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A histomorphological and immunohistochemical analysis of invasive lobular carcinoma of breast: A case series

Meera Suchiang[1], Gunabhi Ram Das[2], Swagata Dowerah[3], Julee Saikia[4], Washima Rahman[5], Mondita Borgohain[6], Gayatri Gogoi[7]

[1,4,5]Second Year Postgraduate Resident, [6]Professor, [7]Associate Professor, Department of Pathology, [2]Associate Professor, Department of General Surgery, Assam Medical College and Hospital, Dibrugarh, [3]Associate Professor, Department of Pathology, Tinsukia Medical College and Hospital, Tinsukia, Assam, India

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ABSTRACT

Invasive lobular carcinoma (ILC) is the second most common special subtype of invasive breast carcinoma comprising 5–15%. ILC defines as invasive carcinoma comprising non-cohesive single-file linear pattern in fibrous stroma. The aim of the study was to evaluate the histomorphological features and immunohistochemical analysis of ILC. A total of 19 cases were encountered from March 2020 to February 2024 out of 129 breast cancers. The sociodemographic profiles and clinicopathological parameters of the patients were studied with special emphasis on their morphology and hormone receptor status. The mean age of patients is 42.8 years. Out of 19 cases, 84.2% showed feature of classic type, 5.2% of tubule-lobular, and 10.5% of pleomorphic lobular carcinoma. The majority of cases (63.2%) showed histologic Grade 2, and 10.5% showed Grade 3. On immunohistochemistry examination, 79% were estrogen receptor (ER) and progesterone receptor (PR) positive with 10.5% of cases was human epidermal growth factor receptor 2/neu (HER2/neu) positive. Our study showed higher cases of classic type ILC, mostly of histologic Grade 2; higher ER-PR receptor positivity and HER2/neu negativity.

Key words: Invasive lobular carcinoma; Pleomorphic lobular carcinoma; Hormone receptor; Human epidermal growth factor receptor 2/neu

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INTRODUCTION

The two most common types of breast cancer are the invasive duct carcinoma or invasive breast cancer of no special type (NST) and the invasive lobular carcinoma (ILC) of breast. The World Health Organization (WHO) classification of breast tumors defines ILC as an invasive carcinoma comprising non-cohesive cells which are either individually dispersed or arranged in a single-file linear pattern in a fibrous stroma. This tumor constitutes 5–15% of invasive breast tumor cases with a rising incidence as compared to invasive breast carcinoma (IBC) NST, possibly related to an increase in hormone replacement therapy and an increased consumption of alcohol in recent times.[1]

Loss of E-cadherin, a transmembrane protein which mediates cell-to-cell adhesion, leads to the characteristic discohesive pattern of growth seen in ILC.[2] They commonly present as an irregular, poorly delimited tumor which is difficult to define macroscopically due to the diffuse growth pattern of the infiltrate.[3] Mammography has a lower sensitivity for the detection of ILC (57–89%) than IBC-NST while ultrasonography is a more sensitive (78–95%) diagnostic modality, although the size of the tumor can be underestimated.[1] Classic ILC is characterized by a proliferation of small cells that lack cohesion and are individually dispersed in a fibrous connective tissue or arranged in linear cords in a single file, often forming a concentric pattern around normal ducts.[1] Other histological

Address for Correspondence:
Dr. Gayatri Gogoi, Associate Professor, Department of Pathology, Assam Medical College and Hospital, Dibrugarh - 786 002, Assam, India.
Mobile: +91-9435030084. **E-mail:** gayatrigogoi303@gmail.com

patterns include solid pattern, alveolar pattern, pleomorphic lobular carcinoma (PLC), and the tubulolobular pattern.

MATERIALS AND METHODS

A retrospective analytic study was done for a period of 4 years from March 2020 to February 2024.

A total of 19 cases were encountered in between this period. The demographic profiles and the clinicopathological features which include patient age, sex, family history, clinical history, site of involvement, tumor size, histopathologic type, and histological grade were considered.

