Proliferative Breast Lesions
Sarah E Pinder

“Intraductal” Epithelial Proliferations

<table>
<thead>
<tr>
<th>UEH</th>
<th>ADH</th>
<th>LG DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular, peripheral slits. Streaming</td>
<td>Features of UEH &amp; of low grade DCIS</td>
<td>Punched-out spaces, rigid bars, micropapillae</td>
</tr>
<tr>
<td>Uneven distribution &amp; overlapping of nuclei. Variation in appearance, including oval nuclei.</td>
<td>Cells similar to low grade DCIS. Microfocal; &lt; 2 duct spaces with complete involvement (mixed with UEH) (or &lt; 2mm)</td>
<td>Evenly-spaced. Small, regular cells. Round nuclei.</td>
</tr>
</tbody>
</table>

Gynaecomastoid Hyperplasia

• Small, micropapillary clusters
• Taper towards lumen
• Small, pyknotic nuclei arranged around outer edge of micropapillae
• Variable nuclei - not regular, evenly spaced, c.f. LG micropapillary DCIS

Tham KT et al. Prog in Surg Pathol. 1989; 10; 101-9
Study Case 6
Panel Results:
H 1
ADH 4
DCIS 1

Complete agreement among all 6 pathologists in 14 cases (58%); 5 or more agreed in 17 (71%); and 4 or more gave same diagnosis in 22 cases (92%).

**Tips for diagnosis of ADH**
- Specific entity, rare
- Low grade and clonal
- If have not considered LG DCIS in diagnosis, then not ADH
- 2 complete spaces; a small lesion
- Levels

**Epithelial proliferation**
- CK5 (5/6), CK14, ER
- Ck5 +ve
- Ck5 -ve, Ck14 –ve, ER +ve
- Ck5, Ck14 & ER mosaicism
- (Intermediate or) high grade morphology

**UEH**
**DCIS**
**ADH, LG DCIS, LISN, FEA**

**IHC and reproducibility**
- 9 pathologists reviewed 81 proliferative lesions in 3 stages for diagnosis of UEH, ADH or DCIS
- H&E & corresponding slides with IHC cocktail of CK 5, 14, 7, 18 and p63
- Interobserver agreement fair (κ=0.34)
- Intraobserver κ ranged from 0.56-0.88
- Complete agreement among 9 pathologists in 9 (11%) cases, at least 8 agreed in 20 (25%) cases and 7 or more agreed in 38 (47%)
- IHC gave significant improvement in interobserver concordance (overall κ =0.50) and significant reduction in total number diagnoses of ADH
Jain RK et al. Mod Pathol 2011;24:917-23
Pathological features
- Margins
- Size of DCIS
- Nuclear grade
- Architectural pattern
- Necrosis

Heterogeneous

Nuclear Grade of DCIS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low grade</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphism</td>
<td>Monotonous</td>
<td>Intermediate</td>
<td>Markedly pleomorphic</td>
</tr>
<tr>
<td>Size</td>
<td>1.5 x to 2 x RBCs or normal duct epithelial nuclei</td>
<td>Intermediate</td>
<td>&gt;2.5 RBCs or normal duct epithelial nuclei</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Usually diffuse, finely dispersed</td>
<td>Intermediate</td>
<td>Usually vesicular, regular chromatin distribution</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Only occasional</td>
<td>Intermediate</td>
<td>Prominent, often multiple</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Only occasional</td>
<td>Intermediate</td>
<td>May be frequent</td>
</tr>
<tr>
<td>Orientation</td>
<td>Polarized</td>
<td>Intermediate</td>
<td>Usually not polarized</td>
</tr>
</tbody>
</table>
Grading System

<table>
<thead>
<tr>
<th>Nuclear Grade</th>
<th>N</th>
<th>N of events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>6 (7.0%)</td>
<td>0.51</td>
<td>0.22-1.15</td>
</tr>
<tr>
<td>2</td>
<td>225</td>
<td>13 (5.8%)</td>
<td>0.44</td>
<td>0.23-0.72</td>
</tr>
<tr>
<td>3</td>
<td>913</td>
<td>135 (14.8%)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Architecture

