

Pleomorphic lobular carcinoma: is it more similar to a classic lobular cancer or to a high-grade ductal cancer?

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Background: Pleomorphic invasive lobular carcinoma (P-ILC) is an uncommon variety of invasive lobular carcinoma with aggressive clinical features. Little is described in the literature regarding this topic.

Materials and methods: We reviewed our experiences from 2010 to 2015 and compared 40 patients with P-ILC, 126 patients with classic-ILC (C-ILC) and 574 cases of high-grade invasive ductal carcinoma (HG-IDC). We studied the histologic and immunohistochemical features, clinical presentation and surgical treatment.

Results: P-ILC is diagnosed at the same age and tumor diameter as those of the other two histologic types. It is associated more frequently with multiple lymph node metastases and high proliferative index, and HER2/neu is amplified in 10% of cases. In spite of sharing some histologic characteristics with C-ILC (same growth pattern, loss of E-cadherin expression, same genetic pathway), its clinical and pathologic features define an autonomous entity. Its surgical treatment is similar to those of C-ILC and HG-IDC.

Conclusion: This is the first review comparing these three pathologic entities. Our findings may be useful in understanding this variety of invasive lobular carcinoma, and further studies are certainly needed in this field.

Keywords: breast cancer, lobular cancer, pleomorphic, mastectomy

Introduction

Invasive pleomorphic lobular carcinoma (P-ILC) was first described in 1982 by Dixon et al¹ and in 1987 by Page et al,² and represents ~2%–4% of invasive carcinomas in two different series.³

P-ILC is associated with worse prognostic factors (i.e., larger tumor size, more frequent axillary metastasis) compared with other lobular carcinomas (LCs), and this explains the higher risk of recurrence and decreased survival rate often reported in literature, although in some reports, no differences are noted.^{1,4,5,6–9} Fundamental histologic characteristics of P-ILC are represented by a growth pattern typical of lobular cancer (Figure 1A) and loss of E-cadherin (Figure 1B), also exhibiting a high degree of atypia and cellular pleomorphism, hyperchromatic nuclei (Figure 1C) and a higher mitotic index than classic-ILC (C-ILC). It is often associated with a pleomorphic “in situ” component with comedonecrosis (Figure 1D). It can also present an apocrine or histiocytoid differentiation.¹⁰

The literature reports that although invasive lobular carcinoma (ILC) is treated with mastectomy more often when compared with infiltrating ductal carcinoma (IDC),

