GMR
The Original

E-CADHERIN–POSITIVE INVASIVE LOBULAR CARCINOMA: A CLINICOPATHOLOGICAL DIAGNOSTIC DILEMMA

Kesava sai pavan sadu[1*], Ajay gokul[2], Madan[3], Mahesh.C[4], Kuberan[5*]

[1]Postgraduate, Department of General Surgery,Sree Balaji medical College and Hospital , Chromepet,600044 Tamil Nadu, India,
E-mail ID: pavan.sadu1234@gmail.com, Phone number: +91 8309541961, ORCID ID: 0009-0003-0029-2314
[2]Senior Resident, Department of General Surgery,Sree Balaji medical College and Hospital , Chromepet,600044, Tamil Nadu, India,
E-mail ID: ajaygokul@gmail.com, Phone number: +91 95788 32444, ORCID ID: 0009-0001-7054-9571
[3]Assistant Professor, Department of General Surgery,Sree Balaji medical College and Hospital , Chromepet,600044 Tamil Nadu, India,
E-mail ID: madan040494@gmail.com, Phone number: +91 95000 54334, ORCID ID: 0000-0003-3169-9750
[4]Associate Professor,Department of General Surgery,Sree Balaji medical College and Hospital , Chromepet,600044 Tamil Nadu, India,
E-mail ID: maxchandran@gmail.com, Phone number: +91 99627 32444, ORCID ID: 0000-0002-1116-9675
[5*]Professor,Department of General Surgery,Sree Balaji medical College and Hospital , Chromepet,600044 Tamil Nadu, India Tamil Nadu, India,
E-mail ID: drkubers@gmail.com, Phone number: +91 98400 42867, ORCID ID:0000-0003-1181-4512

ABSTRACT

Breast carcinoma remains the most frequently diagnosed malignancy among women worldwide. Invasive lobular carcinoma (ILC) constitutes approximately 10–15% of all breast cancers and is classically associated with loss of E-cadherin expression. We report a case of a 76-year-old female presenting with a gradually enlarging right breast lump with associated nipple retraction. Imaging suggested a suspicious lesion (BI-RADS IV). Histopathological examination following trucut biopsy confirmed malignancy. The patient underwent modified radical mastectomy with axillary clearance. Final histopathology revealed invasive lobular carcinoma with vascular invasion and metastasis to one lymph node. Immunohistochemistry demonstrated ER positivity (90%), PR negativity, HER2 equivocal (2+), Ki-67 index of 15%, and retained E-cadherin expression. This unusual immunophenotype posed a diagnostic challenge. This case highlights the importance of correlating histomorphology with immunohistochemical findings to ensure accurate tumor classification and appropriate management.

KEYWORDS: Breast cancer, E-cadherin, elderly breast cancer, immunohistochemistry, invasive lobular carcinoma, modified radical mastectomy

INTRODUCTION

Breast cancer remains the most commonly diagnosed malignancy and a leading cause of cancer-related morbidity and mortality among women worldwide [1]. Recent global estimates indicate a rising incidence, emphasizing the growing public health burden and the need for improved diagnostic and therapeutic strategies [2]. Among the histological subtypes, invasive lobular carcinoma (ILC) accounts for approximately 10–15% of all breast cancers and represents the second most common subtype after invasive ductal carcinoma [3]. ILC originates from the terminal duct-lobular unit and demonstrates distinct biological and morphological characteristics that differentiate it from other breast cancer subtypes.

A hallmark feature of ILC is the loss of E-cadherin expression, a transmembrane cell adhesion molecule encoded by the CDH1 gene, which plays a crucial role in maintaining epithelial integrity [4]. The absence of E-cadherin leads to reduced cellular cohesion and contributes to the characteristic single-file infiltration pattern observed histologically. This unique growth pattern also accounts for the subtle clinical and radiological presentation of ILC, often lacking a well-defined mass and thereby posing challenges in early detection and diagnosis [5].

