Int J Clin Exp Pathol 2011;4(2):200-205
www.ijcep.com /IJCEP1012011

Case Report

Invasive pleomorphic lobular carcinoma, negative for ER, PR and Her/2neu - a case report

Varsha Manucha, Natalya Khilko, Kathleen Reilly[1], Xinmin Zhang

Department of Pathology and Laboratory Medicine and [1]Department of Surgery, Temple University School of Medicine, Philadelphia, PA, USA.

Received December 27, 2010; accepted January 21, 2011; Epub January 30, 2011; published February 15, 2011

Abstract: Pleomorphic variant of lobular carcinoma is a recently described variant of invasive lobular carcinoma. It is reported to be positive for estrogen receptors and progesterone receptors and over express Her2/neu in most cases. We present here a case of invasive variant of pleomoprhic lobular carcinoma with coexisting classic and pleomorphic variants of lobular carcinoma in situ along with focal ductal carcinoma in situ. The immunohistochemical results on hormone receptors and high molecular weight cytokeratins in all the above components of the tumor are presented. The invasive tumor was negative for estrogen receptors, progesterone receptors and Her2/neu. Most foci of lobular carcinoma in situ showed morphogenic heterogeneity and a corresponding heterogenous staining for hormone receptors. The high molecular weight cytokeratins (CK5/6 and CK 903) were non contributory in establishing diagnosis.

Keywords: Invasive lobular carcinoma, variants, pleomorphic variant of lobular carcinoma, lobular carcinoma in situ, hormone receptors

Introduction

Invasive pleomorphic lobular carcinoma (IPLC) is a rare and aggressive variant of invasive lobular carcinoma (ILC). Though its morphological features have been well described by different authors [1 -6], there is conflicting data in the literature concerning the presence of estrogen receptor, progesterone receptor and Her2/neu receptor. Both invasive and in situ variants of pleomorphic lobular carcinoma are known to be positive for hormone receptors, to over express HER2/neu and to lack E-cadherin [1-3].

We report a case of triple negative invasive pleomorphic lobular carcinoma with coexisting extensive pleomorphic lobular carcinoma in situ (PLCIS) along with classic lobular carcinoma in situ (LCIS) and focal ductal carcinoma in situ (DCIS).

Case Report

A 67-year-old African American woman presented with vague asymmetric density on mammogram. She had been followed at six month intervals for the preceding year. An ultrasound at the time of this presentation revealed a hypoechoic mass with irregular margins measuring 1.2 x 1.2 x1.5 cm. She had taken birth control pills for several years in the distant past and had undergone previous stereotactic biopsy on the contralateral breast several years prior with benign results. Medical and surgical history was otherwise non contributary. There was no family history of breast, ovarian, uterine or colon cancer.

On examination no adenopathy was appreciated. A vague palpable mass was identified in the 6'O clock region of the breast, approximately 4 cm from the nipple very far posteriorly. The palpable mass was confirmed to correspond to the mammographic and ultrasonographic findings within an office ultrasound. No additional abnormalities were appreciated in either breast.

An ultrasound guided biopsy of the left breast mass was performed which showed an invasive

