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E-CADHERIN EXPRESSION IN RARE HISTOLOGICAL VARIANTS OF BREAST CARCINOMA: CLINICOPATHOLOGICAL CORRELATION AND PROGNOSTIC IMPLICATIONS

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ABSTRACT
Breast cancer is the most common malignancy among women worldwide and remains a leading cause of cancer-related mortality. (1) Although invasive breast carcinoma of no special type accounts for nearly 70–80% of all cases, several rare histological variants contribute to a small but clinically important proportion of breast malignancies. (2) These uncommon variants exhibit diverse biological behaviour, molecular profiles and prognostic outcomes. (3) Metaplastic carcinoma is characterised by epithelial-mesenchymal differentiation and is often associated with aggressive behaviour and poor prognosis. (4) In contrast, adenoid cystic carcinoma generally demonstrates indolent clinical behaviour despite frequently exhibiting a triple-negative phenotype. (5) Invasive micropapillary carcinoma is recognised for its high incidence of lymphovascular invasion and nodal metastasis, while medullary-pattern carcinoma often exhibits favourable outcomes despite high-grade morphology. (6)

INTRODUCTION
E-cadherin is a calcium-dependent transmembrane glycoprotein encoded by the CDH1 gene and is a major component of epithelial adherens junctions. (7) It plays a crucial role in maintaining cell polarity, tissue architecture and intercellular adhesion. (8) Loss or reduction of E-cadherin expression results in disruption of cellular cohesion, facilitating tumour invasion, epithelial-mesenchymal transition and metastatic dissemination. (7) Previous studies have established the prognostic significance of E-cadherin in conventional breast carcinoma. However, literature evaluating its expression specifically in rare histological variants remains limited. Understanding the pattern of E-cadherin expression in these uncommon tumours may provide valuable insights into their biological behaviour and metastatic potential. Therefore, the present study was undertaken to evaluate E-cadherin expression in rare histological variants of breast carcinoma and correlate its expression with clinico-pathological parameters including tumour grade and nodal status.

MATERIALS AND METHODS
Study Design and setting
A retrospective analytical study was conducted in the Department of Pathology, Sree Balaji Medical College and Hospital, Chennai. Institutional Ethical Committee approval was obtained prior to commencement of the study. The duration of the study was 18 months from August 2024 to March 2026.

Sample Size
A total of 40 Histo-pathologically confirmed cases of breast carcinoma were included in the study.

Eligibility Criteria
The study included mastectomy specimens diagnosed as breast carcinoma with available lymph node specimens and adequately preserved tissue blocks suitable for immunohistochemistry analysis. Male breast carcinoma cases, benign breast lesions, and tissue samples that were inadequate or showed evidence of autolysis were excluded from the study to ensure accurate histopathological and immuno-histochemical evaluation.

Data Collection Procedures
Clinical details including age, histological type, tumor grade, and nodal status were collected from pathology records and case files. All specimens were fixed in 10% neutral buffered formalin. Representative sections were processed

routinely and stained with hematoxylin and eosin. Tumors were classified according to WHO classification and graded using the modified Bloom–Richardson grading system. Immunohistochemical staining for E-cadherin was performed using monoclonal antibodies. Membranous staining in tumor cells was assessed. The intensity and percentage of positive tumor cells were evaluated.

Scoring System

E-cadherin expression was assessed using a standardized scoring system based on two parameters: staining intensity and the percentage of positively stained tumor cells. Staining intensity was categorized as weak, moderate, or strong according to the degree of membranous staining observed in tumor cells. The percentage of positive tumor cells was classified into three categories: less than 10%, 10–50%, and greater than 50% positive cells. Based on the combined assessment of these parameters, the final E-cadherin expression was categorized as either preserved expression or reduced/lost expression.

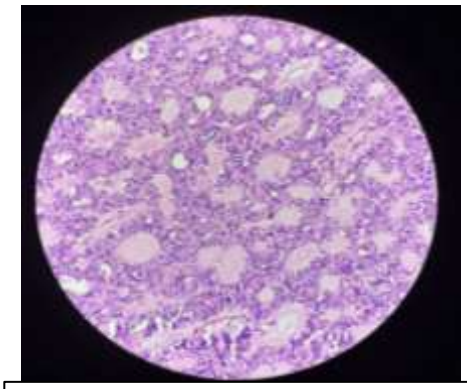
Statistical Analysis

Data was entered into Microsoft Excel and analyzed using SPSS software. Associations between E-cadherin expression and clinico-pathological variables were assessed using Chi-square test. A p-value less than 0.05 was considered statistically significant.