<table>
<thead>
<tr>
<th>Architecture</th>
<th>N</th>
<th>N of events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>731</td>
<td>111</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Cribriform</td>
<td>372</td>
<td>27</td>
<td>0.47</td>
<td>0.31-0.71</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>91</td>
<td>13</td>
<td>0.37</td>
<td>0.14-1.71</td>
</tr>
<tr>
<td>Papillary</td>
<td>30</td>
<td>3</td>
<td>0.50</td>
<td>0.2-2.01</td>
</tr>
</tbody>
</table>

"Very High" Grade = High cytonuclear grade, comedo-type necrosis in >50% ducts, >50% solid architecture

Microinvasion

- DCIS with one or more foc of invasion <1mm in maximum dimension
- [In non-specialised, interlobular or interductal connective tissue]
- Uncommon lesion – beware overdiagnosis
- Usually associated with high grade DCIS
- Assess low power - lobular architecture of cancerisation
- Collagen IV, laminin, myoepithelial stains & additional levels

Cancerisation of lobules

Figure 1: Recurrence of ipsilateral DCIS or invasive carcinoma by new grading system for DCIS.
Presentation of Pleomorphic LCIS (PLCIS) - microcalcification
- 80% of 10 cases (Sneige)
- 84% of 26 cases (Downs-Kelly)
- 92% of 12 cases (Chivukula)
- 81% of 31 cases (Chen); 3 (10%) also mass
- 100% of 10 screen-detected cases (Carder)

- Often screen detected
- Previously classified as high grade DCIS

Pleomorphic LCIS (& Pleomorphic Apocrine LCIS (PALCIS))
- Lack E-cadherin & beta-catenin
- Gain of 1q & loss of 16q - typical of lobular carcinoma
- Higher Ki67 index, lower ER & PgR expression, higher HER2 gene amplification & amplification of c-myc than classical LCIS
- Lobular immunohistochemical profile & genetics
- More “aggressive” re proliferation, HER2 etc
- Very limited data on clinical behaviour

Clinical Implications of Margin Involvement by Pleomorphic Lobular Carcinoma In Situ (PLCIS) - Undergoing Surgical Management

<table>
<thead>
<tr>
<th>Table 3: Pathologic Features of 23 Patients with Pleomorphic Lobular Carcinoma In Situ (PLCIS) undergoing Surgical Management</th>
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<tr>
<td>Pathologic Feature</td>
</tr>
<tr>
<td>PLCIS margin + DCIS</td>
</tr>
<tr>
<td>Pleomorphic LCIS (PLCIS) margin + DCIS</td>
</tr>
<tr>
<td>Extensive or multifocal PLCIS</td>
</tr>
<tr>
<td>Positive margin</td>
</tr>
<tr>
<td>15-year retrospective ‘chart review’</td>
</tr>
<tr>
<td>23 pure PLCIS on diagnostic biopsy</td>
</tr>
<tr>
<td>21 surgical excision following diagnostic biopsy, 33.3% (7/21) had invasive carcinoma and 19% (4/23) DCIS</td>
</tr>
<tr>
<td>Extensive or multifocal PLCIS in 47.6% (10/21), corresponding to at least one PLCIS-positive or close margin in 71.4% (15/21)</td>
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<td>11 local re-excisions in 9 patients &amp; 12 mastectomies</td>
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<tr>
<td>No ipsilateral breast cancer events, including in those with positive or close surgical margins at mean follow-up 4.1 years</td>
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Management of PLCIS

- 15-year (2000-2014) retrospective ‘chart review’
- 23 pure PLCIS on diagnostic biopsy
- 21 surgical excision following diagnostic biopsy, 33.3% (7/21) had invasive carcinoma and 19% (4/23) DCIS
- Extensive or multifocal PLCIS in 47.6% (10/21), corresponding to at least one PLCIS-positive or close margin in 71.4% (15/21)
- 11 local re-excisions in 9 patients & 12 mastectomies
- No ipsilateral breast cancer events, including in those with positive or close surgical margins at mean follow-up 4.1 years

• "Long-term follow-up studies are needed to further define the natural history of PLCIS and its optimal management”
• "Clinical follow-up studies will be required to define the natural history and most appropriate management of these lesions”

Sneige N et al. Mod Pathol. 2002;15:1044-50

• “High quality evidence to inform guidance is lacking, thus recommendations are relatively vague. However, based on the available evidence, it would seem prudent to treat PLCIS in a similar manner to DCIS.”