Formalin-fixed paraffin-embedded tissue sections were stained with hematoxylin and eosin. Detailed microscopic findings were studied regarding the type of ILC. For tumor grading, modified Bloom-Scarff-Richardson grading system was used, based on degree of tubule formation, nuclear pleomorphism, and mitotic figures. By adding these scores, 3–5 points are Grade I, 6–7 is Grade II, and 8–9 is Grade III.[4] Axillary lymph node status was examined for evidence of metastasis. Immunohistochemical analysis for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2/neu (HER2/neu) was assessed.

ER, PR, HER2/neu interpretation, and scoring were based on American Society of Clinical Oncology/College of American Pathologist Recommendations 2010.[5]

ER interpretation

Distinct nuclear staining in at least one or more tumor cells was interpreted as positive.

PR interpretation

Distinct nuclear staining in at least one or more tumor cells was interpreted as positive.

However, we also followed Allred scoring system where the proportion and intensity of positive tumor cells which are scored from 0 to 5 and 0–3, respectively. The total score is obtained by the sum of proportion score and intensity score, ranging from 0 to 8 (Table 1).[6]

HER2/neu scoring is a semiquantitative system based on the intensity of staining and percentage of membrane-positive cells, giving a score range of 0–3+ (Table 2).[6]

Inclusion criteria

All histologically confirmed ILCs with available demographic information were included in the study.

Exclusion criteria

All other histopathological types of IBC were excluded from the study.

Table 1: ER/PR score

Score for proportion
0=No staining
1≤1% Nuclei staining
2=1–10% Nuclei staining
3=11–33% Nuclei staining
4=34–66% Nuclei staining
5=67–100% Nuclei staining
Score for intensity
0=No staining
1=Weak staining
2=Moderate staining
3=Strong staining

A score >2 has been adjudged the minimum score for defining estrogen receptor and progesterone receptor positive breast cancer

Table 2: HER2/neu scoring

3+: More than 30% invasive BRCA cells showing strong complete homogenous membrane positive by HER2/Neu was interpreted as positive
2+: More than 30% invasive BRCA showing moderate or incomplete membrane-positive HER2/Neu was interpreted as equivocal
1+: Any proportion of invasive BRCA cells showing weak or incomplete membrane positive by HER2/Neu was interpreted as 1+, clinically taken as negative
0: No stain in any tumor cells, negative

HER2/neu: Human epidermal growth factor receptor 2/neu

RESULTS

A total of 19 cases of ILC of the breast were encountered between March 2020 and February 2024 out of a total of 129 breast carcinoma cases in the histopathology section of a tertiary care center in Northeast India (Table 3). The clinicopathological features are given in (Table 4) along with hormone receptor status and HER2 status (Tables 5 and 6). The youngest patient was 26 years old while the oldest was 65 years. Maximum cases were in the age group of 36–45 years (7 cases) followed by 26–35 years (5 cases) and 46–55 years (5 cases). About 84% of the patients were housewives and 84% were married. None of the cases except one had any family history of breast cancer. All were non-diabetic and all the cases belonged to low-income group. Breastfeeding history was present in 87.5% of cases, and early menarche was seen in only one case. Ethnically, 53% belonged to other backward classes followed by scheduled tribe in 21% of cases. About 26% of cases were nulliparous. All the cases were non-alcoholic, non-smoker, with no history of tobacco intake and all were non-vegetarian in their food habits. Average body mass index of the patients was 21.1.