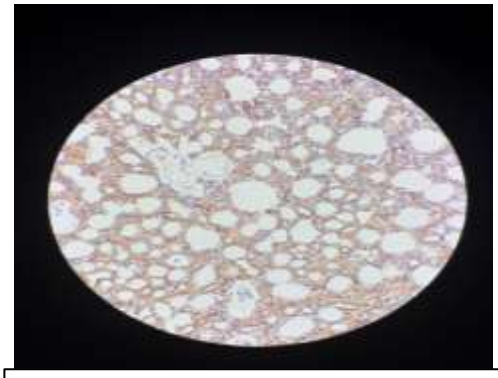
RESULTS

Table 1: Basic characteristics of the Cases (N = 40)

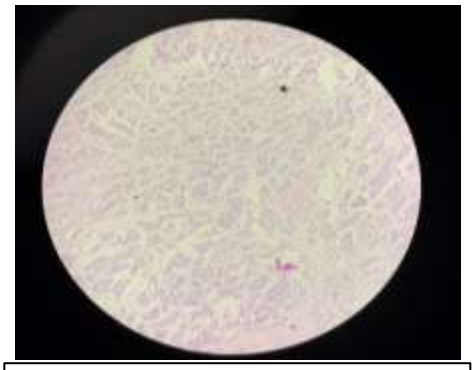
HISTOLOGICAL TYPE	FREQUENCY	PERCENTAGE
Metaplastic breast carcinoma	1	2.5
Adenoid cystic carcinoma	1	2.5
Micro-papillary Breast carcinoma	2	5.0
Invasive breast carcinoma with Medullary pattern	2	5.0
Other types	34	85.0



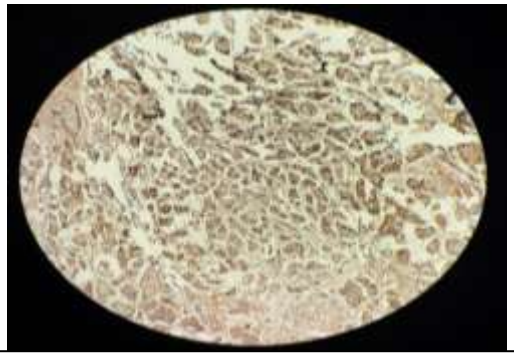
Adenoid cystic breast carcinoma (H&E, X400)



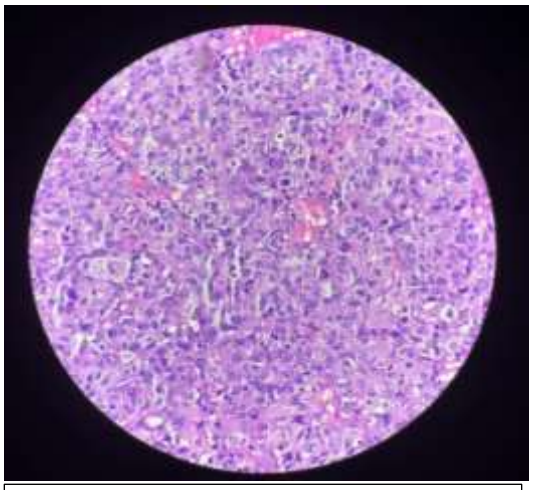
Adenoid cystic breast carcinoma showing weak membranous positivity for E-Cadherin (IHC, X400)



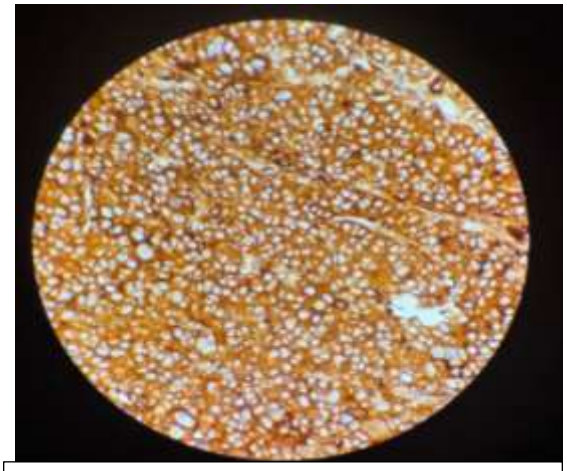
Invasive Micro-papillary Breast Carcinoma (H&E, X100)



Invasive Micro-papillary breast carcinoma showing high intensity for E-Cadherin (IHC, X100)



Invasive carcinoma with medullary pattern (H & E, X400)



Invasive carcinoma with medullary pattern showing high intensity staining for E-Cadherin (IHC, X400)

Table 2: Association between Histological type and E – cadherin Expression

Histological Type	**E - Cadherin Expression N (%)**		**P - Value**
	Preserved	**Reduced**	
Metaplastic carcinoma	1 (100.0)	0 (0.0)	**0.025****
Adenoid cystic carcinoma	0 (0.0)	1 (100.0)	
Micro Papillary carcinoma	1 (50.0)	1 (50.0)	
Medullary pattern carcinoma	2 (100.0)	0 (0.0)	
Other breast carcinomas	31 (91.2)	3 (8.8)	
Total	**35 (87.5)**	**5 (12.5)**	

Preserved expression was observed in 100% of metaplastic and medullary pattern carcinomas, whereas 100% of adenoid cystic carcinoma and 50.0% of micropapillary carcinoma exhibited reduced E-cadherin expression. Among other breast carcinomas, 31 (91.2%) showed preserved expression and 3 (8.8%) showed reduced expression. A statistically significant association was observed between histological type and E-cadherin expression (p = 0.025).

