nuclei. On histological

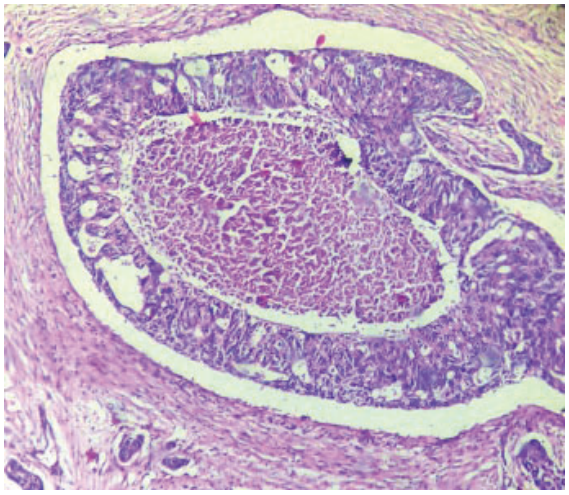

Figure-1: Comedo Pattern DCIS (H&E 100x)

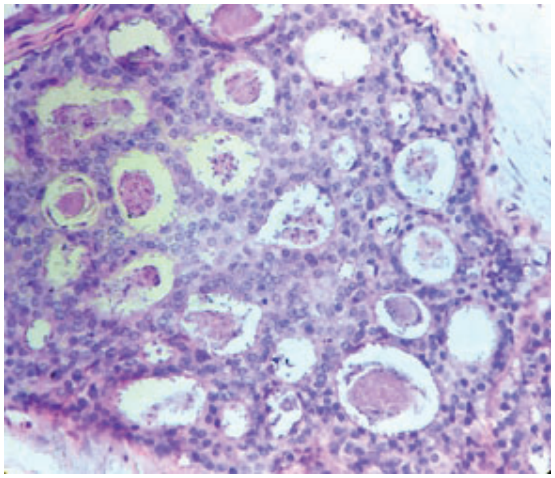

Figure-2: Cribriform pattern DCIS with low nuclear grade (H&E 400x)

Histological grade IDC (Bloom Richardson)	Solid (n=24)	Comedo (n=35)	Cribriform (n=8)	Micropapillary (n=2)	Mixed Pattern (n=31)
Grade 1	11 (46%)	0	1(12.5%)	2 (100%)	3 (10%)
Grade 2	13(54%)	13(37%)	7(87.5%)	0	21 (68%)
Grade 3	0	22(63%)	0	0	7(22%)
Total	24	35	8	2	31

Table-1: Correlation of histological grade of IDC with architectural patterns of DCIS

Histological Grade IDC (Bloom Richardson)	High Grade DCIS (n=49)	Intermediate Grade DCIS(n=43)	Low Grade DCIS(n=8)
Grade I	4(8%)	6(14%)	7(87.5%)
Grade II	22(45%)	31(72%)	1(12.5%)
Grade III	23(47%)	6(14%)	0
Total	49	43	8

Table-2: Association of the nuclear grade of DCIS with histological grade of IDC

grading of all the 100 IDC cases by using Nottingham modification of Bloom and Richardson grading system 17 cases (17%) were found to have grade I, 54 cases (54%) grade II and 29 cases (29%) grade III IDC. The correlation of histological grading of IDC with architectural patterns of DCIS is shown in Table 1. The comedo pattern DCIS was significantly associated with grade III IDC, (p value of 0.001) and solid pattern with grade II IDC (p value 0.001). The cribriform and micropapillary pattern were found to be associated with grade II and I IDC. (p value=0.001). The association of the nuclear grade with histological grade of IDC (Table 2) was also found to be statistically significant (p value <0.0013).

DISCUSSION

Various classification schemes have been used to grade DCIS, which are primarily based on architectural pattern, nuclear grade and the presence or absence of necrosis. These classification systems are useful in predicting the biological behavior of DCIS as well in surgical management.[11] There is merit in comparing the morphologic features and biologic profile of the preinvasive tumor with those of the concurrent IDC. A biologic similarity of both lesions supports their clonal relationship, and comparison of the grade of DCIS and IDC validate the relevance of the DCIS grading system. When DCIS is associated with a concurrent IDC, it is likely to be one of similar grade and similar biologic characteristics, suggesting that they represent neoplastic cells of the same clonal population. DCIS can show single as well as mixed architectural patterns of growth. In the present study, 69% cases were showing single and 31% cases were showing mixed architectural patterns of growth. Comedo pattern was the most common (51%) single architectural pattern. This is because comedo DCIS is seen more in mixed DCIS/IDC cases as compared to pure DCIS cases.[12] Non comedo DCIS has been associated with a lesser risk of recurrence after wide local excision as compared to comedo DCIS which has been associated with more recurrences after tylectomy and a significantly large number of of biopsy proven comedo DCIS cases tend to show invasive stromal component on subsequent mastectomy.[13,14] In the present study, a significant association was noticed between architectural pattern of DCIS and histological grade of IDC. Grade III IDC was present in 63% cases of comedo pattern DCIS, grade II in 37% of comedo DCIS and none of the cases of grade I IDC had comedo pattern DCIS. Conversely, none of the grade III IDC cases had micropapillary or cribriform pattern DCIS. However, there is marked disagreement between the observers when assessment is made using architectural pattern alone. Therefore, the traditional architectural classification of DCIS has been criticized on the ground that individual lesions often show more than one pattern resulting in a large mixed category.[15] Apart from the comedo DCIS, which has been shown in many studies to be an aggressive lesion, other architectural patterns are not predictive of biological behavior of DCIS.[16,17] Hence, this has led to the development of newer classification schemes which incorporate cytonuclear grade and the presence or absence of necrosis.

There exists an association between the architectural growth pattern and the nuclear grade of DCIS. Comedo DCIS have a higher nuclear grade whereas most micropapillary and cribriform in situ carcinomas are of low nuclear grade and relatively indolent. Centrally necrotic comedo architectural pattern is usually not found in cases with low grade DCIS.[18,19] In the present study, 68.6% of comedo DCIS had high nuclear grade, 31.4% had intermediate grade nuclei and none was seen with low grade DCIS. All cases of cribriform and micropapillary DCIS had intermediate to low grade nuclei; none was seen to have high grade nuclei.

Histopathological studies of invasive carcinoma with an associated in situ component have shown a close link between the grade of the in situ component and that of invasive component. DCIS nuclear grade 1 or 2 is usually associated with well or moderately differentiated infiltrating ductal carcinoma, whereas majority of grade 3 DCIS are associated with poorly differentiated carcinoma.[20] In the current study, 87.5% cases of low grade DCIS were associated with grade I IDC, 72% of intermediate grade DCIS with grade II IDC and 47% cases of high grade DCIS were associated with grade III IDC (p value <0.0013).

CONCLUSION

In conclusion, evaluation of histomorphological patterns and cytonuclear grading of DCIS occurring concurrent with infiltrating ductal carcinoma is important. This is because it helps in predicting the histological grade of IDC which is one of the most important prognostic factors of the disease. Comedo pattern DCIS is usually associated with grade III IDC,

whereas cribriform and micropapillary patterns are usually associated with lower grade IDC. Similarly, high nuclear grade of DCIS usually results in high grade IDC. Therefore, comedo pattern DCIS cases with high grade nuclei are more likely to have high grade IDC and this can help in better timely management of the patients.

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