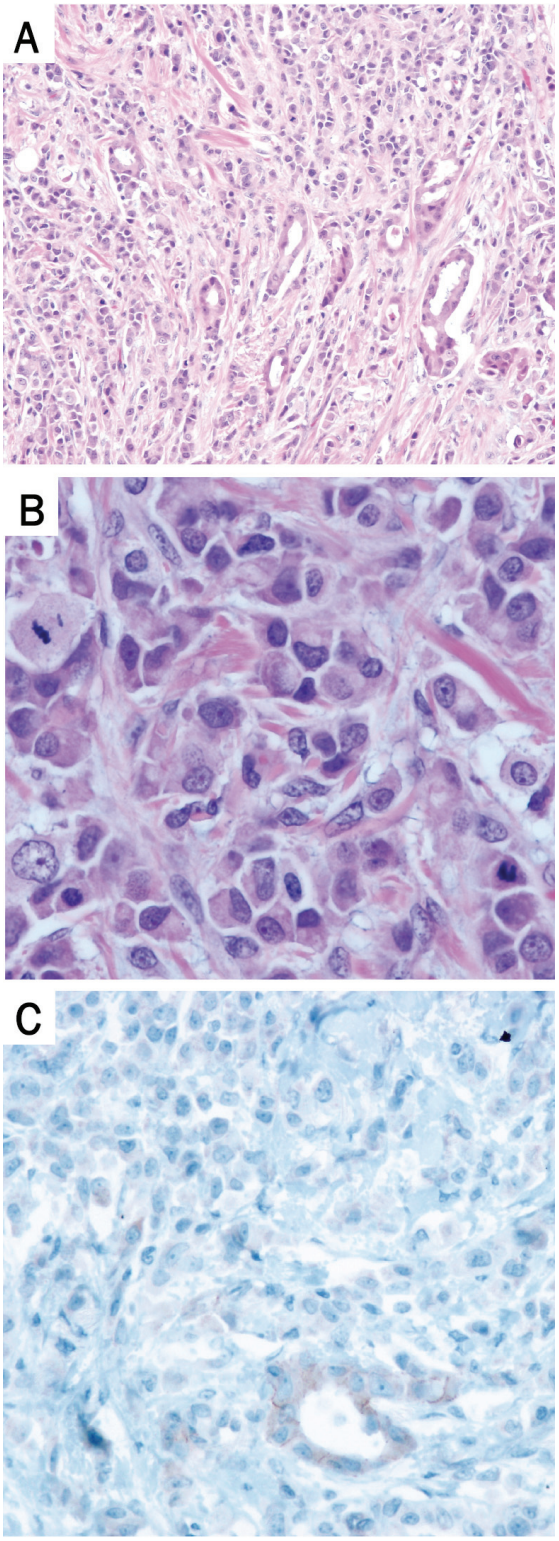

Figure 1. Invasive pleomorphic lobular carcinoma including the focus of ductal differentiation (A) Hematoxylin & Eosin, 100X (**B**) Hematoxylin & Eosin, 400X (**C**) E Cadherin , 200X.

mammary carcinoma, with features of lobular and focal ductal differentiation coexisting with high grade ductal carcinoma in situ.

A detailed evaluation for metastases was negative.

The patient underwent left breast lumpectomy with axillary sentinel lymph node biopsy. On gross exam two separate solid lesions, measuring 1.7 cm and 1.5 cm in maximal dimension with an intervening distance of 1.7 cm were identified. On microscopic exam the larger lesion was an invasive carcinoma with highly atypical tumor cells infiltrating in a trabecular and cord like pattern (**Figure 1A**). A small intervening focus of ductal differentiation was noted (**Figure 1A**). The tumor cells had a prominent apocrine differentiation with focal signet ring cell like features. The cells were large with relatively abundant eosinophilic cytoplasm, enlarged nuclei with vesicular chromatin and prominent nucleoli (**Figure 1B**). Mitotic figures varied from 1-3 per high power field (**Figure 1B**). Cells with similar morphology were seen distending the acini along with a pagetoid spread in the ducts (**Figure 2A**). These coexisted with other foci of classic variant of lobular carcinoma in situ (**Figure 2A**). Additionally there were foci where ducts were lined by 2 to 3 layers of moderately to highly atypical cells with indeterminate features (**Figure 3A**). No lympho vascular invasion was seen.

The second lesion identified on gross examination revealed pseudo angimatous stromal hyperplasia. Sentinel lymph nodes and five additional axillary lymph nodes were negative for metastatic carcinoma.