Table 3: Association between Histological type and Nodal Status

Histological Type	**Node Positive N (%)**	**Node Negative N (%)**	**P -value**
Metaplastic carcinoma	1 (100.0)	0 (0.0)	**0.018****
Adenoid cystic carcinoma	0 (0.0)	1 (100.0)	
Micro Papillary carcinoma	2 (100.0)	0 (0.0)	
Invasive carcinoma with medullary pattern	1 (50.0)	1 (50.0)	
Other breast carcinomas	12 (35.3)	22 (64.7)	

Total	**16 (40.0)**	**24 (60.0)**	

All cases of metaplastic carcinoma (100%) and micropapillary carcinoma (100%) were node positive, whereas the adenoid cystic carcinoma (100%) was node negative. Among medullary pattern carcinomas, one case (50.0%) each was node positive and node negative. Among other breast carcinomas, 12 (35.3%) cases were node positive and 22 (64.7%) were node negative. A significant association was observed between histological type and nodal status (p = 0.018).

Table 4: Association between Nodal Status and E-Cadherin Expression

Nodal Status	**E – Cadherin Expression**		**P - Value**
	Preserved N (%)	Reduced N (%)	
Positive	13 (81.3)	3 (18.7)	**0.03****
Negative	22 (91.7)	2 (8.3)	
Total	**35 (87.5)**	**5 (12.5)**	

Among the 16 node-positive cases, 13 (81.3%) demonstrated preserved E-cadherin expression, while 3 (18.7%) showed reduced expression. In contrast, among the 24 node-negative cases, 22 (91.7%) exhibited preserved expression and 2 (8.3%) had reduced expression. Overall, 35 (87.5%) tumors showed preserved E-cadherin expression and 5 (12.5%) demonstrated reduced expression. A statistically significant association was observed between nodal status and E-cadherin expression (p = 0.03), indicating that reduced E-cadherin expression was more frequent in node-positive tumors.

DISCUSSION

The present study evaluated E-cadherin expression in rare histological variants of breast carcinoma and its association with histological subtype and nodal status. Among the present cases, preserved E-cadherin expression was observed in 87.5% of tumors, while reduced expression was noted in 12.5%. Significant associations were identified between histological subtype and E-cadherin expression (p=0.025) as well as between histological subtype and nodal status (p=0.018). Furthermore, reduced E-cadherin expression was significantly associated with lymph node metastasis (p=0.03), suggesting that alterations in cell adhesion may contribute to the metastatic behavior of selected rare breast carcinoma variants.

Rare histological variants of invasive breast carcinoma, although relatively uncommon when considered individually, collectively constitute a significant proportion of breast cancers and exhibit marked biological and clinical heterogeneity. In the present study, metaplastic carcinoma, adenoid cystic carcinoma, micropapillary carcinoma, and medullary-pattern carcinoma together accounted for 15% of all cases, reflecting the diversity of these uncommon subtypes. This observation is consistent with the findings of Weigelt et al. (2010), who reported that special histological types collectively comprise approximately one-quarter of invasive breast carcinomas. (9) Furthermore, the heterogeneity observed in our study is supported by Lam et al. (2024), who demonstrated considerable variation in the clinicopathological characteristics and prognosis among rare breast cancer histotypes. (10) Similarly, Dieci et al. (2014) highlighted the wide spectrum of biological behavior across these tumors, ranging from the indolent course of tubular carcinoma to the aggressive nature of metaplastic carcinoma. (11) Han et al. (2020) also reported substantial prognostic heterogeneity among different histological subtypes, emphasizing differences in hormone receptor expression, tumor grade, stage at diagnosis, and survival outcomes. (12) These findings reinforce the concept that rare breast carcinoma variants should not be regarded as a homogeneous group, as their distinct biological characteristics have important implications for prognosis and individualized therapeutic management.

