ORIGINAL ARTICLE

Role of E-cadherin Expression in Breast Carcinoma

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ABSTRACT

Introduction: Cancer of breast has emerged as the leading site of cancer in India. E-cadherin (E-CD) is one of calcium-dependent transmembrane glycoprotein mediating cell–cell adhesion. It has its application in differentiating invasive ductal carcinoma not otherwise specified (IDC-NOS) *vs* invasive lobular carcinomas (ILCs) and predicting the aggressiveness of the tumor. In this study, we intend to see E-CD expression in breast carcinoma by immunohistochemistry (IHC), comparing its status with histological grade and type.

Materials and methods: A total of 47 breast tissue specimens were included in the study. The histomorphological grading (Modified Scarf Bloom Richardson system) and immunohisto-chemical scoring were done. Chi-square formula was applied to check the association between E-CD expression and various variables.

Results: The mean age was 51 years. The most common type was IDC-NOS (79%) and grade II (38%). Majority (62%) were lymph node negative. The E-CD IHC performed showed most cases (55%) were severely reduced E-CD, while well-expressed E-CD and moderately reduced E-CD were 28 and 17% respectively. The E-CD expression was statistically significant (p < 0.05) with histological grade and lymph node status. Though the p-value of E-CD expression *vs* histopathological type was not significant, all ILCs showed complete loss of E-CD expression compared with IDC-NOS.

Conclusion: The E-CD expression is well preserved in well-differentiated carcinomas and reduced in poorly differentiated carcinomas. Loss of E-CD expression is seen in lymph node metastasis breast carcinomas and in high-grade breast carcinomas, which proves E-CD can be used as a marker of tumor invasion and tumor aggressiveness. Complete loss of E-CD is seen in all ILC, which can also be helpful in differentiating IDC NOS from ILC.

Keywords: Bloom Richardson score, Breast carcinoma, E-cadherin, Immunohistochemistry.

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INTRODUCTION

Breast cancer is one of the most common human neo-plasms, accounting for approximately one-quarter of all cancer in females. It is said to be associated with Western lifestyle, and incidence rates are, therefore, highest in countries with advanced economies.[1]

Breast cancer is ranked number one cancer among Indian females with age-adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. According to GLOBOCAN 2012, India along with United States and China collectively accounts for almost one-third of the global breast cancer burden. India is facing challenging situation due to 11.54% increase in incidence and 13.82% increase in mortality due to breast cancer during 2008 to 2012. The main reasons for this observed hike in mortality are due to lack of inadequate breast cancer screening, diagnosis of disease at advanced stage, and unavailability of appropriate medical facilities. The age-adjusted rate in Delhi is 41.0 (per 100,000) followed by Chennai 37.9, Bangalore 34.4, and Thiruvananthapuram district 33.7.[2] The incidence of breast carcinoma in females is 26%, of which 15% mortality account due to the same.[3]

The important morphologic prognostic factors in invasive carcinoma of breast include size of primary tumor, microscopic grade, axillary lymph node metasta-sis, blood and lymph vessel emboli, tumor necrosis, skin invasion, and nipple invasion.[3] Other possible prognostic parameters like cell proliferation index, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 neu receptor status, p53, B-cell lymphoma 2 are of growing interest.[4]

Immunohistochemistry is useful in characterizing intracellular proteins or various cell surface proteins in all tissues. Individual markers or more panels of two various marker proteins are used to characterize various tumor subtypes, confirm tissue of origin, distinguish metastatic from primary tumor, and provide additional information which is important for prognosis, predicting response to therapy or evaluating residual tumor posttreatment.[5] Cadherins are divided into more than 10 subclasses depending upon their tissue distribution. These include E- (epithelial), N- (neural), P- (placental) cadherins. E-cadherin (120 kDa, chromosome 16q) also known as uvomorulin, liver cell adhesion molecule (CAM), cell-CAM 120/80, or Arc-1. E-cadherin is a classical cadherin and forms an important functional component of adherent junction in epithelial cells. Many studies have proved that E-CD acts

as invasion suppressor molecule in carcinomas. Loss of E-CD facilitates the invasion of tumor cells to surrounding normal tissues. Loss of E-CD gene locus on chromosome 16 occurs in many cancers, including the breast cancers.[6]

Histomorphological study of breast carcinoma with the E-CD IHC expression will help in early detection of lymph node metastasis and prognosis. Hence, this study has been undertaken.

MATERIALS AND METHODS

We have taken 47 specimens of patients attending outpatient department and in-patients, who are diagnosed or suspected to have breast carcinomas at Sri Siddhartha Medical College Hospital and Research Centre, Tumkur, Karnataka, India.

A detailed history about patient age, sex, onset of symptoms, along with family history will be obtained from the case sheet of the respective patient through medical records.