Left breast was involved in 58% of cases and the right breast in 42% of cases. The majority of our cases were of the classical type with discohesive single cells arranged in Indian file pattern in a fibrous stroma (Figures 1 and 2) while there was one tubule lobular variant and 2 pleomorphic variant of ILC (Figure 3). Tumor-infiltrating lymphocytes were not seen. Grading of the tumors showed Grade 1 in

Table 3: Cases of ILC

Features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age (years)	35	26	42	36	30	55	38	40	40	26
Sex	Female	Female	Female	Female	Female	Female	Female	Female	Female	Female
Laterality	Left	Right	Left	Right	Left	Left	Left	Right	Right	Left
Tumor size	<5 cm	<5 cm	<5 cm	5–10 cm	5–10 cm	10–15 cm	<5 cm	5–10 cm	<5 cm	5–10 cm
Histomorphology type	Classic	Classic	Tubulolobular	Classic	Classic	Pleomorphic	Classic	Classic	Classic	Classic
Grade	2	2	1	2	2	3	2	2	1	2
No. of positive lymph node	0	1	0	0	3	3	0	5	0	3
Lymphovascular invasion	No	no	no	no	no	Yes	no	yes	no	no
ER/PR/HER2/neu	+/+/-	+/+/-	+/+/-	+/+/-	+/+/-	-/-/+	+/+/-	+/+/-	NA	+/+/-
Features	**Case 11**	**Case 12**	**Case 13**	**Case 14**	**Case 15**	**Case 16**	**Case 17**	**Case 18**		**Case 19**
Age (years)	56	28	50	50	55	65	42	45		55
Sex	Female	Female	Female	Female	Female	Female	Female	Female		Female
Laterality	Right	Left	Left	Right	Left	Left	Right	Right		Left
Tumor size	10–15 cm	<5 cm	10–15 cm	5–10 cm	<5 cm	5–10 cm	<5 cm	10–15 cm		10–15 cm
Histomorphology type	Classic	Classic	Classic	Classic	Classic	Pleomorphic	Classic	Classic		Classic
Grade	2	1	2	2	1	3	1	2		2
Number of positive lymph node	6	0	6	0	0	1	0	5		3
Lymphovascular invasion	yes	no	no	no	no	no	no	no		no
ER/PR/HER2/neu	+/+/-	NA	+/+/-	+/+/-	+/+/-	-/-/+	+/+/-	+/+/-		+/+/-

ILC: Invasive lobular carcinoma, ER: Estrogen receptor, PR: Progesterone receptor, HER2/neu: Human epidermal growth factor receptor 2/neu

Table 4: Clinicopathological features

Age at presentation	Number of patients	Percentage
26–35	5	26.3
36–45	7	36.8
46–55	5	26.3
56–65	2	10.5
Tumor size		
<5 cm	8	42.1
5–10 cm	6	31.5
10–15 cm	5	26.3
Laterality of involvement		
Left	11	57.9
Right	8	42.1
Histomorphology type		
Classic	16	84.2
Tubulolobular	1	5.2
Pleomorphic	2	10.5
Grade		
1	5	26.3
2	12	63.2
3	2	10.5
Lymphovascular invasion		
Yes	3	15.8
No	16	84.2
Number of positive lymph node		
0	9	47.3
1–3	6	31.5
>3	4	21.2

Table 5: Hormone receptor status

ER status	Number of cases	Percentage
Positive	15	79
Negative	2	10.5
Unknown	2	10.5
PR status		
Positive	15	79
Negative	2	10.5
Unknown	2	10.5

ER: Estrogen receptor, PR: Progesterone receptor

Table 6: HER2/neu status

HER2/neu status	Number of cases	Percentage
Positive	2	10.5
Negative	15	79
Unknown	2	10.5

HER2/neu: Human epidermal growth factor receptor 2/neu

five cases, Grade 2 in 12 cases, and Grade 3 in two cases. Lymphovascular invasion was seen in three cases.