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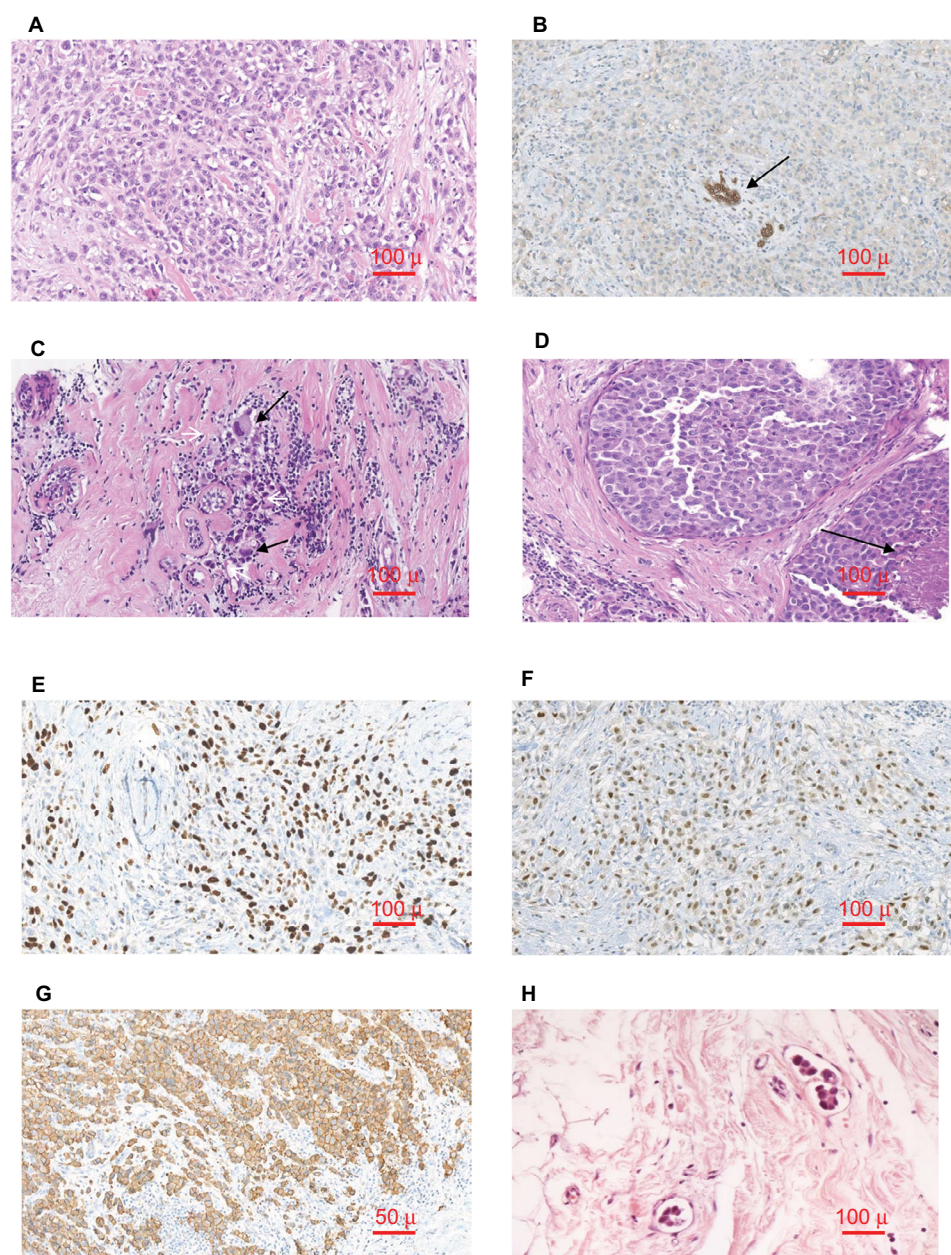


Figure 1 (A) H–E staining. P-ILC shows the same growth pattern as C-ILC. (B) Low expression or negativity for E-cadherin. The arrow indicates residual ductal structures. (C) H–E staining. Pleomorphic histiocytoid cells with nuclear hyperchromasia (arrows). (D) H–E staining. Comedonecrosis (arrow – in situ component). (E) High Ki67 in P-CLL. (F) neu overexpression (score 3+). (G) p53 overexpression, with weak positivity in more than 50% of cells (score 2). (H) H–E staining. LVI. **A to G** magnification $\times 20$, **H** magnification $\times 40$.

Abbreviations: H–E, hematoxylin–eosin; LVI, lymphovascular invasion; P-ILC, pleomorphic invasive lobular carcinoma; C-ILC, classic invasive lobular carcinoma.

survival and risk of local recurrence are similar, and therefore, the debate regarding surgical options for patients with lobular cancer is of particular interest.¹¹

Although P-ILC and high-grade IDC (HG-IDC) are two distinct pathologic entities, they share similarities regarding nuclear grade, biomolecular and clinical characteristics.

The purpose of our study is to retrospectively analyze our experience with P-ILC and to compare its clinicopathologic features and surgical treatment with those of C-ILC and HG-IDC.

Materials and methods

From January 2010 to June 2015, 1542 patients with primary breast cancer were treated at our Breast Unit. Recurrent cases or cases after neoadjuvant chemotherapy were excluded. Mixed cases (C-ILC with pleomorphic or IDC areas) were also excluded.

Data available for each case were age, stage according to International Union against Cancer and the American Joint Committee on Cancer (UICC/AJCC) 2010, histologic grade (G) according to the modified Scarff, Bloom and Richardson

score (Nottingham Combined Histologic Grade), multifocality (m), lymphovascular invasion (LVI) and type of surgery (S).^{12,13} If LVI was suspected, immunohistochemistry (IHC) with CD31 antibody was evaluated to distinguish it from artifacts.

