

Original Research Article

Invasive Lobular Carcinoma of Breast Histopathological Subtypes: Clinicopathological Study

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ABSTRACT

Introduction: Lobular carcinoma of breast is second most common type of breast cancer after invasive breast carcinoma-NST. The incidence of invasive lobular carcinoma appears to be increasing, particularly in post-menopausal women and it may partly be related to hormonal treatment.

Aim and Objectives: To evaluate the clinicopathological features of 13 cases of lobular carcinoma of breast with special emphasis on histopathological variants and its significance.

Materials and methods: Our study includes 13 cases of invasive lobular carcinoma in a total of 292 consecutive cases of malignant breast tumors removed surgically during study period from May 2007 to April 2016. The detailed clinicopathological study of 13 cases of lobular carcinoma of breast includes clinical presentation, site, size of tumor, gross features, lymph node status, histopathological diagnosis, tumor grade and immunohistochemical study.

Observations: Out of total 13 cases 7 showed features of classical lobular carcinoma (53.8%), 2 showed features of pleomorphic lobular carcinoma (15.4%), 3 cases showed mixed lobular carcinoma (23%) and 1 case was of signet ring type invasive lobular carcinoma (7.7%). The age of presentation ranged from 40 to 70 years with a mean age of 52.8 years. Largest tumor size was 7 cm and smallest tumor was of size 2 cm with a mean tumor size of 4.54 cm. Out of total 13 cases, 8 showed axillary nodal metastasis and on immunohistochemical study 84.6% were ER/PR positive and 23% were positive for HER2.

Conclusion: Our study showed invasive lobular carcinoma is associated with higher age of diagnosis, larger tumor size, bilateral breast involvement, multifocal tumor, mostly grade-II on histopathology, more ER/PR receptor positivity, HER2 negativity and patient presents with distant metastasis at the time of diagnosis.

Key words: Lobular lesions of breast, Breast cancer, Lobular carcinoma histopathology.

INTRODUCTION

The commonest human cancer throughout world is breast cancer. Its incidence and mortality is particularly high in developed countries. ^[1] Now a days early diagnosis of breast cancer is emphasized by using techniques like clinical examination of breast, sonomammography and use of fine needle aspiration cytology. Also

techniques like stereotactic biopsy, frozen section etc. helps in immediate pathological diagnosis and also aids surgeons to treat patient early.

Breast carcinomas are broadly classified into invasive breast carcinoma-NST and special type cancer. ^[2] Invasive lobular carcinoma is the second most common type of invasive breast carcinoma

having incidence between 0.6-20%. [3-5] The incidence of invasive lobular carcinoma is increasing, which is postulated to be secondary increase in use of combined replacement hormonal therapy. [6,7]

Invasive lobular carcinoma has a distinct histological behaviour compared with invasive breast carcinoma-NST and other special types of breast carcinoma. In comparison to invasive breast carcinoma-NST, Invasive lobular carcinoma is seen in advanced age, bilateral breast involvement, multifocal, larger tumor size, commonly grade-II tumor, more ER/PR receptor positivity and with distant metastasis. [7] The objective of this study is to categorize invasive lobular carcinoma into various subtypes depending on histopathological features and its clinical correlation.

MATERIALS AND METHODS

This is a retrospective, analytical study done at a tertiary care centre for a period of 9 years from May 2007 to April 2016. The clinical data was retrieved from medical records of the institute. The standard protocol was used for clinicopathological features which included patient age, sex, clinical history, size of lump, site, quadrant of breast involved, gross specimen details and histopathological features with diagnosis. Additional help of fine needle aspiration cytology report, sonomammography, immunohistochemical and other radiological finding were considered and correlated. Formalin fixed, paraffin embedded tissue sections were stained with hematoxylin and eosin. Detailed microscopic findings were studied. Axillary lymph node status was studied for microscopic evaluation for evidence of metastasis, perinodal spill. Contralateral lesions if present were studied. ER/PR/HER2 antibodies were assessed using DAKO reagent two step procedure.