About 79% cases were ER, PR positive (Figures 4 and 5); 10.5% ER, PR negative; and ER, PR status unknown in two cases. HER2/neu was positive in 10.5% of cases (Figure 6)

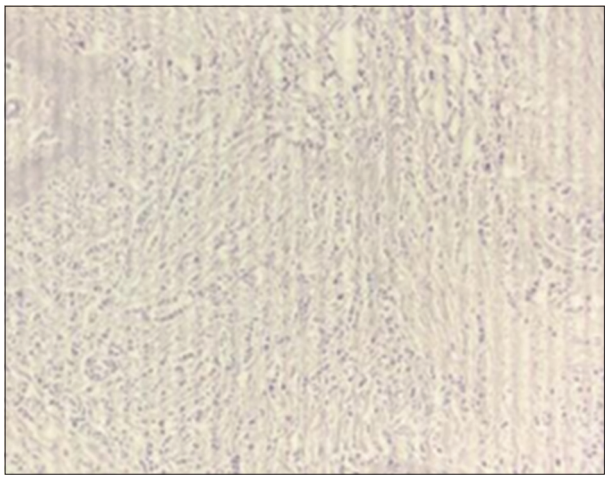

Figure 1: Invasive lobular carcinoma, classic type showing tumor cells arranged in linear cords in a single file that invades the stroma (low power)

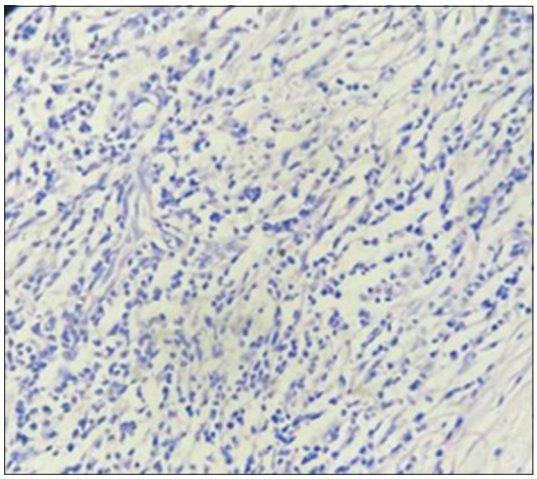

Figure 2: Invasive lobular carcinoma showing small round tumor cells that lack cohesion and are individually dispersed in a fibrous connective tissue

