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Research Article

Clinicopathologic and Radiologic Characteristics of Pleomorphic Lobular Breast Cancer

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Abstract

Objectives: The objective of the study was to evaluate clinicopathologic and radiologic features of patients with pleomorphic lobular breast cancer (pleomorphic lobular carcinoma [PLC]).

Methods: We retrospectively evaluated the clinicopathologic and radiologic features of 25 PLC patients treated in our division from 2012 to 2018.

Results: Median age was 50 (range, 42–55) and 48% were postmenopausal. The presence of spiculated mass was 92%. Median tumor size was 21.9 mm (SD±12.7 mm) and axillary lymph node positivity was 44%. Frequency of microcalcification was 12% and frequency of occult breast cancer was 8%. About 72% of patients had Stage 2 or 3 disease. De novo metastatic disease was 8% and another 8% developed metastasis during follow-up. ER, PR, and Her2/neu were positive in 76%, 44%, and 8%, respectively, and 16% of patients were triple negative. All tumors were Grade III. Median Ki-67 was 22% (range 3–90%). Frequency of lymphovascular invasion was 52%. Patients were followed median of 34.5 months (95% CI, 22.2–46.8), since during this period, two patients recurred and five died, median disease-free survival and overall survival could not be reached.

Conclusion: Our data suggest that patients with PLC present with poor prognostic features such as large tumor size, axillary lymph node positivity, and high lymphovascular invasion and tumor grade and Ki-67.

Keywords: Breast cancer, pleomorphic lobular carcinoma

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Breast cancer is the most common type of cancer among women[1] and most common subtype is invasive ductal carcinoma (IDC) (75%) followed by invasive lobular carcinoma (ILC) (8-14%).[2-4] Pleomorphic lobular carcinoma (PLC) is regarded as a rare variant of ILC which accounts for less than 1% of all epithelial breast cancers and less than 15% of ILCs.[1] This subtype was first described by Page in 1987 and aggressive behavior of the disease was emphasized in the following studies.[5-7] The World Health Organization (WHO) defined PLC in 2003.[8]

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PLC morphologically and immunophenotypically overlap with both IDC and ILC.[9] Histological structure and invasion pattern seem to be parallel with ILC, however, there is also similarity with IDC both showing cellular pleomorphism and nuclear atypical features. PLC patients tend to be older, have large tumors, and exhibit more axillary lymph node involvement at the time of diagnosis.[10-12] In addition, PLC often displays evidence of lymphovascular invasion, higher proliferative index, and high tumor grade[3,13] and has been shown to be associated with shorter relapse time and higher rates of distant metastasis.[6,7]

Very few studies have been published on the radiological features of PLC. Most PLCs demonstrated a spiculated mass or architectural distortion with or without calcifications on mammography and ultrasound, and also presented as a mass with type 3 contrast enhancement pattern (washout) on MRI.[14] Due to its diffuse growth pattern, PLC can behave as mammographically occult, with up to 19% of associated mammograms being negative. In addition, multicentricity and multifocality are other common findings on imaging.[14]

In the present study, we aimed to analyze the clinicopathologic and radiological features of patients diagnosed with PLC in our center between 2012 and 2018 and to discuss the results with a review of literature.

Methods

Data of patients diagnosed with PLC between August 2012 and July 2018 at our center were evaluated retrospectively. Age, menopause status, radiological characteristics at the time of diagnosis, core needle biopsy (bx), and histological features of surgical specimens were recorded. Tumor type was assessed according to the criteria outlined in the WHO classification of tumors. Pleomorphic subtype is separated mostly on the basis of nuclear morphology such as increased nuclear size, nuclear pleomorphism, nucleolar prominence, and increased mitotic activity. Stage was recorded according to the American Joint Committee on Cancer (AJCC) 2010. Histologic grade was evaluated according to the Nottingham histologic score system. Lymphovascular invasion, tumor proliferation index (Ki-67), and tumor grade were recorded. We performed immunohistochemistry (IHC) for ER, PR, and her2/neu amplification. Her2/neu was evaluated according to the American Society of Clinical Oncology guidelines. Cases which were scored 2+ with IHC were evaluated with dual color fluorescence in situ hybridization (FISH), according to the ASCO/CAP guidelines. Surgical procedure was recorded in three subtypes; modified radical mastectomy (MRM), mastectomy, and breast conserving surgery (BCS). All types of treatments and final status were recorded. RECIST 1.1 criteria were used for response evaluation. The data were analyzed with SPSS version 22.0.