Three different blocks of the tumor were subjected to immunohistochemical analysis so as to analyze all the components of the tumor (Table I). The invasive tumor was E- cadherin negative and was diagnosed as IPLC (**Figure 1C**). Morphologically similar cells distending the acini and the ducts were also negative for E-cadherin and were labeled as PLCIS (**Figure 2B**). The invasive and in situ pleomorphic variants were negative for both estrogen recptor (ER) and progesterone recptor (PR), unlike the classic variant of lobular carcinoma in situ (**Table 1**). It was interesting to note that some of the lobules that showed a morphologic spectrum ranging from bland classic type LCIS to pleomorphic

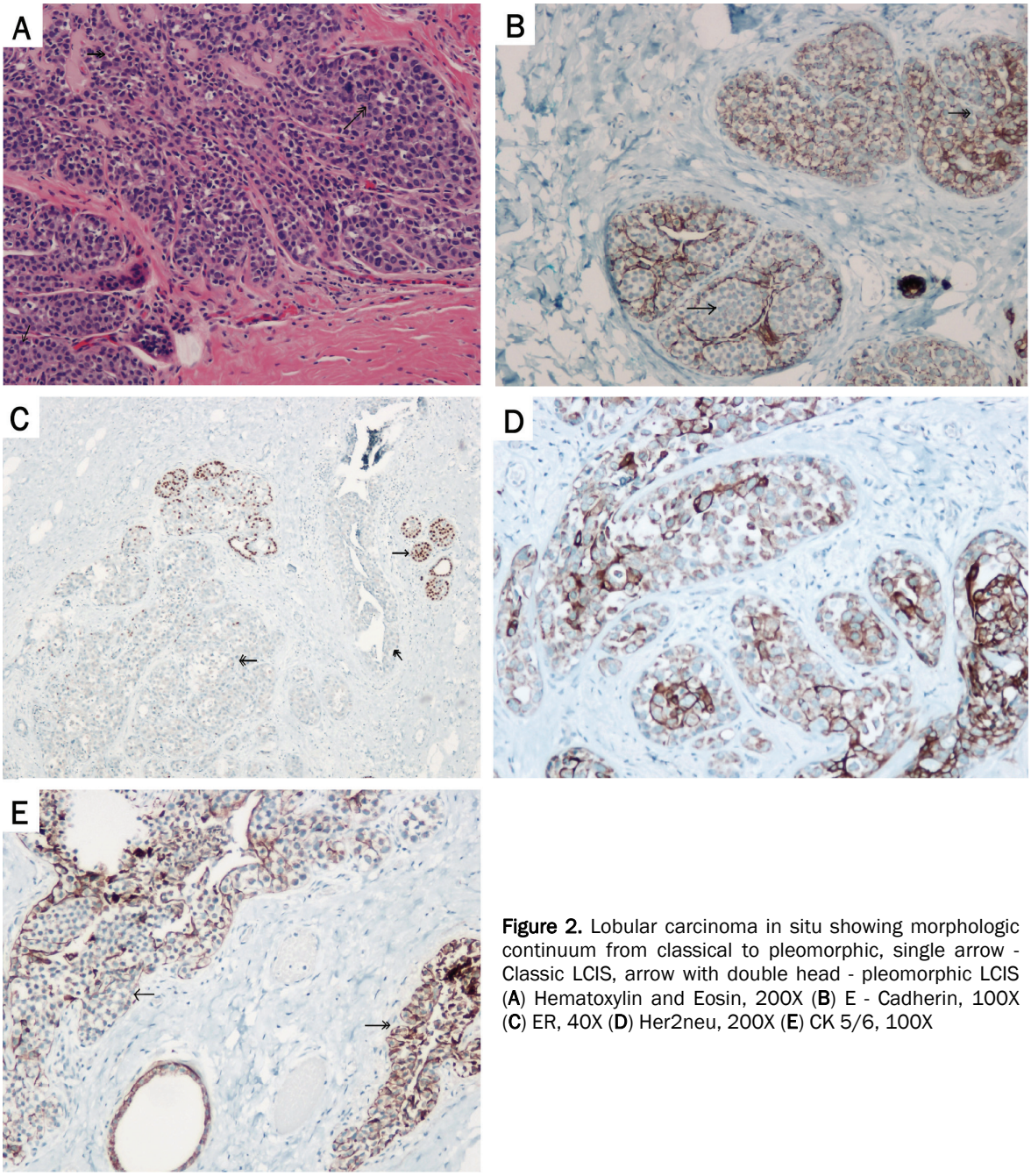

Figure 2. Lobular carcinoma in situ showing morphologic continuum from classical to pleomorphic, single arrow - Classic LCIS, arrow with double head - pleomorphic LCIS (**A**) Hematoxylin and Eosin, 200X (**B**) E - Cadherin, 100X (**C**) ER, 40X (**D**) Her2neu, 200X (**E**) CK 5/6, 100X

LCIS showed the positivity for ER in a similar pattern (**Figure 2C**). The IPLC was negative for Her2/neu, while in PLCIS expression of Her2neu varied from being negative to complete membranous positivity of moderate density in 5-10% cells in few foci (**Figure 2D**). Focal ductal differentiation noted within the invasive tumor was negative for all the hormone receptors and E-cadherin, highlighting that PLC could harbor a ductal pattern as well (**Figure 1C**). Rare foci of carcinoma in situ with indeterminate features were positive for E-Cadherin and the hormone receptors (**Figure 3B** and **C**). These were interpreted as ductal carcinoma in situ. The stains for high molecular weight cytokeratin (CK 5/6 and CK 903) showed patchy membranous staining in PLCIS and DCIS and were not contributory in differentiating between the two components