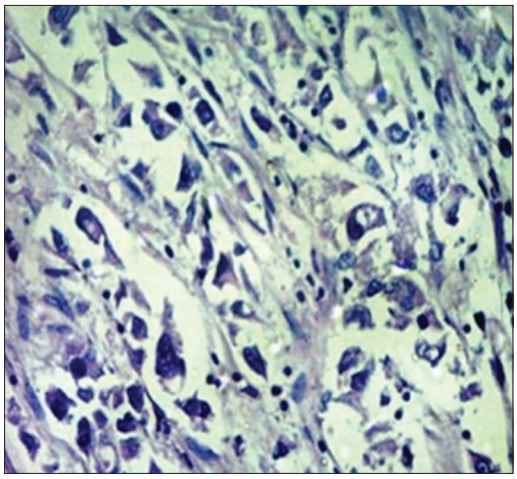

Figure 3: Pleomorphic lobular carcinoma showing marked nuclear pleomorphism

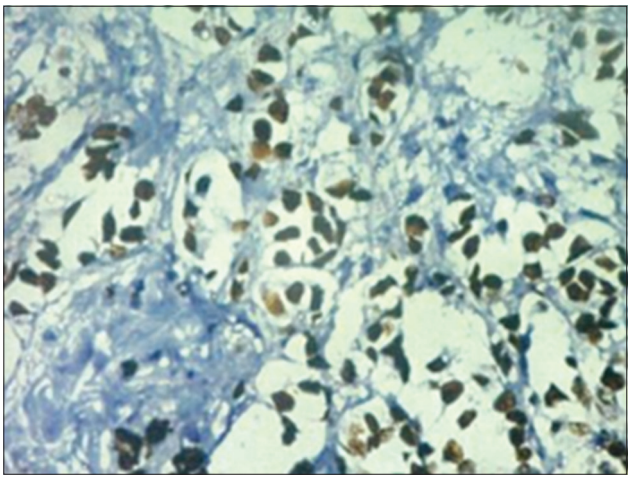

Figure 4: Strong estrogen receptor, positive (nuclear) in invasive tumor cells

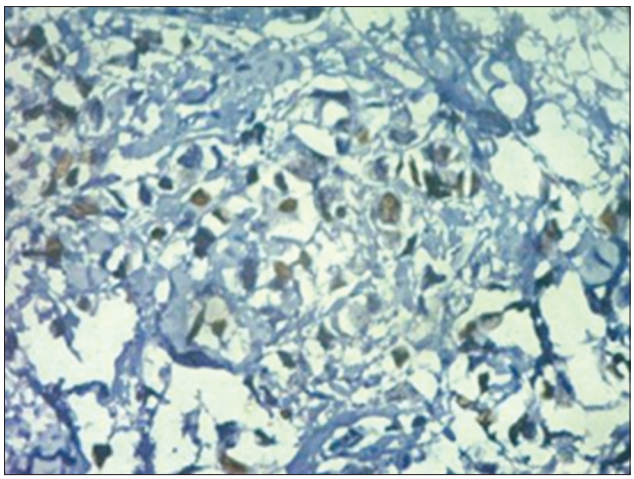

Figure 5: Moderate progesterone receptor positive (nuclear) in invasive tumor cells

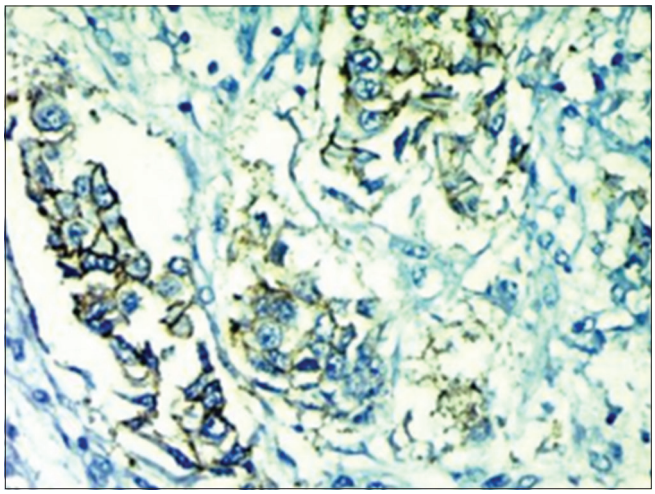

Figure 6: Human epidermal growth factor receptor 2 positive (membrane) strong, complete, homogenous in >10% invasive tumor cells

and negative in 79% of cases and immunohistochemistry (IHC) was not done in two cases. Fifteen cases were of the luminal type, i.e., of luminal A like, 2 cases were HER2 positive (non-luminal) and there were no triple-negative cases.

DISCUSSION

Invasive lobular breast cancer (ILC ~10–15%) happens to be the second most common subtype of breast cancer after IBC-NST, which comprises the majority (~75%) cases of breast cancer diagnosed worldwide.[7] At our center, ILC comprised 15% of all breast cancer cases, being the most common special type of breast cancer. In a study by Danzinger et al., ILC comprised 16.6% of breast cancer cases which is comparable to our study.[8] ILC is primarily diagnosed on histopathological examination of standard hematoxylin and eosin staining (H and E). According to the 5th edition of the WHO classification of breast tumors, IHC is not necessary for diagnosing ILC, as a proportion of shows expression of E-cadherin in spite of having the typical morphological features of ILC.[1] Nevertheless, many pathologists routinely use E-cadherin IHC to diagnose a case as ILC. In our study, we diagnosed the cases of ILC based on histomorphology alone.

The mean age of our patients was 42.8 years. In a study by Jagtap et al.,[9] the mean age of the patients was 52.8 years while in the study by Danzinger et al., it was 59.1 years. According to the literature, 80% of women diagnosed with ILC were in the postmenopausal category.[10,11] In our population, the mean age of occurrence was lower than in other studies. The incidence of a contralateral ILC is higher (8–19%) in ILC as compared to that of IBC NST.[1] All our cases were unilateral. Patil et al., also did not see any bilaterality in their study.[12] The left breast was more commonly involved than the right in our study.

