Lobular Carcinoma in Situ and Problematic in Situ Lesions (Non-classical forms of LCIS)

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Definition

LCIS is a monotonous proliferation of small, dyshesive neoplastic epithelial cells which fills and distends the TDLU

Natural History

- LCIS usually constitutes an incidental microscopic finding
- Age at presentation 44-54 years
- Most commonly seen in premenopausal women
- But increasing incidence among postmenopausal women
  - due to screening
  - increase in pathologist recognition of the lesion
Natural History

- Reported to be multifocal and bilateral
- ALH confers a 4-5x increased risk of breast cancer
- LCIS confers a 8-10x increased risk of breast cancer
- Risk is bilateral (suggests marker lesion), but preponderance of ipsilateral (suggests precursor lesion) cancers
- Excess of invasive lobular carcinoma

Histopathology

- LCIS cells are small and monotonous with a centrally located round to ovoid nucleus
- Clear to pale eosinophilic cytoplasm
- Mucin-filled intracytoplasmic vacuoles may be present
- Pagetoid growth pattern
- Described as Haagensen type A (small cells) or type B (larger cells)
Immunophenotype and Genetics

LCIS is ER positive and E-cadherin negative

Some P-LCIS are HER2 positive

ER+, HER2- low prolif rate

“Rosen Triad”
Brandt et al., Adv Anat Pathol, 2008
Tubular carcinoma

Columnar cell lesions
LCIS

(Rosen, Am J Surg Pathol, 1999)
Proposed Evolutionary Pathway for Lobular Neoplasia through Columnar Cell Lesions

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Required Genetic Changes</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
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<tr>
<td>Low grade intraepithelial neoplasia</td>
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<tr>
<td>Columnar cell lesions</td>
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<tr>
<td>ADH/DCIS</td>
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<tr>
<td>TLC</td>
<td></td>
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<tr>
<td>Tubular Ca</td>
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<tr>
<td>ILC</td>
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Adapted from Ellis, Mod Pathol 2010

Abdel-Fatah et al, AJSP, 2007
Differential Diagnosis

In most cases the diagnosis of LCIS is straightforward

DCIS  LCIS
But, there is an increasingly recognized heterogeneity.

The diagnosis of LCIS is not always straightforward.

It is often the non-classical forms of LCIS that pose diagnostic difficulty.
Benign lesions that may mimic LCIS

**Myoepithelial hyperplasia**
- Myoepithelial cells may have abundant clear cytoplasm and a small, round, centrally located nucleus during the luteal phase of the menstrual cycle
- Location under the native epithelium may mimic Pagetoid growth of LCIS cells
Benign lesions that may mimic LCIS

Clear cell change
- A descriptive term of no specific etiology
- Sometimes involves entire lobules mimicking LCIS
- E-cadherin may be helpful in problematic cases
Benign lesions that may mimic LCIS

Tissue Preservation
– Poor preservation may result in cellular dyshesion mimicking LCIS
– However, there is no proliferation of cells, or expansion of lobules

Problems in the Diagnosis of LCIS

LCIS mimicking DCIS

Collagenous spherulosis with LCIS
DCIS vs. LCIS

Some cases are diagnostic problems

Problematic lesions increasingly common in breast biopsies performed because of mammographic microcalcifications

Problems in Distinguishing DCIS from LCIS

- Overlap in distribution within ductal-lobular system
  - DCIS can involve identifiable lobules
  - LCIS can involve ducts

- Some LCIS lesions have features more commonly associated with DCIS

- Some DCIS lesions have features more commonly associated with LCIS
Features Usually Associated with DCIS That May Be Seen in LCIS

- Nuclear pleomorphism
- Comedo necrosis
- Cribriform-like pattern
- Prominent apocrine differentiation

Features Usually Associated with LCIS That May Be Seen in DCIS

- Small monomorphic cells
- Solid growth pattern
- Intracytoplasmic vacuoles
- Pagetoid involvement of ducts
Features Usually Associated with DCIS That May Be Seen in LCIS

- Nuclear pleomorphism
- Comedo necrosis
- Cribriform-like pattern
- Prominent apocrine differentiation
Features Usually Associated with DCIS That May Be Seen in LCIS

- Nuclear pleomorphism
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Pleomorphic LCIS

- First described in 1996
- Post-menopausal women
- Growth pattern similar to classical LCIS
- Classical LCIS often co-exists
- Nuclear pleomorphism (2-3 fold variation in size)
- Mitoses may be present and numerous
- Comedo necrosis may be present
  - May present with mammographic microcalcifications mimicking high grade DCIS
- Non-apocrine and apocrine types

Non-Apocrine Type
Apocrine Type

E-cadherin

Biomarkers in Pleomorphic LCIS
Chen, AJSP 2009

- When compared with classical LCIS, pleomorphic LCIS:
  - Less often ER+
  - Higher proliferation rate (Ki67)
  - More often HER2+
Genomic Alterations in Pleomorphic LCIS
Chen, AJSF 2009

• 16q loss, 1q gain (“lobular” signature)
• More numerous in apocrine than in non-apocrine types (including amplification at 17q and 11q13.3)