Excised specimens received by the Department of Pathology will be processed and paraffin blocks are prepared. Thin sections of 3–5 μm size are cut and stained with hematoxylin and eosin (H&E). The representative sections were selected for IHC. The E-CD expression was evaluated based on extent and intensity of immunohistochemical expression in cytoplasm alone or along with membrane stain and classified semi-quantitatively.

Reporting of E-cadherin

Grading of staining intensities of cell membrane: from 0 (equivalent to background staining of the acellular stroma) to +3 (intense stain equivalent to normal breast epithelium).[7]

The abundance of E-CD positive cells is graded from 0 to 4 by counting at least 100 tumor cells in areas of heterogeneous E-CD expression.[7]
- 0 = <5% of positive cells
- 1 = 5 to 25% of positive cells
- 2 = 26 to 50% of positive cells
- 3 = 51 to 75% of positive cells
- 4 = 76 to 100% of positive cells

Composite score was obtained by adding the values of immunostaining intensity and relative abundance.[7]
- 6–7: Preserved/well-expressed (WE) E-CD expression
- 5: Moderately reduced (MR) E-CD expression
- 0–4: Severely reduced (SR) E-CD expression

RESULTS

Forty-seven breast carcinoma specimens were received in which 44 were modified radical mastectomy specimens and 3 were lumpectomy specimens. The age of patients ranged from 35 to 69 years. The mean age was 50.02 years.

The highest incidence was in the age group 51 to 60 years (47%) followed by 41 to 50 years (26%).

In the present study, the predominant histologic subtype was IDC-NOS amounting to 37 cases (79%), followed by 5 cases (11%) of ILC, 3 cases (6%) of invasive papillary carcinoma, and 2 cases (4%) of mucinous carcinoma. Histological grading was done by Bloom Richardson Scoring System; 18 cases (38%) were of histological grade II, followed by 15 cases (32%) of grade II and 14 cases (30%) of grade III. Fifteen cases (32%) showed lymph node positive, 29 cases (62%) were lymph node negative, in 3 cases (6%) lymph nodes were not available. In the present study, 15 cases (32%) were grade I tumors. Among these, 13 cases (28%) showed WE E-CD, 2 cases (4%) showed SR E-CD, none of the grade I tumors showed MR E-CD. Eighteen cases (38%) were grade II tumors; among these, 8 cases (23%) showed MR E-CD, 10 cases (15%) showed SR E-CD, and none of the grade II tumors showed WE E-CD. Fourteen cases (30%) were grade III tumors; among these, 14 cases (30%) showed SR E-CD and none of the grade III tumors showed WE E-CD or MR E-CD. In the present study among 44 cases, 15 cases (34%) had lymph node metastatic deposits and all of them showed SR E-CD expression. Twenty-nine cases were negative for lymph node metastasis; among these, 11 cases (25%) showed SR E-CD, 10 cases (23%) showed WE E-CD, 8 cases (18%) showed MR E-CD expression. In the present study, 37 cases (79%) were IDC-NOS; among these, 13 cases (28%) showed WE E-CD, 6 cases (13%) showed MR E-CD, and 18 cases (38%) showed SR E-CD expression. Two cases (4%) were mucinous carcinoma; among these, 1 case (2%) showed MR E-CD and the other case showed SR E-CD. Three were invasive papillary carcinoma; among these, 1 case (2%) showed MR E-CD and 2 cases (4%) showed SR E-CD expression. Five cases (11%) were ILC and all 5 cases (11%) showed SR E-CD expression. Chi-square test was applied for E-CD expression *vs* histological grade, lymph node status, and histological type. The p-value was statistically significant (<0.005) for histological grade and lymph node status but was not significant for histological type.

DISCUSSION

Understanding of the molecular pathways is highly essential as it has important implications in diagnosis, treatment, and prognosis of the patients.