We performed IHC for estrogen receptor (ER), progesterone receptor (PR), proliferative index (Ki67), p53 expression (p53) and HER2/neu oncogene expression. In cases of doubtful histotype, IHC for E-cadherin was performed. The clones used are reported in Table 1.

p53 was evaluated semi-quantitatively by using a scoring system as shown in Table 2.

HER2/neu was evaluated according to American Society of Clinical Oncology, College of American Pathologists (ASCO/CAP) 2013 guidelines, and cases prior to 2013 were re-evaluated. Cases scored 2+ were evaluated with dual-color fluorescence in situ hybridization on the centromere of chromosome 17 and on oncogene HER2/neu (locus 17q12, Kreatech™) according to ASCO/CAP 2013.¹⁴

P-ILC was defined as a high nuclear grade malignancy (significant cytologic atypia and pleomorphism) with lobular characteristics (loosely cohesive cells and negativity for E-cadherin), while HG-IDC was defined as IDC with a Scarff, Bloom and Richardson modified score (Nottingham Combined Histologic Grade) superior to 7.¹³

All treatments were discussed at the multidisciplinary weekly conference, and decisions regarding treatments verbalized in a standard format.

We recorded the type of surgery (mastectomy or partial resection, with or without removal of the nipple–areola complex [NAC]).

We also examined the quantity and type of neoplastic involvement of the NAC. When removed, the NAC was completely sectioned into 3–4 mm thick slices and histologically examined.

Table 1 Immunohistochemistry

	Clone	Source
ER	SP1	Roche™
PR	1E2	Roche
Ki67	30–9	Roche
p53	DO-7	Roche
HER2/neu	CB11	Cell Marque™
CD31	JC70	Cell Marque
E-cadherin	36	Roche

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

Table 2 p53 semi-quantitative score

Score 0	Positivity in less than 10% of cells
Score 1	Weak positivity in more than 10% and less than 50% of cells
Score 2	Strong positivity in more than 10% and less than 50% of cells or weak positivity in more than 50% of cells
Score 3	Strong positivity in more than 50% of cells

Two pathologists reviewed the histologic material independently (LC and DC). Assessment of tumor type was performed according to the criteria outlined in the World Health Organization Classification of Tumors.¹⁵

Statistical analysis was performed with a statistical package. Student's *t*-test for significance between means and binomial analyses using Pearson's χ^2 test were performed.

The study was conducted according to the principles laid down in the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Review Board of the San Giovanni-Addolorata Hospital, and we received a waiver for obtaining patient consent to review their cases, as data were analyzed in aggregate.

Results

Clinicopathologic data are presented in Table 3. There were 40 cases of P-ILC, while 126 were defined as C-ILC and 574 as HG-IDC.

The median age and tumor size were not significantly different in the three groups.

Both P-ILC and C-ILC were more frequently multicentric or multifocal than HG-IDC.

Lymph node metastases were more frequently diagnosed in P-ILC compared to C-ILC ($P<0.05$), and more than three lymph node metastases were more frequently diagnosed in P-ILC (20%) than in C-ILC (11%; $P<0.05$).

Hormone receptor positivity was more frequently expressed in P-ILC and C-ILC compared to HG-IDC ($P<0.01$), and differences in average ER/PR value between P-ILC and C-ILC were noted.

While C-ILC was never HER2/neu+, 20% of HG-IDC and 10% of P-ILC were amplified ($P<0.01$). Absolute values of Ki67 were higher for HG-IDC and lower for C-ILC, while P-ILC showed intermediate results ($P<0.01$).

Similar findings were registered for LVI positivity ($P<0.01$).

p53 was rarely positive in C-ILC. In P-ILC, it was weakly to moderately positive in 17.5% of cases (Figure 1F), while it was variably positive, from weak to strong, in 41.6% of cases of HG-IDC. These results were statistically significant ($P<0.01$).

