

Volume 4, Number 2 – March 4, 2010

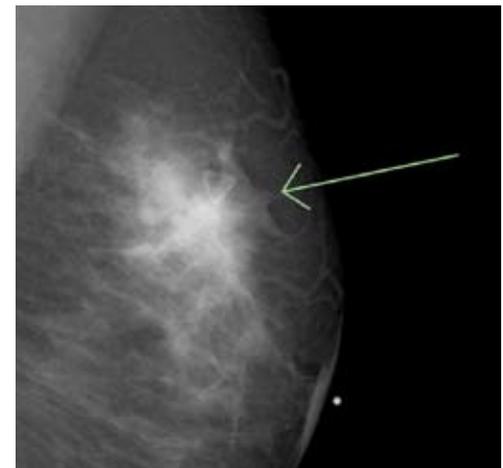
## INVASIVE LOBULAR BREAST CARCINOMA: Pathology and genetics reflected by MRI

Invasive lobular carcinoma (ILC) can elude diagnosis due to its variable appearances. Knowledge of its pathology explains why this tumor can grow under the radar of mammography and why recognizing the MRI pattern of lobular carcinoma requires special understanding. This issue of *The WCC Note* on invasive lobular carcinoma reviews its gross and microscopic features and summarizes recent literature profiling its genetic, molecular, and biobehavioral footprints.

### Incidence of ILC

#### What is the incidence of invasive lobular carcinoma (ILC)?

1. ILC represents between 5% and 15% of breast cancer, and often has accompanying in situ lesions. The histology is diverse, ranging from the classical variety, which has a more favorable outcome, to solid, and to pleomorphic. The majority are hormone receptor-positive. HER2 gene overexpression is lower than in infiltrating ductal carcinoma (IDC). (1)
2. Of the special types of breast cancer, ILC is the most frequent. Most are histologically low-grade, express hormone receptors, and lack HER2 gene overexpression. A variant of ILC is the pleomorphic variety which displays atypical cells with pleomorphic nuclei and is reported to display an aggressive clinical behavior. (2)
3. ILC was first described by Foot and Stewart in 1941, with subsequent subtypes described in the 1970s and 1980s, including alveolar, solid, pleomorphic, signet ring cell, histiocytoid, and apocrine. (3)
4. ILC carries distinct prognostic and biological implications compared to IDC. (4)
  - a. A review of 12,206 breast cancer patients from 15 international breast cancer study group trials performed between 1978 and 2002 by the International Breast Cancer Study Group, revealed the following percentages: 70.5% IDC, 6.2% ILC, and 23.2% other.
  - b. The ILC patients were noted to be of an older age and have larger lesions, better differentiation, ER-positive tumor association, and less vessel invasion.



**Left Mammogram MLO view. Arrow points to palpable area of irregular density and architectural distortion.**

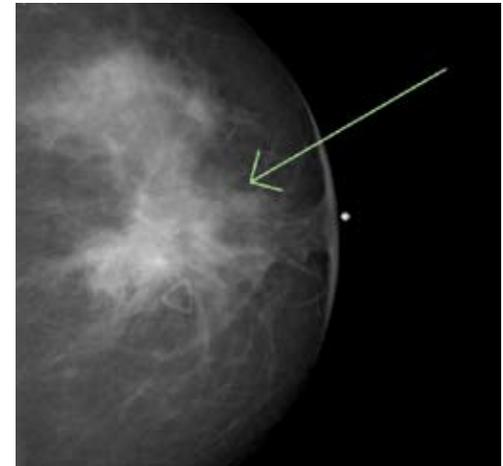
Continued on next page

- c. The ILC cohort demonstrated a significant early advantage in disease-free survival and overall survival, followed by a significant late advantage for the IDC cohort.
  - d. ILC had association with increased incidence of bone events but decreased regional and lung events. (4)
5. According to The Centers for Disease Control and Prevention, the ILC incidence decreased 20% between 1999 and 2004. The CDC Cancer Surveillance Branch reported that the decreased incidence coexisted with reduced use of combined hormone replacement therapy, though they noted that other factors could also be responsible. (5)

**Gross  
anatomic  
appearance  
of ILC**

**What is the gross anatomic appearance of invasive lobular carcinoma?**

1. Roughly one-fourth show diffuse invasion without marked desmoplasia.
2. Most show irregular margins, appearing firm to hard.
3. A discrete mass may not be present; instead diffuse thickening may be the hallmark. (6)
4. Metastases of ILC differ from other breast cancers. They preferentially involve the peritoneum, retroperitoneum, gastrointestinal tract, ovaries, uterus, and leptomeninges rather than the lungs and pleura. (6)