Results

Study included 25 patients. Baseline characteristics of patients are summarized in Table 1. Core needle bx was performed for 24 patients at the time of diagnosis. Histological diagnosis of core needle bx and surgical specimens was different (Table 2). PLC histology was reported in only 7 (28%) patients with core needle bx materials, while pure PLC histology was detected in all surgical specimens. Features of surgical specimens are shown in Table 2.

Sixteen (64%) patients with locally advanced disease received neoadjuvant chemotherapy (NAC). The response was assessed as complete remission (CR) in one patient and as partial remission (PR) in four patients. Adjuvant treatments were administered in accordance with stage and hormone expression profile, as shown in Table 3. Surgical resection of primary tumor was performed for 21 patients.

Four (16%) patients having metastatic disease had Grade 3 tumors and three out of four tumors' were triple negative. One of the patients receiving NAC, developed leptomeningeal involvement during treatment. She also had triple-negative tumor and died 7 months after the initial diagnosis.

Since only two patients recurred and five died, median disease-free survival and overall survival could not be reached.

Table 1. Baseline characteristics

Age, years	
Median (range)	50 (42–55)
Menopausal status, n (%)	
Premenopausal	13 (52)
Postmenopausal	12 (48)
Radiological mass, n (%)	
Yes	23 (92)
No	2 (8)
Multicentric disease, n (%)	2 (8)
Microcalcification, n (%)	3 (12)
Primary tumor size*, mm	
Mean (±SD)	21.9 (12.7)
Positive axillary lymph node(s), n (%)	
Yes	11 (44)
No	14 (56)
Stage, n (%)	
Stage 1	5 (20)
Stages 2–3	18 (72)
Stage 4	2 (8)

*Longest diameter in PET-CT or USG.

Table 2. Histopathologic characteristics

Characteristic	Patient number (%)
Histology in core biopsy	
Invasive ductal carcinoma	6 (24)
Invasive lobular carcinoma	6 (24)
Pleomorphic lobular carcinoma	7 (28)
Invasive carcinoma	4 (16)
Malign cytology	1 (4)
IDC+ILC mixt	1 (4)
Histology in surgical specimen	
Pleomorphic lobular carcinoma	25 (100)
LVI, n (%)	
Yes	13 (52)
No	12 (48)
Tumor grade in surgical specimen	
Not evaluated	3 (12)
Grade 1	0 (0)
Grade 2	3 (12)
Grade 3	19 (76)
Molecular feature	
ER positive	19 (76)
PR positive	11 (44)
HER2 positive	2 (8)
Triple negative	4 (16)
Pathological stage	
I	5 (20)
II	12 (48)
III	6 (24)
IV	2 (8)
	Mean (range)
Ki-67	22% (3–90%)

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinom; LVI: Lymphovascular invasion; ER: Estrogen receptor; PR: Progesterone receptor.

Table 3. Local and systemic treatments

Treatment	Patient number (%)
Neoadjuvant chemotherapy	
Yes	6 (24)
No	19 (76)
Adjuvant chemotherapy	
Yes	14 (56)
No	11 (44)
Surgery	
None	3 (12)
MRM	10 (40)
BCS	11 (44)
Mastectomy	1 (4)
Adjuvant anti-hormonal	
Yes	19 (76)
TMX	9
TMX + Trastuzumab	1
AI	8
Trastuzumab	1
No	6 (24)
Adjuvant radiotherapy	
Yes	17 (68)
No	8 (32)

MRM: Modified radical mastectomy; BCS: Breast conservative surgery; TMX: Tamoxifen; AI: Aromatase inhibitor.

Discussion

The data on PLC of breast are so limited with mostly consisting of only case series with few patients. As a result, it has been difficult to understand the clinical behavior, prognosis and if treatment strategies should be different for this subtype. Although there are discrepancies between previous studies, it has been reported that patients with PLC often presented with poor prognostic factors, such as large tumor size, axillary lymph nodes positivity, presence of lymphovascular invasion, high grade, and high proliferative index.