Incidence of mastectomy or breast conservation did not differ among the three groups (Table 4). The NAC was

Table 3 Clinicopathologic characteristics

	P-ILC (n=40), %	C-ILC (n=126), %	HG-IDC (n=574), %	P-value		
				P-ILC/HG-IDC	P-ILC/C-ILC	C-ILC/HG-IDC
Age (years), median	66	64	63	NS	NS	NS
Multifocality	11 (27.5)	38 (30)	96 (17)	<0.01	NS	<0.01
Size (cm)						
<2	24 (60)	82 (65)	351 (61)			
>2	16 (40)	44 (35)	223 (39)	NS	NS	NS
Nodal status						
Negative	23 (57.5)	86 (68)	351 (61)	NS	NS	0.1
Positive	17 (42.5)	40 (32)	223 (39)	NS	<0.05	<0.05
>3 Lymph nodes	8 (20)	14 (11)	95 (16.5)	NS	<0.05	<0.05
ER+	38 (95)	126 (100)	431 (75)	<0.01	NS	<0.01
Average ER value	92±25	98±10	72±43	<0.01	<0.05	<0.01
PR+	30 (75)	224 (75)	362 (63)	<0.05	NS	<0.05
Average PR value	57±38	58±39	42±40.5	<0.05	NS	<0.05
Ki67 average value	27±15	10±6	39±22	<0.01	<0.01	<0.01
p53						
Score 0	33 (82.5)	118 (94)	335 (58)	<0.01	<0.01	<0.01
Score 1+	6 (15)	8 (6)	97 (17)			
Score 2+	1 (2.5)	0	54 (9)			
Score 3+	0	0	88 (15)			
HER2/neu	4 (10)	0	114 (20)	<0.01	<0.01	<0.01
LVI+	4 (10)	3 (2)	129 (22.5)	<0.01	<0.01	<0.01

Abbreviations: C-ILC, classic invasive lobular carcinoma; ER, estrogen receptor; HG-IDC, high-grade invasive ductal carcinoma; LVI, lymphovascular invasion; NS, nonsignificant; P-ILC, pleomorphic invasive lobular carcinoma; PR, progesterone receptor.

Table 4 Surgical treatment

	P-ILC (%)	C-ILC (%)	HG-IDC (%)	P-value
Mastectomy	10 (25)	41 (32.5)	153 (26.6)	NS
Partial resection	30 (75)	85 (67.5)	421 (73.4)	NS

Abbreviations: C-ILC, classic invasive lobular carcinoma; HG-IDC, high-grade invasive ductal carcinoma; NS, nonsignificant; P-ILC, pleomorphic invasive lobular carcinoma.

removed in 175 cases (23.6%); in the remaining cases, a nipple-sparing approach was adopted, with no differences noted among the three groups. NAC more frequently involved in lobular cases rather than in HG-IDC cases ($P<0.05$). However, the type of involvement was different, as the NAC involved direct infiltration of the tumor or cancer in situ (pagetoid spreading) in the former and lymphovascular invasion of the nipple in the latter (Table 5).

Discussion

To our knowledge, this is the first clinicopathologic study comparing P-ILC with C-ILC and HG-IDC. Our experience shows that P-ILC is rare, representing ~3% of all breast cancer cases. While P-ILC shares some features with each of the other two histologic forms, it represents an uncommon, autonomous entity.

P-ILC is a high-degree malignancy of the breast, with frequent lymph node metastases, and often involves more

than three lymph nodes, thus differing from C-ILC. However, lymph node positivity and multiple lymph node involvement were similar when P-ILC was compared to HG-IDC. P-ILC rarely does not express ER positivity, and this may be explained by an apocrine differentiation in some of these cases. Similarly, there was a different PR expression between LCs (classic and pleomorphic) and HG-IDC, while no difference was found between C-ILC and P-ILC.

Ki67 in P-ILC was intermediate between those of C-ILC (usually very low, below 15%) and HG-IDC (usually high; in any case >20%, and frequently as high as 90%), as shown in Figure 1E.

While HER2/neu was amplified in 20% of HG-IDC, it was never amplified in C-ILC and it was positive in 10% of P-ILC. This is similar to a previous report.¹⁶ The latter may be associated with a histiocytoid variant, previously described with low expression of hormone receptors, as we reported in our experience.^{17–19}

p53 was rarely and weakly expressed in C-ILC, while it was positive in 17.5% of cases of P-ILC (Figure 1G) and in over 40% of cases of HG-IDC.