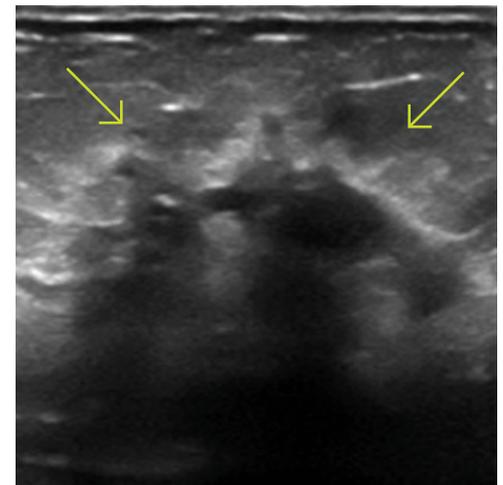


**Left Mammogram CC view: Arrow points to palpable irregular mass with architectural distortion.**

**Microscopic  
anatomic  
appearance  
of ILC**

**What is the microscopic appearance of invasive lobular carcinoma?**

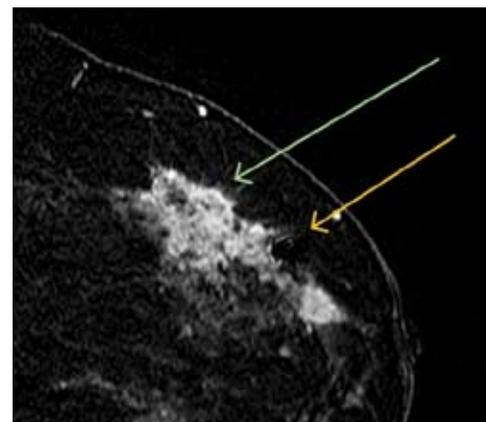
1. Single cells infiltrate and can do so in single file or in loose clusters or sheets.
2. Cells lack cohesion, not forming tubules or papillae.
3. Tumor cells often align in concentric rings around normal ducts.
4. Variants include those with large groups of cells and marked pleomorphism. (6)
5. A report published in *Cancer* of 530 patients with pure ILC showed:
  - a. 57% classic, 19% alveolar, 11% solid, and 13% pleomorphic, signet ring cell, histiocytoid, or apocrine features.
  - b. Significant prognostic factors were noted to be size, nodal involvement, and hormone status, with “classic” type showing lower nodal involvement and lower grade, and “non-classic” types demonstrating an increased number of breast events, decreased disease-free survival, and overall survival. (3)
6. Nottingham grading of breast carcinoma is a subjective evaluation of three morphologic features: tubule formation, nuclear pleomorphism, and mitosis. (7)



**Left Ultrasound at 12:00 shows irregular mass with shadowing. (arrows).**

## What do we know about the genetics and molecular features of invasive lobular carcinoma?

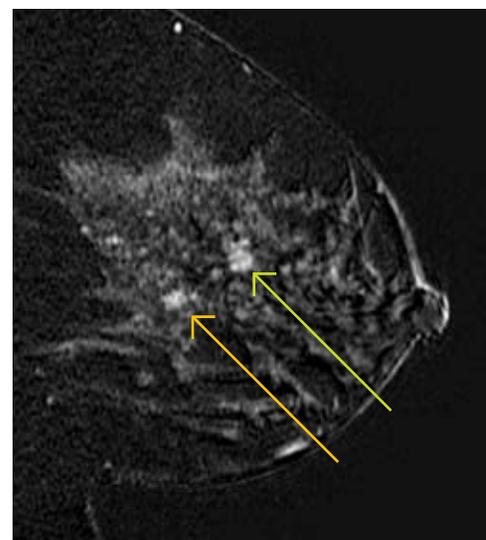
1. Most ILCs demonstrate a regional loss on chromosome 16.
  - a. This area involves genes for cell adhesion such as e-cadherin and beta-catenin. (6)
2. Well-differentiated and moderately differentiated ILC:
  - a. Are usually diploid, have positive hormone receptors, and have associated lobular carcinoma in situ (LCIS).
  - b. Rarely overexpress HER2/neu. (6)
3. Poorly-differentiated ILC are:
  - a. Usually aneuploid with negative hormone receptors.
  - b. May overexpress HER2/neu. (6)
4. The genetic basis of lobular and ductal carcinoma is noted to show a shared genetic abnormality and may share a common precursor lesion. (8)
5. The molecular framework of classic ILC and pleomorphic ILC were found to be remarkably similar in a study from the Netherlands Cancer Institute published in 2010. The authors concluded that both pathologies should be considered as part of a spectrum of lesions. This study also compared subtype matched ILC to IDC tumors, finding different expression of genes for cell adhesion, cell-to-cell signaling, and actin cytoskeleton signaling. (2)
6. A common molecular genetic pathway between the pleomorphic and classic variants of ILC had also been reported by researchers from Brisbane, Australia. (9)



**Left breast MRI in same patient as mammogram and ultrasound: Sagittal post contrast subtracted image with arrows pointing to the irregular area of enhancement. Deep to the bottom arrow is also the biopsy clip susceptibility artifact; biopsy proven ILC.**

