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.

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.

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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)

**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)

**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)
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)

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)
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: 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:


