When Is LCIS Clinically Significant?

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Professor

Disclosures

I have nothing to disclose

Outline of Talk

- Classic LCIS
- Definition of lobular differentiation
- Variants of LCIS
- Clinical significance and management of LCIS

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An incidental microscopic finding that cannot be recognized clinically or by gross path exam

“'It is always a disease of multiple foci. Hence, it is never safe to leave the breast with local excision only........It is our feeling that simple mastectomy is essential'
Lobular neoplasia

- Introduced by Dr. Cushman D. Haagensen in 1978
- Reflect LCIS as a risk factor, rather than a true precursor
- Avoid overtreatment
- Later used as an umbrella term to include both LCIS and ALH

Clinical distinction of LCIS vs DCIS

<table>
<thead>
<tr>
<th></th>
<th>LCIS</th>
<th>DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biology</td>
<td>Risk for future invasive ca*</td>
<td>Direct precursor of invasive ca</td>
</tr>
<tr>
<td></td>
<td>Non-obligate precursor</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>discontinuous, multifocal</td>
<td>Continuous, segmental</td>
</tr>
<tr>
<td>Treatment</td>
<td>Life-long follow-up◊</td>
<td>Surgical excision (XRT, hormonal Rx)</td>
</tr>
<tr>
<td></td>
<td>? Hormonal Rx</td>
<td></td>
</tr>
<tr>
<td>Margins</td>
<td>Not evaluated</td>
<td>Surgical clearance</td>
</tr>
<tr>
<td>On CNB</td>
<td>management controversial</td>
<td>Excision</td>
</tr>
</tbody>
</table>

◊ both LCIS and LG DCIS: 8-10 x risk for subsequent invasive cancer
◊ ~1% risk per year for subsequent invasive cancer, bilateral breasts

Morphologic features of classic LCIS

- **Architecture**--
  - TDLUs: solid proliferation (grape clusters)
  - Loss of cell-cell cohesion

- **Cytology**--
  - Round/polygonal cell shape
  - Round nuclei, homogeneous chromatin
  - Intracytoplasmic clear (mucin-filled) vacuoles/signet ring
  - Targetoid dot-like material in vacuole
  - Minimal atypia, mitosis rare

Classic LCIS: lobulocentric growth, solid pattern grape clusters
Classic LCIS: loss of cell to cell adhesion

Classic LCIS: intracytoplasmic vacuoles (lumen)

Signet rings

Targetoid dots

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**Definition of lobular differentiation**

Loss of cell-cell cohesion due to defective E-cadherin

- *CDH1* gene on chromosome 16q
- Chromosomal loss, mutation, epigenetic inactivation
- Altered E-cadherin-catenin complex

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**IHC distinction between LCIS and DCIS**

<table>
<thead>
<tr>
<th></th>
<th>LCIS</th>
<th>DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-cadherin</td>
<td>Negative</td>
<td>Membrane</td>
</tr>
<tr>
<td>α, β, γ- catenin</td>
<td>Negative</td>
<td>Membrane</td>
</tr>
<tr>
<td>p120 catenin</td>
<td>Cytoplasmic</td>
<td>Membrane</td>
</tr>
<tr>
<td>HMWK (34β12)</td>
<td>Cytoplasmic</td>
<td>Negative</td>
</tr>
</tbody>
</table>

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**E-cadherin-catenin complex for intercellular tight junction**


**E-cadherin stain: distinguish ductal vs lobular lesion**

[Images of DCIS and LCIS with E-cadherin stain results]
Ductal differentiation (DCIS)
Membranous p120

Lobular differentiation (LCIS)
Cytoplasmic p120

Pitfalls in interpreting E-cadherin
Does any positivity excludes lobular ca?

- Entrapped native epithelium/myoepithelium

~15% lobular ca have some E-cad staining

- Aberrant E-cad pattern--
  - Dot-like staining
  - Granular or cytoplasmic staining
  - Partial membrane staining
  - Circumferential yet weak membrane staining

- Circumferential strong membrane staining
  - Usually with impaired E-cad/catenin complex (abnormal staining pattern with other catenins)

*Choi et al: Mod Pathol 2008
Caution in interpreting E-cadherin

- A positive E-cadherin staining does NOT exclude the diagnosis of lobular carcinoma!

- Our current understanding of outcome and risk for LCIS is based on morphology and not IHC
  - Dx based on H&E morphology rather than E-cad or
  - Combined morphology and IHC approach

Algorithm for classifying atypical epithelial lesion using combined H&E and IHC approach

Staining results:

<table>
<thead>
<tr>
<th>Staining pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete absence</td>
<td>Lobular</td>
</tr>
<tr>
<td>Aberrant E-cad pattern</td>
<td>Lobular</td>
</tr>
<tr>
<td>(granular/cytoplasmic, partial membrane, complete weak membrane)</td>
<td>Defer to morphology (± p120 catenin)</td>
</tr>
<tr>
<td>Circumferential strong membrane</td>
<td>Defer to morphology</td>
</tr>
<tr>
<td>If lobular phenotype or abnormal p120</td>
<td>Lobular</td>
</tr>
<tr>
<td>If equivocal/ductal or intact p120</td>
<td>Ductal</td>
</tr>
</tbody>
</table>

60 y F, stereotactic CNB for microcal

ALH involving sclerosing adenosis?

E-cad stain--
circumferential strong membranous staining

? ALH

Back to H&E morphology

Final Dx: ALH

p120
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Classification of non-invasive lobular disease

- Atypical lobular hyperplasia
- Classic LCIS
  - Classic small cell type (type A)
  - Large cell type (type B)
- LCIS variants
  - Pleomorphic
  - Florid or macroacinar
  - Necrotic
  - Signet ring cell

Co-existence of Type A and B cells

Type B LCIS  Pleomorphic LCIS
Pleomorphic LCIS

- Architectural and noncohesive growth of LCIS
- Nuclear pleomorphism
- +/- necrosis and calcifications
- E-cadherin negative

Pleomorphic LCIS-- cytologic criteria?

- Moderate to marked nuclear pleomorphism
- At least some nuclei $\geq 4x$ lymphocyte nucleus

Sneige et al, Mod Pathol 2002
Chen et al, AJSP 2009

- Nuclear diameter $\geq 2x$ lymphocyte nucleus
- At least 2x nuclear size variation

Ho et al: Mod Pathol 2010 (abst)

Pleomorphic LCIS with apocrine cytology
(apocrine PLCIS)
PLCIS characteristics (I)
Chen et al, AJSP 2009, 31 pure PLCIS

- Clinical
  - Older, postmenopausal women
  - Mammographic detection

- Biomarker expression
  - Higher Ki-67
  - Negative or lower ER/PR
  - Higher incidence of HER2 gene amplification

Pleomorphic LCIS: aggressive biomarker profile

Genetics:
- Most 1q +/16q – (genetic signature of classic LCIS)
- More genetic alterations than classic LCIS

Suggestive of more aggressive or advanced lesion

Florid LCIS (Macroacinar LCIS)

- Classic LCIS cells with massive expansion of the involved spaces, mimicking solid DCIS
**Florid LCIS characteristics**

- Older women
- 1q+/16q-, but more genomic changes than classic LCIS
- Increased risk of subsequent invasion
- High incidence of adjacent invasion (~80%), almost all ILC

*Suggestive of more aggressive or advanced lesion*

*Fisher et al: Cancer 1996;1403-1416
*Shin et al: Mod Pathol 2002:52A
*Page et al: Hum Pathol 1991;1232-1239
*Shin et al: Mod Pathol 2010:313A

**LCIS variant with necrosis**

Cytologic and architectural features of classic LCIS, E-cadherin negative, but with comedo-type necrosis

**Positioning of Necrotic Lobular Intraepithelial Neoplasias (LIN, Grade 3) Within the Sequence of Breast Carcinoma Progression**

- Associated with calcifications
- 44% with invasive cancer
- 25% HER2+
- 1q+/16q-, but more genomic changes than classic LCIS

*Genetically advanced lesion with considerable resemblance to carcinomas, ? the transition state from in situ to invasive carcinoma*
Distinction of LCIS variant vs classic LCIS
(both: solid pattern, discohesive cells, E-cadherin negative)

<table>
<thead>
<tr>
<th>LCIS variant</th>
<th>Classic LCIS</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Postmenopausal (~60 y)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Mammographic detection</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Adjacent Invasive ca</td>
<td>Higher incidence majority ILC</td>
</tr>
<tr>
<td>Genetics</td>
<td>1q+/16q-, and more changes</td>
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LCIS in a core needle biopsy: Is excision needed?

Controversial!

Problems in literature:

- Not all studies have pathology verified
- Some studies lump all LCIS types together
- Some studies lump all clinical/radiologic settings together
- Different size/gauge needles used
- Selection bias in who got excision
- Small numbers of patients

LCIS in a core needle biopsy: Is excision needed?

Which LN in CNB will be upgraded to malignancy (DCIS, invasion)?

Outcome of lobular neoplasia in a CNB (I)

- 27% upgrade to DCIS/invasive ca in excision
  - 789 patients, range 0-60%

- Upgrade rate correlates with types of LN on CNB
  - 19% ALH
  - 32% LCIS
  - 41% PLCIS
  - 29% unspecified LN

Outcome of lobular neoplasia in a CNB (II)

- Most upgrade occurring in
  - LCIS variant
  - Discordant imaging
  - Imaging for high-risk indications (vs routine screen)
  - Concurrent ADH, FEA

Cancer in some excisions even without apparent discordance or risk factors (4-5%)
Management of LN in a core needle biopsy

Consider excision if:
- Mass lesion
- Discordant radiology-pathology
- Imaging for high-risk indication
- LCIS variants
  - Necrosis
  - Florid
  - Pleomorphic
- Any worse lesion (ADH, flat epithelial atypia, etc)
- Extensive LN (definition)

Controversial if:
- None of the above
- ALH or minimal LCIS

Take home message for LCIS

- Most classic LCIS as an incidental microscopic finding; LCIS variants by mammographic detection
- Most as risk factor for subsequent invasive cancer; some likely a direct precursor, especially LCIS variants
- LCIS variants: aggressive biomarker profile, more genetic changes, ↑ risk of adjacent cancer
- Classic LN in CNB: management controversial; prudent to excise or discuss in multidisciplinary tumor board
- LCIS variants: manage as DCIS

Management of LCIS variants--A topic of ongoing inquiry, overall manage like DCIS

Found in core needle biopsy:
- Recommend excision

Found in excision:
- Report margin status
- Recommend re-excision if close or at the margin
- ? Adjuvant hormone therapy and radiation

Selected references

Thank you!