Inclusive criteria: All invasive lobular carcinoma were included in the study

Exclusive criteria: All other histopathological types apart from invasive lobular carcinoma were excluded. Cases of

lobular carcinoma in situ, benign lobular lesions were excluded.

For tumor grading Bloom-Scaff-Richardson grading system was used, based on tubule formation, nuclear pleomorphism and mitotic figures. We have used Olympus microscope with 10x eye piece and seen on 40x field (field diameter 0.44mm) mitosis per 10 high power fields for histopathological slide examination.

RESULTS

A total of 292 consecutive cases of surgically removed breast specimens (mastectomy/modified radical mastectomy) for breast malignancy were analyzed. Out of which 13 cases of invasive lobular carcinoma were studied. The detailed analysis for clinicopathological features of classical lobular carcinoma is given in [Table-1](#) and of other variants of lobular carcinoma is given in [Table-2](#).

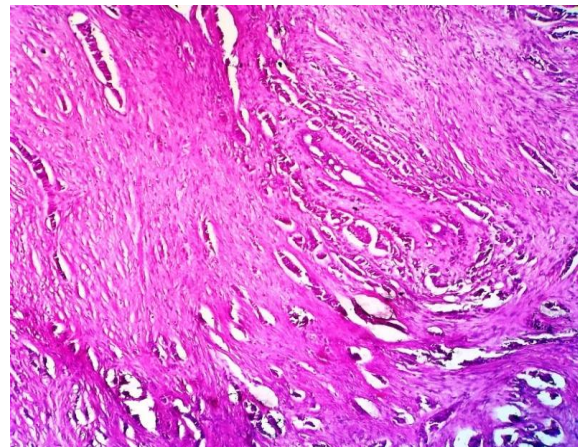


Fig-1 Photomicrograph showing classical invasive lobular carcinoma with Indian file pattern (40x H and E stain)

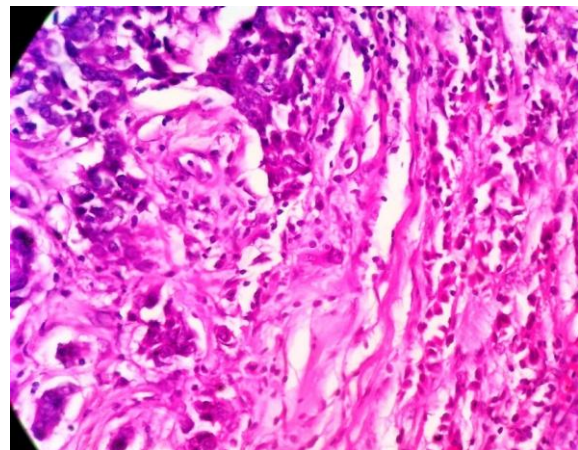


Fig-2 Photomicrograph showing pleomorphic lobular carcinoma (100x H and E stain).

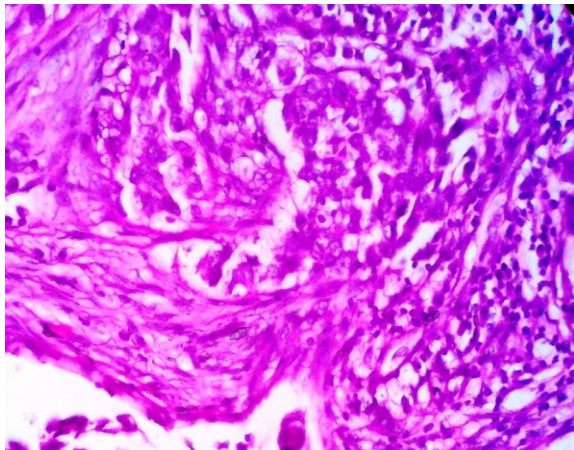


Fig-3, Photomicrograph showing signet ring variant of invasive lobular carcinoma (400x H and E stain).