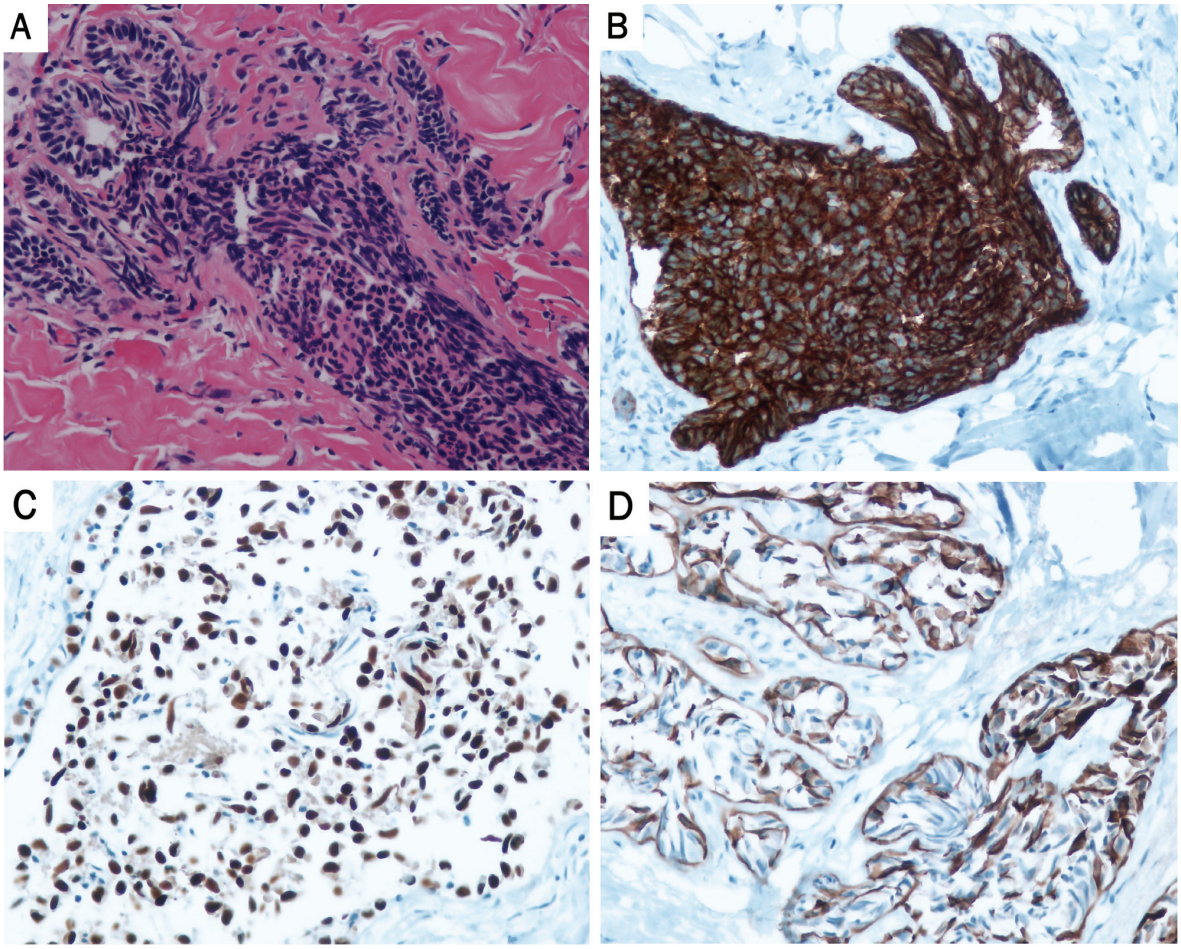

Figure 3. Ductal carcinoma in situ (**A**) Hematoxylin and Eosin, 200X (**B**) E Cadherin, 200X (**C**) ER, 200X. (**D**) CK5/6, 200X.

(**Figure 2E** and **Figure 3D**).

The classic LCIS was positive for ER and PR and, as expected, negative for E-cadherin and Her2/neu.

Discussion

Invasive pleomorphic lobular carcinoma has been reported to account for <1% of all epithelial malignancies in the breast. Unlike the classic variant, the tumor cells of the pleomorphic variant of ILC are larger, have abundant eosinophilic cytoplasm with large pleomorphic hyperchromatic nuclei that show prominent nucleoli which can be irregular in some cases, thereby making it difficult to differentiate from a high grade invasive ductal carcinoma. Duct formation is distinctly absent in most cases described [1], but its focal presence may be seen as in our case. Very often the cells appear plasmacytoid or have a predominant signet ring cell or apocrine [4] morphology. IPLC has been identified as a distinct entity from classic ILC and is reported to be associated with a more aggressive clinical behavior than classic ILC [5 – 8].

PLCIS and invasive PLC possibly develop through a molecular genetic pathway similar to that of classic lobular carcinomas, as these lesions harbor the hallmark molecular genetic features of lobular carcinomas (loss of CDH1 gene, located on 16q22.1) associated with lack of E-cadherin and β-catenin expression and, due to a possible more complex pattern of change [9-11]. Morphologically this is represented by areas in the present case where foci of PLCIS coexisted in the same labule with classic and intermediate grade LCIS and exhibited a heterogeneous staining pattern for ER and PR recep-

Table 1. Immunohistochemical results in different components of the tumor

	Classic LCIS	Pleomorphic LCIS	IPLC	DCIS	Benign
ER	>90%, strong	Negative	negative	30% to 50% strong	>90%, strong
PR	20-40% strong	Negative	negative	10-15% strong	>30% strong
Her2/neu	Negative	variable	negative	Negative	Negative
E-cadherin	Negative	Patchy membranous staining	negative	Strong membranous positive	Strong membranous positive
CK5/6	Negative	Patchy membranous staining	negative	Patchy membranous staining	Strong membranous positive
CK903	Negative	Patchy membranous staining	negative	Patchy membranous staining	Strong membranous positive

tors.