Furthermore, ILC demonstrates distinct clinicopathological and molecular features, including a higher frequency of hormone receptor positivity and unique metastatic patterns, which influence management and prognosis. Immunohistochemistry (IHC) serves as an essential adjunct in confirming the diagnosis and distinguishing ILC from morphologically similar entities. However, rare variants exhibiting aberrant or retained E-cadherin expression have been increasingly reported, creating diagnostic dilemmas and highlighting the limitations of relying solely on a single biomarker.

In this context, we present a case of invasive lobular carcinoma with retained E-cadherin expression, emphasizing the importance of correlating histomorphological findings with immunohistochemical profiles to achieve accurate diagnosis and optimal patient management.

Case Presentation

A 76-year-old postmenopausal woman presented with a gradually progressive swelling in the right breast of one-year duration. The swelling was insidious in onset and initially painless but gradually increased in size and became associated with intermittent pricking pain. She also noticed recent onset of right nipple retraction. There was no history of nipple discharge, preceding trauma, fever, loss of appetite, weight loss, or other constitutional symptoms. She had no known

medical comorbidities or significant family history of breast or ovarian malignancy. Her past surgical history included a lower-segment cesarean section several decades earlier and hysterectomy. On presentation, the patient was conscious, oriented, hemodynamically stable, and afebrile. Routine preoperative investigations demonstrated mild anemia (hemoglobin 9.9 g/dL), while renal function tests, liver function tests, coagulation profile, and other baseline biochemical parameters were within acceptable limits for surgery.

Clinical Examination

On local examination, the right breast appeared asymmetrical compared with the left. A firm, irregular mass measuring approximately 5 × 4 cm was palpated, extending from the 9 o'clock to the 2 o'clock position. The lesion was fixed to the surrounding breast tissue but remained mobile over the underlying pectoral muscles, indicating no chest wall involvement. Retraction of the nipple–areola complex was evident. The overlying skin appeared normal without ulceration, peau d'orange, erythema, sinus formation, or dilated superficial veins. No nipple discharge was observed. Bilateral axillary, supraclavicular, and infraclavicular examinations revealed no clinically palpable lymphadenopathy. Examination of the contralateral breast was unremarkable. Systemic examination of the cardiovascular, respiratory, abdominal, and neurological systems was within normal limits.

Diagnostic Investigations

Ultrasonography of the Breast

Ultrasonographic evaluation demonstrated a well-defined heteroechoic lesion measuring 4.4 × 4.2 × 3.7 cm located in the inner quadrant of the right breast. The lesion exhibited lobulated margins with multiple internal cystic areas. Color Doppler imaging revealed both internal and peripheral vascularity. A few subcentimetric right axillary lymph nodes with preserved fatty hila were identified, suggestive of reactive morphology. The contralateral breast showed no abnormality. Based on these imaging findings, the lesion was categorized as BI-RADS IV, indicating a suspicious abnormality with a differential diagnosis that included phyllodes tumor. Histopathological confirmation was therefore recommended.

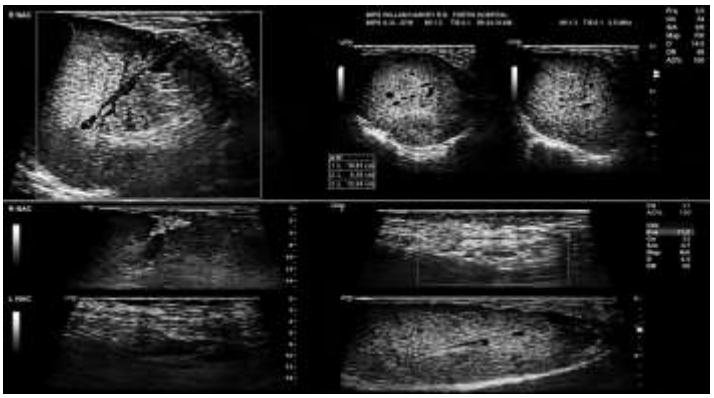

Figure 1. Preoperative ultrasonography of the right breast showing a BI-RADS IV heteroechoic lesion with lobulated margins, internal cystic changes, and internal/peripheral vascularity.

Trucut Biopsy

An ultrasound-guided trucut biopsy of the right breast lesion was performed. Histopathological examination revealed breast parenchyma infiltrated by malignant epithelial cells arranged predominantly in nests and clusters separated by delicate fibrous septae. The tumor cells were medium-sized and polygonal, exhibiting moderate eosinophilic cytoplasm with round to oval nuclei, conspicuous nucleoli, and mild-to-moderate nuclear pleomorphism. The overall morphological features were consistent with an invasive malignant epithelial neoplasm of the breast, warranting further immunohistochemical characterization for definitive histological classification.

Immunohistochemistry Findings

Immunohistochemical evaluation demonstrated strong nuclear positivity for estrogen receptor (ER) in approximately 90% of the tumor cells, while progesterone receptor (PR) expression was negative. Human epidermal growth factor receptor 2 (HER2/neu) immunostaining showed an equivocal 2+ membranous staining pattern. The Ki-67 proliferation index was approximately 15%, indicating moderate proliferative activity. Notably, the tumor cells retained membranous E-cadherin expression, an uncommon immunophenotypic finding in invasive lobular carcinoma that posed a diagnostic challenge because classical invasive lobular carcinoma typically demonstrates complete loss of E-cadherin expression. In view of the equivocal HER2 result, fluorescence in situ hybridization (FISH) testing was recommended to determine HER2 gene amplification status and guide subsequent systemic therapy. Correlation of the histomorphological features with the immunohistochemical profile favored the diagnosis of E-cadherin-positive invasive lobular carcinoma.

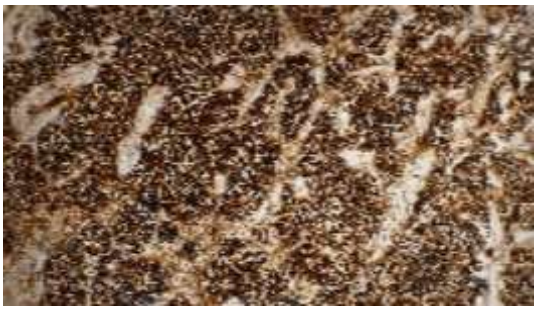

Figure 2: Immunohistochemistry showing retained membranous E-cadherin expression in tumor cells

Final Diagnosis

Based on the combined histopathological and immunohistochemical findings, the final diagnosis was invasive lobular carcinoma of the right breast, pathological stage pT2N1M0 (Stage IIB) according to the American Joint Committee on Cancer (AJCC) TNM staging system. The tumor demonstrated retained E-cadherin expression, strong estrogen receptor positivity (90%), progesterone receptor negativity, equivocal HER2 (2+) status, and a Ki-67 proliferation index of approximately 15%.

Surgical Management

Following histopathological confirmation of malignancy on ultrasound-guided trucut biopsy, the patient was planned for definitive surgical management under general anesthesia after routine preoperative evaluation and anesthetic fitness assessment. An initial breast-conserving procedure (wide local excision/lumpectomy) was undertaken with the aim of achieving adequate oncological margins. The excised specimen was immediately subjected to intraoperative frozen section examination for assessment of margin status.

Frozen section analysis demonstrated the presence of malignant cells at the resection margins, indicating incomplete tumor clearance. In view of the positive margins and to ensure complete oncological excision, the procedure was intraoperatively converted to a Modified Radical Mastectomy (MRM).