Published data demonstrated that PLC mostly diagnosed in postmenopausal women between the ages of 60 and 80 years.[10,12,15] In the present study, median age at diagnosis was 50 years and this seemed to be much younger when compared with the previous studies. In addition, the number of patients with postmenopausal and premenopausal status was similar.

Median tumor size was large with 21.9 mm which was similar to Buchanan et al.'s and Monhollen et al.'s series,[15,16] however, most of series determined larger tumors as median size being more than 3 cm.[11,14,17] Middleton et al. reported the largest tumor size as 25 cm.[10] Larger size of tumor in PLCs at diagnosis may be explained by a rapid growth rate. Positivity of axillary lymph nodes was found as 44% and compatible with Jung SP et al.'s series with 40%,[11] but lower than Jung HN et al., Buchanan et al., and Monhollen et al.'s series, with being 54%, 57%, and 57%, respectively.[14-16] Numbers of mastectomy and BCS performed were similar in the present study. Buchanan et al. reported mastectomy more often with 63.5% in their series. This difference may be caused by the high axillary lymph node positivity in Buchanan's series. As a result, initial characteristics of the study population were favorable when compared to the former studies.

PLC was determined in only 28% of core needle bx material. This might be explained by the distinction difficulty on pathology since ILC and IDC may overlap with morphologi-

cal and immunophenotypic features of PLC. Moreover, this might also be related to the fact that e-cadherin has not been studied in some of the core bx materials, since PLCs are distinguished from ductal carcinomas by the loss of e-cadherin expression.

All the tumors were reported as high grade (Grades 2 and 3) and were consistent with Monhollen et al.'s and Jung HN et al.'s data.[14,16] In addition, there are more series reported with high grades of tumors as well.[13,18] Poor histologic grade strongly correlates with poor prognosis. Lymphovascular invasion was detected as 52%, which was much higher than the literature, such as 5.9% in Neandra et al.'s series and 19.2% in Buchanan et al.'s series.[12,15]

Frequency of Her2/neu overexpression in PLC has been variably reported. Early studies of PLC did not indicate Her2/neu status,[13,19] as it is relatively new target in breast cancer. Middleton et al. reported that 81% of PLC had Her2/neu overexpression (2+ and 3+ by immunohistochemistry), whereas Jacobs et al. reported that none of their patients had Her2/neu overexpression.[3,10] However, most of the studies demonstrate Her2/neu amplification in approximately one-quarter of the PLC patients.[11,12,14,16,20] Her2/neu overexpression was 8% in the study population and apparently lower than other series.

ER positivity was determined as 76% similar to newer studies, however, PR positivity was lower (about 44%) than the other series. Hereby, most of patients could be classified as luminal type A and this added another good feature to the baseline favorable characteristics.

There is inconsistency between data on hormone receptor status in PLC in the literature. While early studies reported ER and PR positivity as 9% and 20%,[13,19] they were reported it 57%–96% in later studies.[11,12,14,16,20]

Two patients with triple-negative tumor developed metastatic disease during follow-up and one with de novo metastatic disease, which was also related with advanced disease as expected. Only a few studies reported triple-negative PLC of breast with being between 12.5% and 22.5% which is similar to our results.[14,16,20]

Very few studies had detailed the radiographic features of PLC in the literature. Jung HN et al. demonstrated the presence of a spiculated mass in 86% of patients and microcalcifications were not found in any mammograms.[14] The presence of a mass on imaging was similar but microcalcifications were seen more frequently in our series. The other common findings are multicentricity and multifocality. Neandra et al. reported multicentricity in 7.8% of patients, similar to our findings.[12] In study population, the frequency of microcalcifications was higher than the previous studies. However, occult breast cancer and multicentricity rate were similar to previous data and higher than other subtype of breast cancers. These features were compatible with radiological findings of classical PLC.[14]

Conclusion

Factors indicating prognosis were heterogeneous in the present study. Baseline characteristics were more favorable than other PLC case series, even so indicated poor prognosis than classical invasive ductal and lobular carcinoma. Unfortunately, there is still a clear lack of data on whether this clinical course is a result of poor prognostic factors or PLC histology itself. To determine right treatment strategy, it is very substantial to understand the histopathology of PLC and its behavior. Therefore, new studies carried out with higher number of patients are required.

Disclosures

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee (09.2019.873).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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References

1. Al-Baimani K, Bazzarelli A, Clemons M, Robertson SJ, Addison C, Arnaout A. Invasive pleomorphic lobular carcinoma of the breast: Pathologic, clinical, and therapeutic considerations. Clin Breast Cancer 2015;15:421–5.
2. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: Tumor characteristics and clinical outcome. Breast Cancer Res 2004;6:R149–56.
3. Jacobs M, Fan F, Tawfik O. Clinicopathologic and biomarker analysis of invasive pleomorphic lobular carcinoma as compared with invasive classic lobular carcinoma: An experience in our institution and review of the literature. Ann Diagn Pathol 2012;16:185–9.
4. Tavassoli FA, Devilee P. Classification of tumours. In: Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Geneva: World Heal Organization; 2003.
5. Page DL. Diagnostic Histopathology of the Breast. Edinburgh: Churchill Livingstone; 1987. p. 219–23.
6. Weidner N, Semple JP. Pleomorphic variant of invasive lobular carcinoma of the breast. Hum Pathol 1992;23:1167–71.
7. Eusebi V, Magalhaes F, Azzopardi JG. Pleomorphic lobular carcinoma of the breast: An aggressive tumor showing apocrine differentiation. Hum Pathol 1992;23:655–62.

8. Lakhani SR, Hoon Tan SJ, Van de Vijver PM. WHO Classification of Tumors of the Breast. 4th ed. Lyon, France: World Health Organization; 2012.
9. Butler D, Rosa M. Pleomorphic lobular carcinoma of the breast: A morphologically and clinically distinct variant of lobular carcinoma. Arch Pathol Lab Med 2013;137:1688–92.
10. Middleton LP, Palacios DM, Bryant BR, Krebs P, Otis CN, Merino MJ. Pleomorphic lobular carcinoma: Morphology, immunohistochemistry, and molecular analysis. Am J Surg Pathol 2000;24:1650–6.
11. Jung SP, Lee SK, Kim S, Choi MY, Bae SY, Kim J, et al. Invasive pleomorphic lobular carcinoma of the breast: Clinicopathologic characteristics and prognosis compared with ınvasive Ductal carcinoma. J Breast Cancer 2012;15:313–9.
12. Narendra S, Jenkins SM, Khoor A, Nassar A. Clinical outcome in pleomorphic lobular carcinoma: A case-control study with comparison to classic invasive lobular carcinoma. Ann Diagn Pathol 2015;19:64–9.
13. Bentz JS, Yassa N, Clayton F. Pleomorphic lobular carcinoma of the breast: Clinicopathologic Features of 12 cases. Mod Pathol 1998;11:814–22.
14. Jung HN, Shin JH, Han BK, Ko EY, Cho EY. Are the imaging features of the pleomorphic variant of invasive lobular carcinoma different from classic ILC of the breast? Breast 2013;22:324–9.
15. Buchanan CL, Flynn LW, Murray MP, Darvishian F, Cranor ML, Fey JV, et al. Is pleomorphic lobular carcinoma really a distinct clinical entity? J Surg Oncol 2008;98:314–7.
16. Monhollen L, Morrison C, Ademuyiwa FO, Chandrasekhar R, Khoury T. Pleomorphic lobular carcinoma: a distinctive clinical and molecular breast cancer type. Histopathology. 2012 Sep;61(3):365-77.
17. Ohashi R, Matsubara M, Watarai Y, Yanagihara K, Yamashita K, Tsuchiya SI, et al. Pleomorphic lobular carcinoma of the breast: A comparison of cytopathological features with other lobular carcinoma variants. Cytopathology 2017;28:122–30.
18. Simpson P, Reis-Filho J, Lambros M, Jones C, Steele D, Mackay A, et al. Molecular profiling pleomorphic lobular carcinomas of the breast: Evidence for a common molecular genetic pathway with classic lobular carcinomas. J Pathol 2008;215:231–44.
19. Radhi JM. Immunohistochemical analysis of pleomorphic lobular carcinoma: Higher expression of p53 and chromogranin and lower expression of ER and PgR. Histopathology 2000;36:156–60.
20. Harbhajanka A, Lamzabi I, Singh RI, Ghai R, Reddy VB, Bitterman P, et al. Correlation of clinicopathologic parameters and ımmunohistochemical features of triple-negative ınvasive lobular carcinoma. Appl Immunohistochem Mol Morphol 2014;22:e18–26.