Pieri A, Harvey J, Bundred N. World J Clin Oncol 2014; 5; 546-53

LCIS Vs. Low Grade Solid DCIS

• Both processes - filling of membrane-bound spaces by uniform, regularly-placed cells with clear cytoplasm
• Low power - lobulo-centricity of LCIS, more haphazard lobular & duct distortion in DCIS
• DCIS - sharply defined cell membranes
• LCIS - discohesion
• Intracytoplasmic lumina more often in LCIS

LCIS Vs DCIS

• Ca2+ dependent cell–cell adhesion protein
• Chromosome 16q22.1
• Mutations early - in ALH & LCIS

E-cadherin

• Heterogeneous E-cadherin staining in indeterminate carcinoma in situ


Cases | Absent | Weak/partial | Focal/dot-like
--- | --- | --- | ---
140 LN or ILC | 121 (86%) | 15 (12%) | 4 (3%)

Choi YJ et al. Mod Pathol. 2008;21:1224-37
Lobular in Situ Neoplasia

- Follow-up of 39 of 48 patients
- 0.5% of 10,542 benign breast biopsies
- Higher risk with LCIS (9x) = (8 cells across)
- Lower risk with ALH (4-5x)

Page DL. Human Pathol. 1991; 22: 1232-1239
Effect of LCIS on Cancer Recurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Ipsilateral recurrence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moran, Int J Radiat Biol Phy 1998</td>
<td>1096 WLE + RT - 117 with LCIS</td>
<td>Ipsilateral rec free survival 77% with LCIS, 94% without (NS)</td>
<td></td>
</tr>
<tr>
<td>Alme, Cancer 2000</td>
<td>112 invasive ca BCT/RT - 117 with LCIS</td>
<td>4 yr LR 12% with LCIS, 12% without (NS)</td>
<td></td>
</tr>
<tr>
<td>Ben-David, Cancer 2006</td>
<td>121 stage 0-1 Ca without LCIS &amp; 64 with LCIS</td>
<td>No difference in LR if LCIS present, (100% &amp; 89% local control for LCIS vs no LCIS)</td>
<td></td>
</tr>
<tr>
<td>Jolly, Int J Radiat Oncol Bio Phys 2006</td>
<td>607 invasive breast ca - 64 LCIS present</td>
<td>LCIS independently predicted for ipsilateral rec. (10 yr ipsilat rec 14% if LCIS, 3% without)</td>
<td></td>
</tr>
<tr>
<td>Adepoju, Cancer 2006</td>
<td>207 DCIS - BCT</td>
<td>No difference in LR if LCIS present, (overall 14% LR)</td>
<td></td>
</tr>
<tr>
<td>Ciocca, Ann Surg Oncol 2008</td>
<td>239M BCT stage 0-1, 290 with LCIS, 64 LCIS at margin</td>
<td>No difference in LR if LCIS present, even if at margin, (6% 10 yr LR rate for both)</td>
<td></td>
</tr>
<tr>
<td>Sadek, Int J Radiat Oncol Bio Phys 2013</td>
<td>238B T1 or T2, WLE + RT, 62 positive/close LCIS margins (&lt;2mm) vs 2232 negative</td>
<td>No difference in LRR (3.2% vs 2.8%) at 5 yrs</td>
<td></td>
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UK National Survey of LCIS
- Questionnaire about management of LCIS sent to 490 UK breast surgeons; 173 (35%) returned
- When LCIS is present in a core biopsy: 61% of breast surgeons perform surgical excision; 22% would not excise but would continue follow-up; remainder perform neither, or set no clear management plan
- 54% follow up with 5 years of annual mammography
- If classic LCIS at margins of wide local excision, 92% would not re-excise
- Conversely, if pleomorphic LCIS were found, 71% would achieve clear margins


Columnar cell lesions
- Columnar cell change
- Columnar cell hyperplasia
- Flat epithelial atypia

