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Research Article

HER2-Positive Classical Invasive Lobular Carcinoma of the Breast in a Young Female: A Rare Clinicopathological Entity Challenging the Conventional Lobular Phenotype

Kannaujia S K[1], Rashmi[2], Maurya Geeta[3], Yadav Alka[4], Joshi Himanshu[5]
[1]Dr. Sanjay Kumar Kannaujia, Associate Professor, Department of Pathology UPUMS Saifai, Etawah.
[2]Dr. Rashmi, Associate Professor, Department of Pathology UPUMS Saifai, Etawah.
[3]Dr. Geeta Maurya, Professor, Department of Pathology UPUMS Saifai, Etawah.
[4]Dr. Alka Yadav, Assistant Professor, Department of Pathology UPUMS Saifai, Etawah.
[5]Dr Himanshu Joshi, Associate Professor, Department of Pathology UPUMS Saifai, Etawah.
Corresponding Author: Dr. GeetaMaurya
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Abbreviations
ILC – Invasive Lobular Carcinoma
cILC – Classical Invasive Lobular Carcinoma
HER2 – Human Epidermal Growth Factor Receptor 2
ER – Estrogen Receptor
PR – Progesterone Receptor
FISH – Fluorescence In Situ Hybridization
LCIS – Lobular Carcinoma In Situ
AR – Androgen Receptor

ABSTRACT
Background: Classical invasive lobular carcinoma (cILC) is usually characterized by hormone receptor positivity, loss of E-cadherin expression, and absence of HER2 amplification. HER2-positive cILC is exceptionally rare and represents a distinct molecular subset of breast carcinoma. **Case Presentation**: A 41-year-old female presented with a palpable left breast lump. Ultrasonography revealed a suspicious irregular hypoechoic lesion. Core needle biopsy demonstrated a malignant epithelial neoplasm composed of discohesive cells infiltrating the stroma in characteristic single-file arrangements. Immunohistochemistry showed complete loss of E-cadherin expression, diffuse HER2 overexpression (3+), GATA3 positivity, and androgen receptor expression, confirming HER2-positive classical invasive lobular carcinoma. **Conclusion:** HER2-positive cILC is a rare but clinically significant variant of breast carcinoma. Recognition of this entity is important because HER2-directed therapies may substantially influence prognosis and treatment outcomes. Continued reporting of such cases is essential to improve understanding of their biological behavior and therapeutic implications.

Keywords: HER2-Positive Invasive Lobular Carcinoma, Classical Invasive Lobular Carcinoma, Breast Carcinoma, E-Cadherin Loss, HER2 Overexpression, Rare Breast Tumor.

INTRODUCTION

Invasive lobular carcinoma (ILC) is the second most common histologic subtype of breast carcinoma after invasive carcinoma of no special type, accounting for approximately 3–15% of invasive breast malignancies. It typically affects postmenopausal women between 55 and 60 years of age and is characterized by loss of cellular cohesion due to inactivation of the CDH1 gene encoding E-cadherin. Histologically, tumor cells infiltrate in single-file linear arrangements or as dispersed individual cells within fibrous stroma.[1–3]

Most classical ILCs demonstrate a luminal phenotype characterized by strong ER and PR expression, low proliferative activity, and lack of HER2 amplification. HER2 positivity is well recognized in invasive ductal carcinoma but remains distinctly uncommon in classical ILC. Recent studies have shown that HER2-positive cILC may represent a biologically unique subgroup with younger age at presentation, lower hormone receptor expression, increased proliferative activity, and potentially more aggressive clinical behavior.[4–6]

Because of its rarity, the clinicopathological characteristics and prognostic implications of HER2-positive cILC remain incompletely understood. We report a rare case of HER2-positive classical invasive lobular carcinoma occurring in a relatively young female and discuss its diagnostic and therapeutic significance in light of current literature.

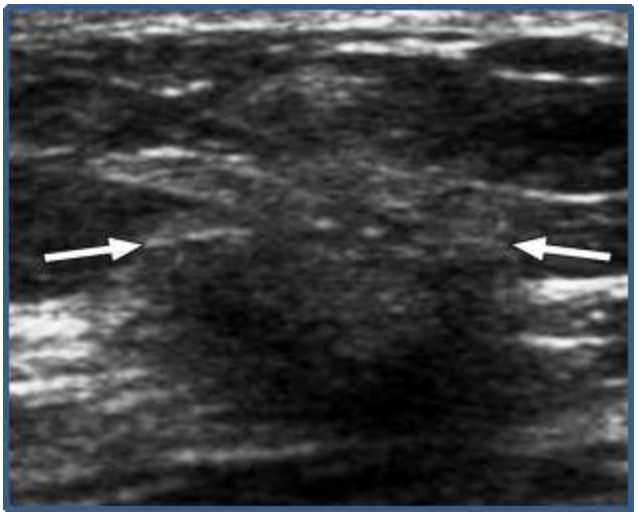
Case Presentation

A 41-year-old woman presented with a palpable lump in the left breast associated with mild discomfort of several months' duration. There was no history of nipple discharge, skin ulceration, breast surgery, hormonal therapy, or prior breast disease. Family history was negative for breast and ovarian carcinoma.