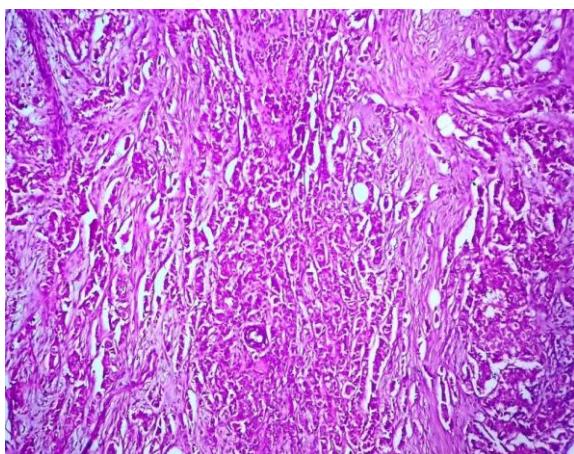


Fig-4, Photomicrograph showing mixed variant of invasive lobular pattern (100x H and E stain).

Clinicopathological findings:

All 13 cases of invasive lobular carcinoma of breast were females. Age range of patients was from 40 years to 70 years with mean age of 52.8 years. All cases

clinically presented with painless lump in the breast for duration ranging from 2 months to 18 months. Lump was unifocal in 92.3% and multifocal in 7.7%, with three lumps in one breast. One case showed bilateral breast lump (7.7%). Nipple discharge was noted in 1 case. Nipple/areola changes were seen in 8 cases. Left side of breast was involved in 30.8% and right side was involved in 69.2%. Fine needle aspiration cytology was done in all cases, and were reported positive for malignant cells, except one case which showed features of atypical proliferative lesion and was eventually confirmed to be malignant on frozen section. On gross tumor size varied from 2 cm to 7 cm with mean size of 4.54 cm. On immunohistochemical study 84.6% were ER/PR positive and 23% were positive for HER2.

Out of 13 cases 7 cases were of classical invasive lobular carcinoma, 3 showed features of mixed invasive breast carcinoma with invasive lobular carcinoma, 2 pleomorphic features and 1 case was of signet ring variant. The axillary nodal metastasis was noted in 61.5% cases. Two cases showed evidence of distal metastasis, both cases were pleomorphic invasive lobular carcinoma metastasizing to brain and other to lung was noted.

Table-1 Showing clinical, gross and microscopic features of classical invasive lobular carcinoma of breast.

Case Number	1	2	3	4	5	6	7
Histopathological diagnosis	Classical ILC	Classical ILC	Classical ILC	Classical ILC	Classical ILC	Classical ILC	Classical ILC
Patient age (years)	56	52	50	67	48	70	40
Duration of breast lump in months	2	2	12	2	4	5	3
Side	R	L	R	R	L	R	R
Quadrant	UIQ	Central	LIQ	UOQ	UIQ	UOQ	UOQ
Size of tumor	2x1.8x1	7x5x3	4x2.5x2	8x3x2	2x1.5x1	2x2x1.5	5x3x1
Tumor emboli	No	Yes	No	No	No	No	No
Consistency	Firm	Firm	Soft	Firm	Firm	Firm	Firm
Tumor fixed/mobile	Fixed	Mobile	Mobile	Mobile	Fixed	Mobile	Mobile
Tumor necrosis	No	No	No	No	No	No	No
Nipple/ areola	Retracted	Normal	Normal	Normal	Retracted	Normal	Normal
Axillary lymph node involved/Total	0/13	6/9	0/11	0/5	0/6	2/16	3/11
Histological tumor grade	Gr-II	Gr-I	Gr-I	Gr-I	Gr-II	Gr-I	Gr-I
Tumor multicentricity	No	No	No	Yes	No	No	No
Tumor bilaterality	No	No	No	No	No	No	Yes
ER/PR/HER2	+/+/-	+/+/-	+/+/-	-/-/-	+/+/-	+/+/+	-/-/-

ILC: invasive lobular carcinoma, R: Right, L: Left, UOQ-upper outer quadrant, UIQ-upper inner quadrant, LIQ-lower inner quadrant, LOQ-lower outer quadrant, + is positive, - is negative, Gr- grade. ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor-2

Table-2 Showing clinical, gross and microscopic features of other variants of invasive lobular carcinoma of breast.