Classic type of ILC was the most common type of ILC encountered comprising 84.2% of our cases while we had two cases of pleomorphic ILC (10.5%) and 1 tubulolobular variant (5.2%). Of the classic types of ILC, 25% were Grade 1 and 75% were Grade 2 tumors. This was in variance with the findings of Jagtap et al.,[9] where 71.4% of cases of classical ILC were of Grade 1 while 28.6% were of Grade 2. The tubulolobular variant was Grade 1 while both cases of PLC were Grade 3. PLC retains the distinctive growth pattern of lobular carcinoma but shows a greater degree of pleomorphism (defined as larger cells with marked nuclear pleomorphism, >4 times the size of lymphocytes/equivalent to that of high-grade ductal carcinoma *in situ*, with or without apocrine features) and a higher mitotic count than classic ILC. The tubulolobular pattern is composed of an admixture of cells showing a tubular growth pattern along with small uniform cells arranged in a linear pattern.[1] We did not get any alveolar, solid, or signet ring type of ILC during our study period.

Regarding hormone receptor status of these tumors, although various studies in the literature suggest that 80–95% of ILCs are ER positive, classic ILCs are almost invariably ER positive.[1] ER was found to be expressed in the classic form and in subtypes, with the highest rate of positivity (100%) in the alveolar subtype and the lowest (10%) in PLC. On the other hand, ERBB2 (HER2) amplification and overexpression were rare in ILC, mostly restricted to the pleomorphic type.[1] Others have also noted that the majority of ILC are estrogen and PR positive and do not express HER2/neu.[13] In our study, however, 79% of cases were ER, PR positive; 10.5% were ER, PR negative; and the ER, PR status is unknown in two cases. About 10.5% were HER2 positive. Jagtap et al., in their study, found that 84.6% were ER/PR positive and 23% were positive for HER2. An ER/PR/HER2-triple-negative immunophenotype is said to be observed in about 2–9% of ILCs.[14,15]

CONCLUSION

With time, the concept of ILC is changing. While currently ILC is mostly a morphological entity with a specific type of growth pattern, it is increasingly being recognized as a distinct morphomolecular entity. ILC has a worse long-term prognosis as compared to IBC-NST, and therefore, this entity needs greater attention in diagnosis and breast cancer research. Our study was an attempt to enumerate the patterns of ILC in our particular geoethnic milieu.

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Authors' Contributions:
MS- Literature search, Clinical studies, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing; **GRD-** Concepts, Clinical studies, Data acquisition, Manuscript review; **SD-** Definition of intellectual content, Data analysis, Manuscript preparation, Manuscript review; **JS-** Literature search, Data acquisition, Data analysis, Manuscript preparation; **WR-** Literature search, Data acquisition, Data analysis, Manuscript preparation; **MB-** Concepts, Clinical studies, Data acquisition, Manuscript review; **GG-** Concepts, Design, Definition of intellectual content, Literature search, Clinical studies, Data acquisition, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review.

Work attributed to:
Assam Medical College and Hospital, Dibrugarh - 786002, Assam, India.

Orcid ID:
Dr. Meera Suchiang - https://orcid.org/0009-0004-4118-4413
Dr. Gunabhi Ram Das - https://orcid.org/0000-0003-2094-7886
Dr. Swagata Dowerah - https://orcid.org/0000-0003-2139-4697
Dr. Julee Saikia - https://orcid.org/0009-0008-4900-8835
Dr. Washima Rahman - https://orcid.org/0009-0002-6770-6182
Dr. Mondita Borgohain - https://orcid.org/0009-0006-8809-8031
Dr. Gayatri Gogoi - https://orcid.org/0000-0001-9845-1835

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