Differences Between Classical and Pleomorphic LCIS

<table>
<thead>
<tr>
<th></th>
<th>Classical LCIS</th>
<th>Pleomorphic LCIS</th>
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<tbody>
<tr>
<td>Age</td>
<td>Younger (premenopausal)</td>
<td>Older (postmenopausal)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Incidental</td>
<td>Mammographic</td>
</tr>
<tr>
<td>ER</td>
<td>+</td>
<td>+ or – (apocrine type)</td>
</tr>
<tr>
<td>HER2</td>
<td>-</td>
<td>- or + (apocrine type)</td>
</tr>
<tr>
<td>Ki67</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Genomic changes (aCGH)</td>
<td>Fewer</td>
<td>More numerous (apocrine type)</td>
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Pleomorphic LCIS
Clinical Significance

• No clinical follow-up studies akin to those available for classical LCIS and DCIS
• Natural history/biologic behavior unknown
• ? More often associated with contemporaneous invasive cancer than classical LCIS
• Appropriate management uncertain
DCIS vs. LCIS
Why is this important?

Differences in management

<table>
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<tr>
<th>DCIS</th>
<th>LCIS</th>
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<tbody>
<tr>
<td>Managed as precursor</td>
<td>Managed as risk factor</td>
</tr>
<tr>
<td>Complete eradication</td>
<td>Observation + tam</td>
</tr>
<tr>
<td>Margin evaluation</td>
<td>No margin evaluation</td>
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What To Do With PLCIS?

- E-Cadherin negative
- LCIS variant
- Manage like LCIS
- Pleomorphic nuclei
- Comedo necrosis
- Bad biomarker profile
- Manage like DCIS

What Does “Treat Like DCIS” Really Mean?

- Excision to negative margins?
- Radiation therapy?
- In the absence of data, is it better to over-treat or under-treat?
Clinical Implications of Margin Involvement by PLCIS
Downs-Kelly, 2011, Arch Pathol Lab Med

- 26 patients with PLCIS on breast excision
- Divided into 4 groups depending on proximity of PLCIS to margin
- 6 pts with PLCIS at margin
- 7 pts with PLCIS <1mm
- 4 pts with PLCIS 1-2mm
- 9 pts with PLCIS >2mm
- Variety of treatments (none, RT, chemoprevention)
- Only one recurrence at 19 mnths in the positive margin group

Practical Considerations
Current understanding of clinical behavior of DCIS and LCIS based on follow-up studies of lesions classified according to histologic features alone (“classical” forms of disease)

Management of patients with histologically ambiguous in situ lesions unknown

Adjunctive Immunostains
- E-cadherin
- HMW-CK
- P120 catenin
E-cadherin Staining May Be of Help in Problematic Cases

DCIS: positive  LCIS: negative

BUT...

- Limitations in use of E-cadherin immunostaining
- While loss of E-cadherin expression by IHC characteristic of LCIS,
- Presence of E-cadherin expression does not preclude diagnosis of LCIS in the context of appropriate histologic features

E-cadherin positivity does not equal DCIS
E-Cadherin Staining in LCIS

- Residual ductal epithelial cells
- Myoepithelial cells
- LCIS cells
E-cadherin positivity seen in 4 of 25 ILC, despite presence of genetic alterations commonly seen in ILC (16q loss, 1q gain)
Evidence to suggest that E-cadherin protein in these cases was dysfunctional
Presence and pattern of E-cadherin expression may be related to molecular mechanism of E-cadherin inactivation

E-cadherin expression seen in 38/239 invasive lobular carcinomas (16%)
Not associated with any clinicopathologic or immunophenotypic features or outcome except for positive association with:
- Lobular subtype and LVI
- Integrity of E-cadherin-catenin complex impaired in most cases (E-cadherin+/cytoplasmic staining with p120 catenin)
Adjunctive Immunostains

- E-cadherin
- HMW-CK
- P120 catenin
Adjunctive Immunostains

- E-cadherin
- HMW-CK
- P120 catenin

P120 Catenin

- Present at junction of cell membrane and cytoplasm
- Involved in linking E-cadherin to actin cytoskeleton
- Normal cells/ductal lesions:
  - membrane distribution
- Lobular lesions:
  - cytoplasmic distribution

Dabbs, AJSP, 2007
E-cadherin and P120 Catenin in DCIS and LCIS

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<tr>
<td>P120 catenin</td>
<td>membranous</td>
<td>cytoplasmic</td>
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Problems in the Diagnosis of LCIS
LCIS and Microinvasion

- Some of the same issues as for microinvasion and DCIS
- May overlook the focus of microinvasion
- More likely with LCIS, since often don’t think about microinvasion in this scenario, as compared with DCIS

Any case of extensive LCIS, look carefully for microinvasion

Any case of LCIS, with associated FEA and ADH, look carefully for tubular carcinoma
Microinvasive Lobular Carcinoma
Ross, 2011, AJSP

- Rare, seen in 0.4% of LCIS cases over 10 year period
- Seen with any form of LCIS (classical, non-classical)
- Low morbidity disease
Problems in the Diagnosis of LCIS

- LCIS in adenosis
- LCIS in benign sclerosing lesion
Conclusions

Discussion of both classical and non-classical forms of LCIS

Diagnosis of classical LCIS straightforward in most cases

Problems with recognition of non-classical forms of LCIS

Current management of non-classical forms of LCIS uncertain