Clinical examination revealed a palpable breast mass in the left breast. Radiologic evaluation suggested a suspicious lesion, and a tru-cut core biopsy was performed for histopathological examination. Additional immunohistochemical studies were undertaken for tumor characterization.

Radiological Findings

Ultrasonography of the left breast revealed an irregular hypoechoic lesion with ill-defined to spiculated margins and posterior acoustic shadowing. Architectural distortion of the surrounding breast parenchyma was noted. The lesion exhibited internal vascularity on color Doppler examination and demonstrated a non-parallel orientation relative to the skin surface. No definite cystic component was identified. The imaging features were highly suspicious for malignancy (BI-RADS 4/5) and were compatible with the infiltrative growth pattern typically encountered in invasive lobular carcinoma.



MATERIALS AND METHODS

Six cores of breast tissue obtained by tru-cut biopsy were submitted for histopathological examination. Specimens were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, and stained with hematoxylin and eosin.

Immunohistochemistry was performed using antibodies against E-cadherin, HER2/neu, GATA3, and androgen receptor (AR). HER2 immunoreactivity was interpreted according to current ASCO/CAP guidelines.

Pathological Findings

Six grey-white soft tissue cores measuring 0.5–2.0 cm in aggregate length were received and entirely processed for histological examination.

Microscopic evaluation revealed breast tissue infiltrated by a malignant epithelial neoplasm composed predominantly of discohesive tumor cells infiltrating through a fibrocollagenous stroma. The tumor cells were arranged singly and in linear cords, producing the characteristic Indian-file growth pattern. Individual cells displayed round-to-oval hyperchromatic nuclei, irregular nuclear contours, inconspicuous nucleoli, and moderate eosinophilic cytoplasm. Occasional intranuclear cytoplasmic inclusions were present. Focal infiltration of adjacent fibroadipose tissue and mild chronic inflammatory infiltrates were identified. No glandular differentiation, cohesive nests, or definite duct formation were observed. The

overall morphological features were diagnostic of classical invasive lobular carcinoma.

Microscopy Figure:

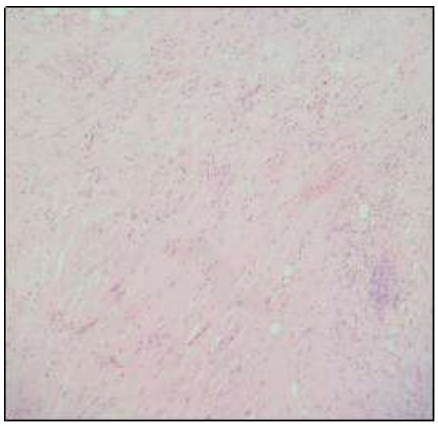


Figure 1 (H&E, 10×): Low-power photomicrograph demonstrating infiltrative growth of discohesive tumor cells arranged in characteristic single-file (Indian-file) linear cords within fibrocollagenous stroma.

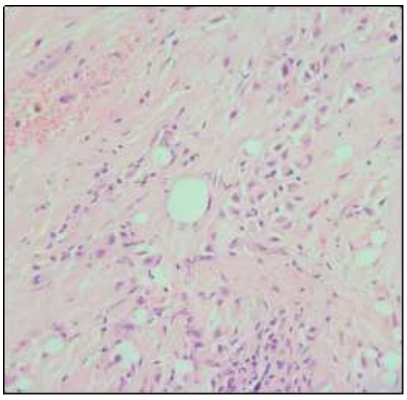


Figure 2 (H&E, 40×): High-power view showing individual malignant cells with hyperchromatic nuclei, irregular nuclear membranes, occasional nuclear inclusions, and moderate eosinophilic cytoplasm.

Immunohistochemistry

Immunohistochemical analysis demonstrated complete loss of E-cadherin expression. HER2/neu showed strong, complete circumferential membranous staining (3+) in approximately 80–90% of tumor cells. GATA3 exhibited strong nuclear positivity, while androgen receptor expression was identified in a substantial proportion of tumor cells. These findings confirmed the diagnosis of HER2-positive classical invasive lobular carcinoma.

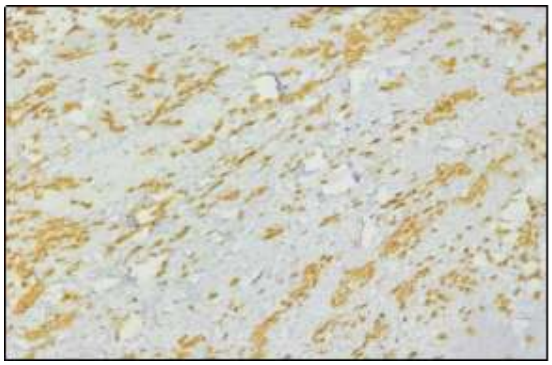


Figure 3 (HER2 IHC, 10×): Diffuse strong circumferential membranous staining involving the majority of tumor cells.

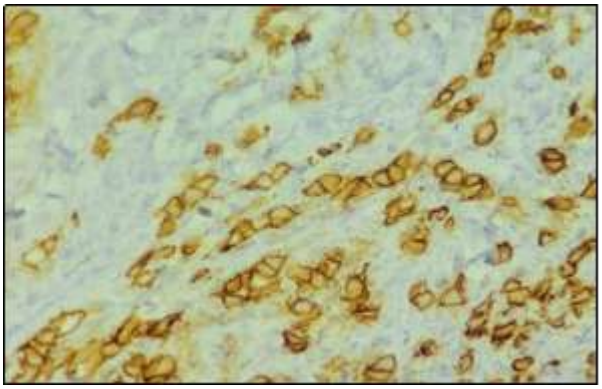


Figure 4 (HER2 IHC, 40×): High-power image confirming intense complete membranous HER2 positivity consistent with HER2 score 3+.

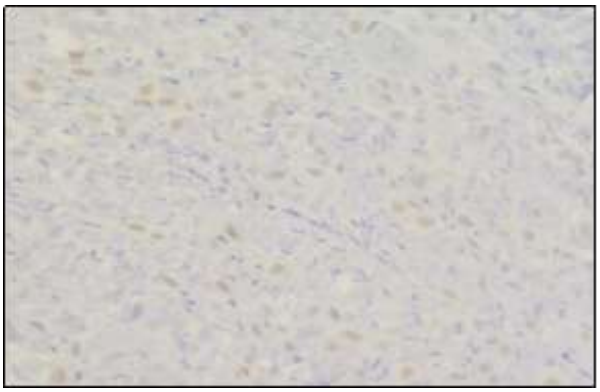


Figure 5 (AR IHC): Tumor cells exhibiting moderate nuclear positivity for androgen receptor.
Immunohistochemical Findings

Immunohistochemistry Demonstrated:

Marker	Result
1. **E-cadherin**	Complete loss
2. **HER2/neu**	Strong complete membranous positivity (3+) in 80–90% cells
3. **GATA3**	Strong nuclear positivity in 30–40% cells
4. **AR**	Nuclear positivity in 40–50% cells

The complete loss of E-cadherin confirmed lobular differentiation, while HER2 overexpression established the diagnosis of HER2-positive classical invasive lobular carcinoma.

Final Diagnosis

HER2-positive Classical Invasive Lobular Carcinoma of Breast (Core Needle Biopsy)

DISCUSSION

Classical invasive lobular carcinoma is characterized by loss of E-cadherin-mediated intercellular adhesion secondary to CDH1 gene alterations. This molecular event is responsible for the hallmark discohesive morphology and single-file infiltrative pattern observed histologically.1,2

HER2 amplification is uncommon in classical ILC, with reported frequencies ranging from approximately 3% to 7%.4 Consequently, HER2-positive cILC remains a rare and relatively understudied breast cancer subtype. Emerging evidence suggests that these tumors may exhibit clinicopathological features distinct from conventional HER2-negative lobular carcinomas.

Studies have demonstrated that HER2-positive cILCs tend to present at a younger age and may show increased proliferative activity, reduced hormone receptor expression, and a greater likelihood of nodal or distant metastasis.4 These observations support the hypothesis that HER2-positive cILC represents a biologically distinct subgroup with potentially more aggressive behavior.

In the present case, the patient was significantly younger than the typical age

group associated with conventional cILC. Despite retaining the characteristic histological features of lobular differentiation and complete loss of E-cadherin expression, the tumor exhibited diffuse and strong HER2 overexpression, highlighting the importance of comprehensive immunohistochemical evaluation.

Activation of HER2-associated signaling pathways, including PI3K/AKT and MAPK cascades, may contribute to tumor progression and therapeutic responsiveness.4,7 Identification of HER2 positivity is therefore clinically relevant because affected patients may benefit from HER2-targeted therapies such as trastuzumab, pertuzumab, and newer anti-HER2 agents.

This case emphasizes the importance of routine HER2 assessment even in tumors displaying unequivocal lobular morphology, particularly in younger patients or those with atypical clinicopathological characteristics.

CONCLUSION

HER2-positive classical invasive lobular carcinoma is an exceptionally rare variant of breast carcinoma. Despite exhibiting the characteristic morphology and E-cadherin loss of conventional cILC, these tumors possess a distinct molecular profile that may confer more aggressive biological behavior.

Identification of HER2 positivity has important therapeutic implications because targeted anti-HER2 therapy can significantly alter patient management. Greater awareness and documentation of such cases will improve understanding of their clinicopathological spectrum and prognostic significance.

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