Columnar alteration with prominent snouts & secretions (CAPSS)
- CAPSS in 42% of 100 consecutive bx for microcalcifications
- Calcifications in CAPSS in 74%


Arise from structurally normal TDLUs

Columnar Cell Change
- Columnar epithelial cells (1 or 2 cell depth) line TDLU, often mildly dilated
- Uniform, ovoid nuclei
- Perpendicular to basement membrane
- Cytologically bland
- Mitotic figures rare
- Apical snouts often present
- Secretions may be present in lumen with Ca²⁺
Columnar Cell Hyperplasia
* Similar to CCC, but stratification > 2 cells depth
* Nuclei morphology as in CCC
* May be more crowding & overlapping of nuclei
* Tufts or hummocks mimicking micropapillae
* Exaggerated apical snouts - hobnail appearance
* Intraluminal secretions often with Ca²⁺

N.B. If true micropapillae, bridges, cribriform pattern etc = consider as ADH/DCIS

Flat Epithelial Atypia
* TDLUs often darker than normal at low power
* 1 or more layers of monotonous, cuboidal to columnar cells, resembling LG DCIS
* Round nuclei
* Mild increase in nuclear/cytoplasmic ratio
* Dispersed or margined chromatin
* Nucleoli sometimes more prominent
* Mitotic figures rare
* May be scattered lymphoid cells
Often a spectrum - columnar cell change to columnar cell hyperplasia to columnar cell hyperplasia with atypia to low grade DCIS

May be subtle

Not necessarily flat

Sample thoroughly
Is not high grade

Flat Epithelial Atypia
- Irregular contours
- Smooth contours
- Irregular contours

IHC unhelpful – all uniform hormone receptors and negative with basal cytokeratins

Flat epithelial atypia
- FEA is clonal
- Genetic changes relatively few in number; on multiple chromosomes
  - LOH: losses on 3p & 11q, 2p, 16q, 17q
  - CGH: losses on 16q, 17p, X, gains on 15q, 16p, 19
- Genetic alterations similar to those of associated DCIS & invasive carcinoma

May co-exist with other low grade neoplastic lesions
Flat epithelial atypia and risk of breast cancer: Mayo

- FEA in excisional breast biopsies in Mayo Clinic Benign Breast Disease Cohort; 11,591 women, 1967 to 2001
- FEA in 282 (2.4%); 130 had associated AH (46%)
- Median follow-up of 16.8 years, standardised incidence ratio for breast cancer in patients with AH plus FEA was 4.74 Vs 4.23 for those with AH without FEA
- The SIR for patients with UEH plus FEA was 2.04 Vs 1.90 for patients with UEH without FEA
- "FEA does not appear to convey an independent risk of breast cancer...."

Breast cancer risk associated with benign disease: systematic review & meta-analysis

- Meta-analysis of existing literature from 1972 to 2010
- 3,409 articles, 32 studies met selection criteria
- Mean age at benign breast biopsy was 46.1 years, mean age of developing breast cancer 55.9 years
- Mean follow-up length 12.8 years (range 3.3-20.6)
- Risk estimate for non-proliferative disease = 1.17
- Proliferative disease without atypia RR = 1.76
- Risk estimate for atypical hyperplasia (not otherwise specified) = 3.93
  Dyrstad SW et al. Breast Cancer Res Treat. 2015;149:569-75

Inter-observer variability in diagnosis

- Retrospective study of original diagnostic reports vs later review by specialist in breast pathology
- 610 specimens sent for consultation and/or 2nd opinion between Jan 2005 and Dec 2010
- Weak correlations for diagnoses of columnar cell change (κ=0.38) & columnar cell hyperplasia (κ=0.32)
- Moderate agreement (κ=0.47) for FEA, ADH (κ=0.44), low-grade DCIS (κ=0.47), intermediate-grade DCIS (κ=0.45) and DCIS with microinvasion (κ=0.56)
- Good agreement for ALH (κ=0.62) & LCIS (κ=0.66) and high-grade DCIS (κ=0.68)
- Poor agreement for diagnoses of pleomorphic LCIS (κ=0.22)
  Gomes DS et al. Diagn Pathol. 2014;9:121