We confirm that peritumoral LVI was rare in C-ILC, and it occurred in 10% of P-ILC and 22.5% of HG-IDC (Figure 1H). The cells of LC are poorly cohesive and often found in chains within “slit-like” spaces not covered by

Table 5 Involvement of NAC when removed

Type of involvement	P-ILC (n=10), %	C-ILI (n=31), %	HG-IDC (n=134), %	P-value
Any	6 (60)	18 (58)	51 (38)	0.06
Carcinoma in situ	1 (10)	3 (10)	21 (16)	0.04
Stromal infiltration	5 (50)	15 (48)	23 (17)	0.9
Lymphatic spread	0	0	7 (5)	0.04

Abbreviations: NAC, nipple–areola complex; C-ILC, classic invasive lobular carcinoma; HG-IDC, high-grade invasive ductal carcinoma; P-ILC, pleomorphic invasive lobular carcinoma.

endothelium (CD34+/CD31+). These areas, known as “pre-lymphatic spaces”, are lined by cells CD31–/CD34+. ²⁰ This network allows quick communication between the stroma and the main lymphatic system. The real invasion of lympho-vascular space (CD31+) was present in only 4.2% of all ILC cases, while it was 10% for P-ILC and 22.5% for HG-IDC.

Due to overlapping morphologic and IHC characteristics between C-ILC and HG-IDC, the origin of P-ILC has been debated. Some authors have suggested that P-ILC is a high-grade IDC with loss of E-cadherin expression. ^{21,22} However, molecular studies have demonstrated that P-ILC and C-ILC share several molecular features such as inactivation or downregulation of E-cadherin and a cell-to-cell adhesion molecule, as well as recurrent genomic changes. Comparative genomic hybridization showed a gain of 1q (1q+) in 100% and a loss of 16q (16q–) in 93% of cases, features that are typical of LCs, but are not seen in HG-IDC. Fluorescence in situ hybridization analysis showed der(1;16)/der(16)t(1;16) rearrangement, a typical “lobular phenotype”. P-ILC may have the same precursor and the same genetic pathway as C-ILC. ^{22,23} Additionally, it has been argued that P-ILC may develop through a molecular pathway similar to that of C-ILC, with the acquisition of further molecular alterations, more typical of high-grade ductal carcinomas, such as gain of HER2/neu, c-myc, p53 positivity and amplification of 8q24, 12q13 and 20q13. ^{6,21–24} So far, there have been no reported studies to establish the frequency of p53 and HER2/neu overexpression in P-ILC.

Radiologic features of LC can vary, as tumors are most commonly detected as a spiculated mass with or without calcifications on mammography or ultrasonography, but C-ILC and P-ILC cannot be differentiated on the bases of imaging findings. One report describes a false-negative rate with mammography in 4.5% of P-ILC and 14.9% of C-ILC. ²⁵ In the same study, magnetic resonance imaging revealed additional foci in five of 13 P-ILCs (38%) and 18 of 40 C-ILCs (45%), but was similar to ultrasound.

Sparse data exist in literature regarding the clinical presentation, prognosis and surgical treatment of P-ILC compared with C-ILC and HG-IDC. Availability of limited data is due

to the relative rarity of P-ILC, and studies usually have small sample sizes. It has been recently emphasized that patients with invasive LC, although presenting more frequently with multifocal and multicentric disease, have similar survival and local control rates compared with invasive ductal carcinoma. ¹¹ Similar findings have been described by a retrospective analysis of 1650 patients comparing these two groups, even when only patients treated with breast conservation were analyzed. ²⁶ When compared to C-ILC, it is reported that P-ILC is diagnosed at a more advanced stage, the tumor diameter can be larger, lymph node metastases are more frequently noted and that overall survival is shorter, with more frequent occurrence of distant metastases. ^{1,5,27} However, similar to our findings, there was no significant difference in the median patient age. ⁶

Conclusion

Our study has several limitations, as it is retrospective in nature and involves a small number of cases. However, it is evident in our experience that P-ILC is an uncommon autonomous entity that shares some features with both C-ILC and HG-IDC. While hormone receptors are almost always positive, HER2/neu is amplified in 10% of cases. Suggested surgical treatment does not differ in our experience, but lymph nodes are more often involved in P-ILC and multiple metastases are encountered in some 20% of patients.

These findings may be useful in understanding this clinical entity, and further studies are certainly needed in order to clarify the clinical options and strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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