E-cadherin plays a central role in maintaining epithelial cell adhesion and tissue architecture. Loss or reduction of its expression facilitates epithelial-mesenchymal transition, increased cellular motility and metastatic dissemination. (13) In the present study, reduced E-cadherin expression was predominantly observed in adenoid cystic carcinoma and micropapillary carcinoma, whereas metaplastic and medullary-pattern carcinomas retained membranous expression. These findings are in agreement with Han et al. (1999), who demonstrated preserved membranous E-cadherin expression in all medullary and metaplastic carcinomas examined, suggesting that these subtypes maintain intact cell–cell adhesion despite their distinct histological features.(14) Likewise, Franchi et al. reported reduced or absent E-cadherin expression

in adenoid cystic carcinoma, particularly in tumors with a predominant solid growth pattern, supporting the decreased expression observed in our study. (15) In contrast, Nagi et al. found E-cadherin positivity in 57% of invasive micropapillary carcinomas, indicating variable rather than consistently reduced expression. (16) This discrepancy may be attributable to differences in sample size, tumor characteristics, or immunohistochemical assessment methods.

An important finding of the present study was the significant association between histological subtype and lymph node status. Invasive micropapillary carcinoma (IMPC) is well recognized for its marked lymphotropism and high propensity for lymph node metastasis. In the present study, IMPC demonstrated frequent nodal involvement, consistent with its aggressive clinicopathological behavior. Similar findings were reported by Badyal et al., who observed lymphovascular emboli in 80% of IMPC cases and lymph node metastasis in 69.2% of patients. (17) Comparable results were documented by Ahadi et al., who reported lymph node involvement in 80.3% of IMPC cases, significantly higher than that observed in invasive ductal carcinoma.(18) Likewise, Kim et al. found nodal metastasis in 70.5% of patients with IMPC, with a significantly greater metastatic nodal burden compared with invasive ductal carcinoma, while Cui et al. (2014) reported axillary lymph node metastasis in 80% of cases. (19) (20) Collectively, these studies consistently demonstrate lymph node involvement in approximately 70–80% of IMPCs, accompanied by frequent lymphovascular invasion, underscoring the aggressive metastatic potential of this rare histological subtype.

In the present study, reduced E-cadherin expression was associated with lymph node metastasis, supporting its role in facilitating tumor invasion and metastatic spread. Similar findings were reported by Hunt et al. (1997), who demonstrated significantly reduced E-cadherin expression in node-positive compared with node-negative breast carcinomas. (21) Likewise, **Li et al. (2012)** observed a significant association between reduced E-cadherin expression and lymph node metastasis in laryngeal squamous cell carcinoma ($P<0.001$), while **Tanaka et al. (2003)** reported significantly greater loss of E-cadherin in metastatic than non-metastatic oral squamous cell carcinoma ($P=0.007$). (22) These studies collectively support the concept that diminished E-cadherin-mediated cell adhesion promotes metastatic dissemination. Nevertheless, **Park et al. (2007)** demonstrated that metastatic lymph nodes may retain or re-express membranous E-cadherin despite reduced expression in the corresponding primary tumors, suggesting that immunohistochemical positivity does not necessarily indicate preserved functional adhesion. (23) This finding highlights that alterations in the E-cadherin–catenin complex and other molecular mechanisms may contribute to metastasis despite apparent protein expression, emphasizing the limitations of relying solely on immunohistochemical assessment to predict metastatic potential.

In the present study, metaplastic carcinoma demonstrated preserved membranous E-cadherin expression despite its aggressive clinicopathological behavior, suggesting that tumor progression may occur through mechanisms independent of complete E-cadherin loss. Similar findings were reported by Gauchotte et al., who observed positive E-cadherin expression in 70% of metaplastic breast carcinomas. (24) In contrast, Zhang et al. documented reduced or absent E-cadherin expression in the metaplastic components of all cases examined, while Gwin et al. (2010) described a gradual loss of E-cadherin at the epithelial–mesenchymal interface during tumor progression. (25) (26) Collectively, these findings indicate that the aggressive behavior of metaplastic carcinoma is driven by complex molecular alterations, rather than by loss of E-cadherin expression alone.

The current findings should be interpreted in light of certain limitations. The study was conducted at a single institution with a relatively small sample size because of the inherent rarity of these histological variants. Some subtypes were represented by only one or two cases, limiting subgroup comparisons and multivariable analyses. In addition, only immunohistochemical assessment of E-cadherin was performed, without molecular evaluation of CDH1 gene alterations or associated adhesion pathway proteins such as β-catenin and p120-catenin, which may provide a more comprehensive understanding of cadherin dysfunction.

Despite these limitations, the study contributes valuable information regarding E-cadherin expression in uncommon breast carcinoma variants. The observed association between reduced E-cadherin expression and lymph node metastasis supports the potential utility of E-cadherin as an adjunct prognostic biomarker in selected rare breast carcinomas. Larger multicenter studies integrating immunohistochemistry with molecular characterization of the CDH1 pathway are warranted to clarify the biological mechanisms underlying tumor progression and to determine the prognostic significance of altered E-cadherin expression in these rare entities.

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