An elliptical incision incorporating the nipple–areola complex was made, and the entire breast tissue was dissected off the pectoralis major fascia. Standard Level I and Level II axillary lymph node dissection was subsequently performed. Throughout the procedure, meticulous attention was paid to preserving the long thoracic nerve and the thoracodorsal neurovascular bundle to minimize postoperative functional morbidity. Hemostasis was achieved, a closed suction drain was placed in the operative field, and the wound was closed in layers. The resected specimen was submitted for definitive histopathological examination.

Final histopathological examination confirmed invasive lobular carcinoma with vascular invasion and metastatic involvement of one of the eleven dissected axillary lymph nodes, while the remaining lymph nodes were free of tumor. The posterior resection margin measured 1.5 mm, and all other surgical margins were uninvolved by tumor, confirming adequate surgical clearance. These findings established the final pathological stage as pT2N1M0 (Stage IIB).

Postoperative Course

The patient's postoperative recovery was uneventful. She received intravenous antibiotics, analgesics, thromboprophylaxis, and routine postoperative care. Oral liquids were initiated on postoperative day (POD) 1 and gradually advanced to a regular diet as tolerated. The Foley catheter was removed on POD 4, bowel function returned on POD 5, and the surgical drain was removed on POD 9. A medical oncology consultation was obtained for planning adjuvant treatment. The patient remained hemodynamically stable throughout her hospital stay and was discharged on POD 11 with advice regarding wound care, drain-site hygiene, outpatient follow-up for immunohistochemistry review, and further oncological management

Figure 3: The patient underwent modified radical mastectomy with axillary clearance. Intraoperative findings revealed an ill-defined infiltrative tumor involving the breast tissue

Figure 4: Postoperative photograph showing surgical wound closure following modified radical mastectomy with drain in situ

Figure 5: Gross examination of the specimen revealed an ill-defined firm tumor within fibrofatty breast tissue

Histopathological Examination

Gross examination of the modified radical mastectomy specimen revealed breast tissue measuring 24 × 10 × 3 cm with attached fibrofatty tissue. On serial sectioning, an ill-defined, firm gray-white nodular lesion was identified within the breast parenchyma. The cut surface demonstrated infiltrative margins with surrounding fibrofatty tissue involvement.

Microscopic examination showed an infiltrating malignant epithelial neoplasm composed of medium-sized polygonal tumor cells arranged predominantly in lobules and nests separated by delicate fibrovascular septae. The tumor cells exhibited round to oval nuclei with prominent nucleoli, moderate eosinophilic cytoplasm, and mild-to-moderate nuclear pleomorphism. Vascular invasion was identified, indicating an increased risk of metastatic dissemination. The overall histomorphological features were consistent with invasive lobular carcinoma.

Lymph Node Evaluation

A total of 11 axillary lymph nodes were retrieved from the surgical specimen. One lymph node demonstrated metastatic carcinoma, while the remaining ten lymph nodes were free of tumor deposits.

Surgical Margins

Histopathological assessment demonstrated a posterior resection margin clearance of 1.5 mm. All remaining surgical margins were free of tumor infiltration, indicating complete excision of the lesion with histologically negative margins

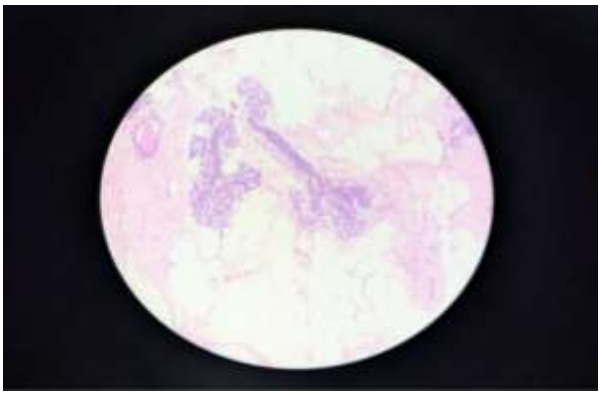

Figure 6: Hematoxylin and eosin-stained section showing invasive carcinoma with tumor cell clusters infiltrating fibrofatty tissue

Final Histopathological Diagnosis

Histopathological examination confirmed invasive lobular carcinoma of the right breast with vascular invasion, metastatic involvement of one of eleven dissected axillary lymph nodes, and tumor-free surgical margins, except for a posterior margin clearance of 1.5 mm. Based on the histopathological and immunohistochemical findings, the final diagnosis was E-cadherin-positive invasive lobular carcinoma, pathological stage pT2N1M0 (Stage IIB).

DISCUSSION

Invasive lobular carcinoma (ILC) is the second most common histological subtype of breast carcinoma, accounting for approximately 10–15% of invasive breast cancers. It is characterized by loss of intercellular adhesion resulting from inactivation of the CDH1 gene, which encodes the transmembrane adhesion molecule E-cadherin. Loss of E-cadherin disrupts epithelial cell cohesion and produces the characteristic discohesive, single-file infiltration pattern that is considered the histological hallmark of ILC [1–3].

Although absence of E-cadherin expression has traditionally been regarded as a defining immunohistochemical feature of ILC, accumulating evidence indicates that a small subset of tumors demonstrates retained or aberrant membranous E-cadherin staining despite exhibiting classical lobular morphology. These uncommon variants represent a significant diagnostic challenge because they may closely resemble invasive ductal carcinoma, potentially leading to inaccurate histological classification if diagnosis is based solely on immunohistochemical findings [4–6].

In the present case, histopathological examination demonstrated classical morphological features of invasive lobular carcinoma, while immunohistochemistry revealed retained membranous E-cadherin expression. This discordance highlights the limitations of relying exclusively on a single biomarker for tumor classification. Recent studies have shown that retained E-cadherin expression may result from dysfunctional E-cadherin proteins, alterations in associated catenin complexes, or epigenetic and post-translational modifications that impair cellular adhesion despite preserved protein expression [7–9]. Consequently, preserved immunostaining does not necessarily indicate intact biological function.

Another noteworthy feature of the present case was the hormone receptor profile. The tumor demonstrated strong estrogen receptor positivity (90%), progesterone receptor negativity, equivocal HER2 (2+) expression, and a Ki-67 labeling index of approximately 15%. This profile is consistent with the well-recognized tendency of ILC to exhibit hormone receptor positivity and relatively low proliferative activity compared with invasive ductal carcinoma. Strong ER expression suggests a favorable likelihood of response to adjuvant endocrine therapy, whereas the equivocal HER2 status appropriately warranted confirmatory fluorescence in situ hybridization (FISH) in accordance with current ASCO/CAP recommendations [10].

Radiologically, ILC frequently presents diagnostic difficulties because of its infiltrative growth pattern and limited desmoplastic response, often resulting in ill-defined lesions that are underestimated on conventional imaging. In our patient, ultrasonography identified a BI-RADS IV lesion with imaging features suggestive of malignancy but also raised the possibility of a phyllodes tumor, emphasizing the limited specificity of imaging alone and reinforcing the importance of histopathological confirmation [11].

Definitive surgical management in this patient required intraoperative conversion from wide local excision to modified radical mastectomy after frozen section analysis demonstrated positive resection margins. Final histopathology confirmed vascular invasion and metastatic involvement of one of eleven axillary lymph nodes, corresponding to pathological stage pT2N1M0 (Stage IIB). These findings underscore the infiltrative nature of ILC and its propensity for occult microscopic extension beyond grossly identifiable tumor margins, making meticulous pathological assessment essential for achieving adequate oncological clearance [12].

Overall, this case reinforces that accurate diagnosis of invasive lobular carcinoma should be based on comprehensive clinicopathological correlation rather than isolated interpretation of immunohistochemical markers. Integration of clinical findings, imaging characteristics, histomorphology, immunohistochemistry, and molecular investigations remains essential for appropriate tumor classification, prognostication, and therapeutic decision-making, particularly in unusual variants exhibiting retained E-cadherin expression [13–15].

CONCLUSION

This case highlights a rare presentation of E-cadherin-positive invasive lobular carcinoma, emphasizing that retained membranous E-cadherin expression does not preclude the diagnosis of invasive lobular carcinoma. Reliance on immunohistochemistry alone may result in diagnostic misclassification, particularly in tumors exhibiting atypical immunophenotypes. Accurate diagnosis requires careful integration of clinical findings, radiological assessment, histomorphological features, immunohistochemistry, and, when indicated, molecular investigations. Recognition of these uncommon variants is essential for appropriate pathological classification, accurate staging, optimal therapeutic decision-making, and improved patient outcomes. Increased awareness among pathologists, surgeons, and oncologists will facilitate timely diagnosis and effective multidisciplinary management of this uncommon entity.

Learning Points

- Retained E-cadherin expression does not exclude the diagnosis of invasive lobular carcinoma.
- Histomorphological features should always be correlated with immunohistochemical findings before establishing the final diagnosis.
- Invasive lobular carcinoma exhibits considerable morphological, molecular, and immunophenotypic heterogeneity.
- Equivocal HER2 (2+) immunostaining requires confirmatory FISH testing in accordance with current ASCO/CAP recommendations.
- Comprehensive clinicopathological correlation is essential to avoid misclassification and to guide appropriate surgical and systemic management.
- A multidisciplinary approach involving pathologists, breast surgeons, radiologists, and medical oncologists improves diagnostic accuracy and optimizes patient outcomes.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48.
3. Kuba M, Brogi E. Update on lobular lesions of the breast. Histopathology. 2023;82(1):36–52.
4. Christgen M, Cserni G, Floris G. Lobular breast cancer: histomorphology and different concepts of a special spectrum of tumors. Cancers (Basel). 2021;13(15):3695.
5. McCart Reed AE, Kalinowski L, Simpson PT, Lakhani SR. Invasive lobular carcinoma of the breast: the increasing importance of this special subtype. Breast Cancer Res. 2021;23(1):6.
6. Cserni G, Bori R, Ambrózay É, et al. Histological patterns and mammographic presentation of invasive lobular carcinoma show no obvious associations. Cancers (Basel). 2024;16(9):1640.
7. Rogges E, Corati T, Amato M, et al. Pleomorphic/solid lobular carcinoma of male breast with PALB2 germline mutation: case report and literature review. Pathologica. 2024;116(1):62–68.
8. Cserni G, Kálmán E, Udvarhelyi N, et al. Evaluation of the routine use of E-cadherin immunohistochemistry in the typing of breast carcinomas: results of a randomized diagnostic study. Histopathology. 2023;83(5):810–821.
9. Christgen M, Kandt L, Antonopoulos W, et al. Interobserver agreement for the histological diagnosis of invasive lobular breast carcinoma. J Pathol Clin Res. 2022;8(3):191–205.
10. De Schepper M, Vincent-Salomon A, Christgen M, et al. Results of a worldwide survey on the currently used histopathological diagnostic criteria for invasive lobular breast cancer. Mod Pathol. 2022;35(12):1812–1820.
11. Rubtsova SN, Zhitnyak IY, Gloushankova NA. Dual role of E-cadherin in cancer cells. Tissue Barriers. 2022;10(1):2005420.
12. Bücker L, Lehmann U. CDH1 (E-cadherin) gene methylation in human breast cancer: critical appraisal of a long and twisted story. Cancers (Basel). 2022;14(18):4377.
13. Dopeso H, Gazzo AM, Derakhshan F, et al. Genomic and epigenomic basis of breast invasive lobular carcinomas lacking CDH1 genetic alterations. NPJ Precis Oncol. 2024;8:50.
14. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol. 2023;41(22):3867–3872.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2024. Available from: https://www.nccn.org