The mean age of our study was 50 years. In our study, reduced E-CD expression was the predominant finding. In our study, significant association has been found between loss of E-CD expression and high histological grade, lymph node metastasis. But no association has been found for E-CD expression and histological type. Study by Singhai et al[8] showed 36.2% high-grade tumors and significant association with loss of E-CD expression.
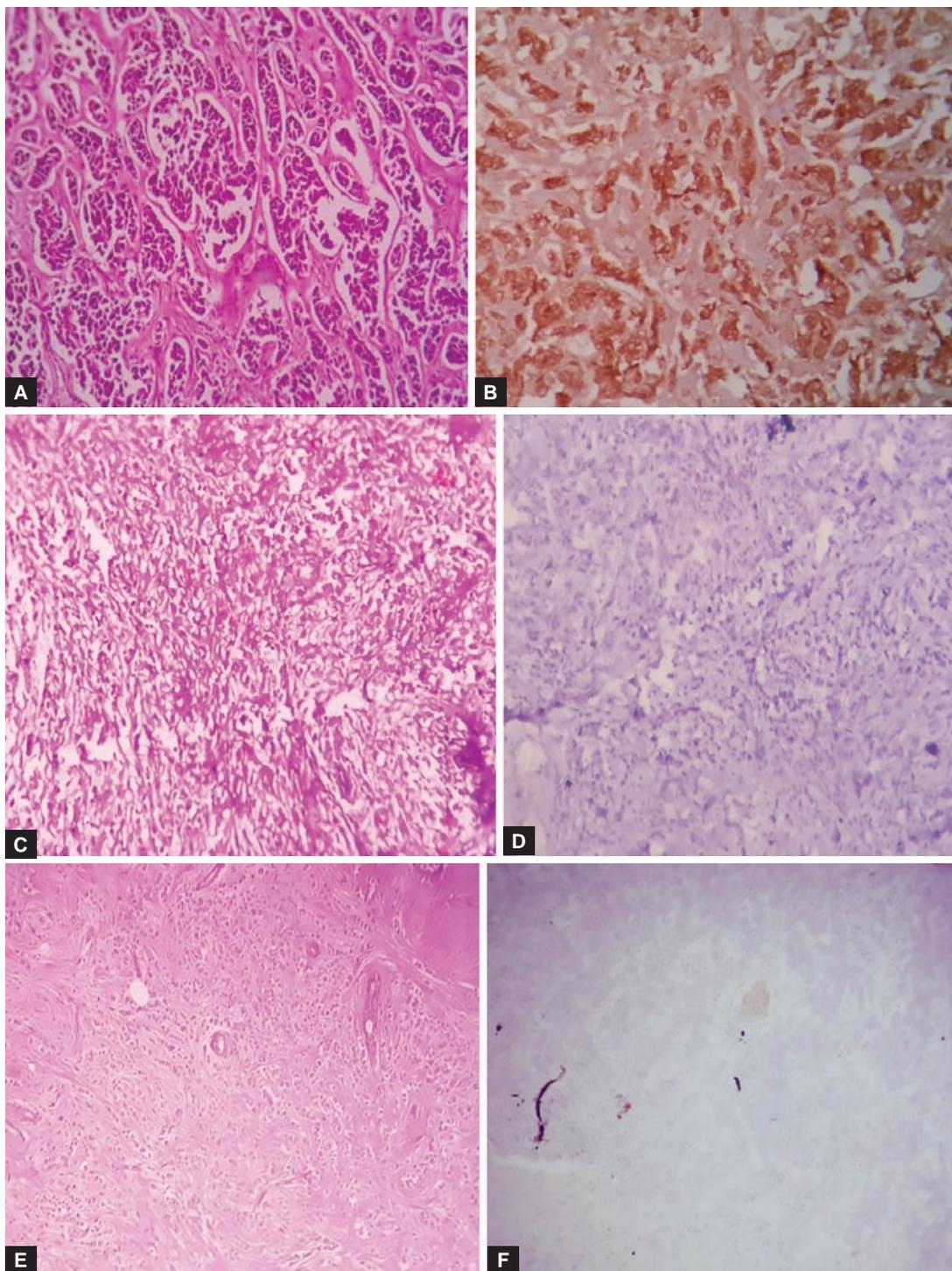
Figs 1A to F: (A) Well-differentiated IDC-NOS, H&E stain (10×), HPE grade I. (B) Well-preserved E-CD expression; (10×) IHC score 6. (C) Poorly differentiated IDC-NOS, H&E (10×), HPE grade III. (D) Severely reduced E-CD expression (10×) IHC score 0. (E) ILC, H&E (10×), HPE grade V. (F) Severely reduced E-CD expression (10×) IHC score 0

Another study by Kashiwagi et al[9] showed 30.8% were lymph node positive and 69.2% were lymph node negative and also showed significant association between loss of E-CD expression and lymph node positivity. Brzozowska et al[10] showed 70.1% IDC, 11.2% ILC, 4.7% other tumors, and this study also showed significant association between E-CD expression and histological type. The study done by McCart Reed et al[11] mentions that approximately 90% of lobular neoplasia and ILCs,

including variants, completely lack E-CD protein expression. Hypermethylation of CDH1 gene and loss of chromosome 16q are seen in almost 21 to 77% of ILC and in turn causes the loss of E-CD expression.

CONCLUSION

The present study shows that E-CD expression is well preserved (Fig. 1) in well-differentiated carcinomas

and reduced in poorly differentiated carcinomas. Loss of E-CD expression is seen in lymph node metastasis breast carcinomas and in higher tumor necrosis factor stages breast carcinomas, which proves E-CD can be used as a marker of tumor invasion and tumor aggressiveness. Complete loss of E-CD is seen in all ILCs, which can also be helpful in differentiating IDC-NOS from ILC.

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