As mentioned above, conflicting data exist in literature concerning the presence of ERs and PRs. PLCIS is known to be immunohistochemically positive for hormone receptors in addition to a high proliferation rate and HER2/neu over expression/ amplification [12]. While around 80% cases of IPLC are positive for ER in most series, positivity for PR varies from 67% to 90% and Her2neu receptor varies from 53% to 81% in different case series [12]. In the present case the IPLC was triple negative. It is unlikely that a prominent apocrine morphology may have contributed to the triple negative hormonal profile as most PLCs have apocrine features. It would be interesting to note if cytogenetics in such a case is different from the more common hormone positive variants of PLC.

Conclusion

PLC is an aggressive form of breast carcinoma that is becoming more frequently identified. Unlike the usual scenario of a positive ER/PR and over expression of Her2/neu, a pleomorphic variant of lobular carcinoma can be triple negative, thereby adding to the challenge of planning the treatment strategy of this aggressive tumor.

Please address correspondence to: Dr. Varsha Manucha, Department of Pathology and Laboratory Medicine, Temple University School of Medicine, B339, Outpatient Bldg. 3401 N Broad Street, Philadelphia, PA 19140, USA. Tel: (215) 707-6744, Fax: (215)-707-8132, E-mail: varsha.manucha@tuhs.temple.edu

References

[1] 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;24:1650–1656.

[2] Sneige N, Wang J, Baker BA, Krishnamurthy S, Middleton LP. Clinical, histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in situ of the breast: a report of 24 cases. Mod Pathol 2002;15:1044–1050.

[3] D Frolik, R Caduff & Z Varga. Pleomorphic lobular carcinoma of the breast: its cell kinetics, expression of oncogenes and tumour suppressor genes compared with invasive ductal carcinomas and classical infilltrating lobular carcinomas. Histopathology 2001; 39, 503-513

[4] Brogi E, Murray MP & Corben AD. Lobular Carcinoma, Not Only a Classic. The breast Journal. The Breast Journal 2010; 16 : 2010 S10–S14.

[5] Bentz JS, Yassa N, Clayton F. Pleomorphic lobular carcinoma of the breast: clinicopathologic features of 12 cases. Mod Pathol 1998;11:814–22.

[6] Weidner N, Semple JP. Pleomorphic variant of invasive lobular carcinoma of the breast. Hum Pathol 1992;23:1167–71.

[7] Buchanan CL, Flynn LW, Murray MP, Darvishian F, Cranor ML, Fey JV, King TA, Tan LK, Sclafani LM. Is pleomorphic lobular carcinoma really a distinct clinical entity? J Surg Oncol 2008;98:314–7.

[8] Eusebi V, Magalhaes F, Azzopardi JG. Pleomorphic lobular carcinoma of the breast: an aggressive tumor showing apocrine differentiation. Hum Pathol 1992;23:655–62.

[9] Chen YY, Hwang ES, Roy R, DeVries S, Anderson J, Wa C, Fitzqibbons PL, Jacobs TW, MacGrogan G, Peterse H, Vincent-Salomon A, Tokuyasu T, Schnitt SJ, Waldman FM.Genetic and phenotypic characteristics of pleomorphic lobular carcinoma in situ of the breast. Am J Surg Pathol 2009;33:1683–94.

[10] Simpson PT, Reis-Filho JS, Lambros MB, Jones C, Steele D, Mackay A, Iravani M, Fenwick K, Dexter T, Jones A, Reid L, DaSilva L, Shin SJ, Hardisson D, Ashworth A, Schmitt FC, Palacios J, Lakhani SR. 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.

[11] Reis-Filho JS, Simpson PT, Jones C, Steele D, Mackay A, Iravani M, Fenwick K, Valgeirsson H, Lambros M, Ashworth A, Palacios J, Schmitt F, Lakhani SR. Pleomorphic lobular carcinoma of the breast: role of comprehensive molecular pathology in characterization of an entity. J Pathol 2005;207:1-13.

[12] Tavassoli F A, Eusebi V: Major variants of carcinoma. In: Tumors of the mammary gland, series 4 AFIP atlas of tumor pathology. Washington, AFIP, 2009, p163.