Case number	8	9	10	11	12	13
Histopathological diagnosis	Signet ring ILC	Pleomorphic ILC	Mixed ILC	Mixed ILC	Pleomorphic ILC	Mixed ILC
Age of patient	60	45	46	40	42	70
Duration of lump in months	4	6	18	3	4	3
Side	L	R	R	R	L	R
Quadrant of breast	UOQ	UOQ	Central	UOQ, UIQ, LOQ	UOQ	UOQ
Size of tumor	4x3x1.5	6x3x2	6x2.5x2	6x5x4, 2x2x1, 2.5x2x2	4x2x2	3x2x2
Tumor emboli	Yes	No	No	No	Yes	Yes
Consistency	Firm	Firm	Firm-Hard	Firm	Firm	Firm
Tumor fixed/mobile	Fixed	Fixed	Fixed	Mobile	Mobile	Mobile
Tumor necrosis	No	No	Yes	No	Yes	Yes
Nipple/ areola	Normal	Normal	Retracted	Retracted	Normal	Normal
Axillary lymph node involved/Total	1/5	0/11	10/10	8/14	1/20	2/16
Histological grade	Gr-III	Gr-III	Gr-II	Gr-II	Gr-III	Gr-II
Tumor multicentricity	No	No	No	Yes	No	No
Tumor bilaterality	No	No	No	No	No	No
ER/PR/HER2	+/-	+/-	+/+	+/-	+/-	+/+

L-left, R-right, UOQ-upper outer quadrant, UIQ-upper inner quadrant, LIQ-lower inner quadrant, LOQ-lower outer quadrant, ILC-invasive lobular carcinoma, + is positive, - is negative, Gr- grade, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor-2

DISCUSSION

In 1941 Foote and Stewart first described lobular carcinoma of breast. [8] In their study they described lobular carcinoma in situ (LCIS) form, which is confined to the lobule and terminal ducts and invasive lobular carcinoma form. The histomorphological features of invasive lobular carcinoma are distinct from that of invasive breast carcinoma-NST. In invasive lobular carcinoma tumor cells are:

- Monotonous and discohesive with prominent intracytoplasmic lumina
- The invasive tumor pattern is frequently in a single file arrangement with a targeted growth pattern around the terminal duct.

On histopathologic morphology the invasive lobular carcinoma are divided into: classic type and other variants like solid variant, [8] signet ring variant, [9] alveolar variant, [5] tubule-lobular variant, [10] histiocytic variant, [11] pleomorphic variant [12] and a mixed lobular carcinoma. [11]

Based on nuclear features Winder and Semple divided invasive lobular carcinoma into classic and pleomorphic subtype. [13]

The classic invasive lobular carcinoma microscopically show uniform round cells with grade-II cytological features. The tumor shows linear infiltration

in surrounding stroma in rows or Indian file pattern or targetoid appearance around the ducts (Fig-1). Tumor cells are poorly cohesive. They may show signet ring differentiation. We use these features as diagnostic criteria. In our study case number 1 to 7 showed these features as shown in Table-1. In classical invasive lobular carcinoma 71.4% of cases were of grade-I while 28.6% were of grade-II. Classic lobular carcinoma is reported to have better prognosis than invasive breast carcinoma-NST, as classic lobular carcinoma is nearly always grade-I tumor. The conditions like lobular carcinoma in situ (LCIS), sclerosing adenosis, lobular hyperplasia should be kept as differential for low grade classic lobular carcinoma.

In case number- 9 and 12 as shown in Table-2, showed features of pleomorphic variant of invasive lobular carcinoma having tumor cells of large pleomorphic type with grade-III nuclear features. Pleomorphic lobular carcinoma is evidenced by its larger tumor size, higher grade cytological features, higher incidence of metastasis and presents with advanced stage. Pleomorphic lobular carcinoma represents 10% of invasive lobular carcinoma. [14] The histological architecture and pattern of tissue invasion is like invasive lobular carcinoma, but cytological

features resemble of high grade invasive breast carcinoma-NST (Fig-2). Therefore high grade invasive breast carcinoma-NST should be kept in mind as differential diagnosis.