## What updates have been reported about the biobehavior of ILC?

1. A 2009 study from Yale University reported their experience with early-stage ILC and IDC. Patients underwent breast conservation treatment and were followed a median of 6.8 years. A higher percentage of ILC patients presented at >40 years of age compared to IDC and had more mammographically occult tumors. ILC patients had higher contralateral breast relapses (26% versus 12%). At 10 years, no difference was noted in breast relapse nor distant relapse, nor cause-specific survival. (10)
2. Invasive lobular carcinoma has been reported as almost always ER-positive, and typically lower-grade than IDC. It has been reported as showing a general decreased response to neoadjuvant chemotherapy compared to IDC but not to a survival disadvantage. Authors from the Swiss Group of Clinical Cancer Research in Berne, Switzerland note that studies of adjuvant hormonal therapy do not generally distinguish between ILC and IDC. (11)



**Right breast MRI: Sagittal post contrast subtracted image with arrows pointing to two unsuspected contralateral lesions that subsequently underwent biopsy and were also invasive lobular carcinoma (same patient as above).**

## What do we know about mixed ILC and IDC?

1. In a study by the University of Nottingham, UK, mixed ductal and lobular breast carcinoma (compared to pure IDC) were reported as showing association with lower grade, ER positivity, and lower frequency of development of distant metastases. (12)
2. ILC and “mixed” carcinoma tends to be diagnosed in a more advanced stage but displays overall superior survival to IDC, according to authors from Washington University School of Medicine. ILC and mixed carcinoma are more likely to be low-grade, ER-positive, PR-positive but have overall higher survival than those patients with IDC, despite being diagnosed at a more advanced stage. (13)

## CONCLUSION

**Conclusion: Classic invasive lobular carcinoma and its subtypes display a range of gross and microscopic diversity. Cellular infiltration can be loose or single file and lack desmoplasia, potentially evading detection by mammography and physical exam, and influencing the MRI appearance. ■**

*The next issue of The WCC Note will discuss the MRI appearance of invasive lobular carcinoma.*

## SOURCES

1. Varga Z, Mallon E. Histology and Immunophenotype of Invasive Lobular Breast Cancer. Daily Practice and Pitfalls. *Breast Dis.* 2009 Oct 21;30:15-19.
2. Weigelt B, Geyer FC, *et al.* The molecular underpinning of lobular histological growth pattern: a genome-wide transcriptomic analysis of invasive lobular carcinomas and grade- and molecular subtype-matched invasive ductal carcinomas of no special type. *J Pathol.* 2010 Jan;220(1):45-57.
3. Orvieto E, Maiorano E, *et al.* Clinicopathologic characteristics of invasive lobular carcinoma of the breast: results of an analysis of 530 cases from a single institution. *Cancer.* 2008 Oct 1;113(7):1511-20.
4. Pestalozzi BC, Zahrieh D, *et al.* Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. *J Clin Oncol.* 2008 Jun 20;26(18):3006-14.
5. Ehemann CR, Shaw KM, *et al.* The changing incidence of in situ and invasive ductal and lobular breast carcinomas: United States, 1999-2004. *Cancer Epidemiol Biomarkers Prev.* 2009 Jun;18(6):1763-9.
6. Lester SC. “The Breast.” In Kumar V, Abbas AK, Fausto N (eds.): Robbins and Cotran, Pathologic Basis of Disease. Philadelphia: Elsevier Saunders, 2005, pp. 119-1154
7. Stevens E, Kimler BF, *et al.* A newly proposed semi-automated method of grading invasive lobular carcinoma: a unifying concept and correlation with prognostic markers and patient survival. *Ann Clin Lab Sci.* 2009 Winter; 39(1):25-31.
8. Wagner PL, Kitabayashi N, *et al.* Clonal relationship between closely approximated low-grade ductal and lobular lesions in the breast: a molecular study of 10 cases. *Am J Clin Pathol.* 2009 Dec;132(6):871-6.
9. Simpson PT, Reis-Filho JS, *et al.* Molecular profiling pleomorphic lobular carcinomas of the breast: evidence for a common molecular genetic pathway with classic lobular carcinomas. *J Pathol.* 2008 Jul;215(3):231-44.
10. Moran MS, Yang Q, *et al.* The Yale University experience of early-stage invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) treated with breast conservation treatment (BCT): analysis of clinical-pathologic features, long-term outcomes, and molecular expression of COX-2, Bcl-2, and p53 as a function of histology. *Breast J.* 2009 Nov-Dec;15(6):571-8.
11. Farese SA, Aebi S. Infiltrating Lobular Carcinoma of the Breast: Systemic Treatment. *Breast Dis.* 2009 Oct 21;30:45-52.
12. Rakha EA, Gill MS, *et al.* The biological and clinical characteristics of breast carcinoma with mixed ductal and lobular morphology. *Breast Cancer Res Treat.* 2009 Mar;114(2):243-50.
13. Bharat A, Gao F, *et al.* Tumor characteristics and patient outcomes are similar between invasive lobular and mixed invasive ductal/lobular breast cancers but differ from pure invasive ductal breast cancers. *Am J Surg.* 2009 Oct;198(4):516-9.