In our study case number-8 as shown in Table-2 showed signet ring variant of invasive lobular carcinoma. This tumor showed (Fig-3) architectural and cytological features of invasive lobular carcinoma with more than 20% signet cell differentiation which was positive for mucin stains. Mucinous carcinomas should be considered as differential diagnosis in cases of signet ring lobular carcinomas.

In this study case number-10, 11 and 13 as shown in Table-2 showed invasive lobular carcinoma mixed pattern (Fig-4). Dixon et al described mixed variant, when invasive lobular carcinoma had classical growth pattern but degree of nuclear pleomorphism was greater. [11] The other histological variants of invasive lobular carcinoma such as alveolar, solid, tubulo-lobular etc was not found in our study.

We used modified RB scoring system (Nottingham) for tumor grading. [15] Our 5 cases of classical invasive lobular carcinoma are of grade-I and 2 cases of grade-II, while pleomorphic and signet cell variant were of grade-III. Mixed variant was of grade-II. Histological grade strongly correlates with prognosis. [16,17] So it is important to grade the tumor properly.

The prevalence of invasive lobular carcinoma recorded in our study is 4.45% (13/292), which is in concordance with various other studies. [3-5] On clinical presentation the patients with invasive lobular carcinoma tend to be slightly older than invasive breast carcinoma-NST, having reported mean age of 57 years compared to 64 years. [17] Data from literature shows 80% of women with invasive lobular carcinoma were postmenopausal. [3,7,18] in our study mean age was 52.8 years.

Incidence of contralateral invasive lobular carcinoma is higher (8-19%) as to that of invasive breast carcinoma NST. [19] In our study 1 case showed bilateral tumor.

Patients usually present with insidious growing ill defined painless palpable breast lump. It is observed that about 60% of patients having invasive lobular carcinoma have axillary lymph node or distant metastasis at the time of diagnosis. It is also observed about 30-80% patients eventually develop metastatic disease following surgery and/or chemotherapy, radiotherapy, hormonal therapy. [20] In our study out of total 13 cases of invasive lobular carcinoma 8 cases (61.5%) showed nodal metastasis.

Histopathological diagnostic criteria are important to give diagnosis, however in high grade tumor and suspicious cases E-cadherin study is helpful. Various studies of invasive lobular carcinoma shows ER and PR positivity in 70-95% of cases and rarely show expression for p53 and HER2. [17,18,21] The absence of E-cadherin membranous staining is characteristic of invasive lobular carcinoma. [22] In our study on immunohistochemistry, 84.6% were ER/PR positive and 23% were positive for HER2.

Overall the 5 years survival rate of invasive lobular carcinoma was reported approximately 85%. [7] In pleomorphic invasive lobular carcinoma prognosis is poor as compared to classic form of invasive lobular carcinoma. This is likely to be related to its recurrence and development to distant metastasis. [22] The surgical treatment of invasive lobular carcinoma has been a matter of debate as invasive lobular carcinoma is more commonly bilateral and multifocal and may recur. Mastectomy has been frequently the treatment of choice. However tumor size, stasis, axillary nodal status, prognosis and reactive markers determine the final mode of treatment. Pleomorphic lobular carcinoma is usually managed more aggressively than invasive lobular carcinoma. [23,24] Overall 5 year survival rate of invasive lobular carcinoma is approximately 85%. [7]

CONCLUSION

This study data shows that invasive lobular carcinoma is a distinct clinical and histopathological entity. We attempted to

study invasive lobular carcinoma and its variants on the basis of strict histomorphological criteria. Our study showed invasive lobular carcinoma is associated with higher age of diagnosis, larger tumor size, bilateral breast involvement, multifocal tumor, mostly grade-II on histopathology, more ER/PR receptor positivity, HER2 negativity and patient presents with distant metastasis at the time of diagnosis.

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