Intraluminal Proliferative Lesions of Terminal Duct Lobular Units

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Intraluminal Proliferative Lesions of Terminal Duct Lobular Units

Four distinct but related entities –
Columnar cell lesions
Ductal hyperplasia
Ductal carcinoma-in-situ
Lobular neoplasia
Columnar cell lesions

- Blunt duct adenosis
- Atypical cystic lobules
- Cancerization of small ectatic ducts of the breast by ductal carcinoma in situ cells with apocrine snouts
- Hypersecretory hyperplasia
- Columnar alteration with prominent apical snouts and secretions (CAPPS)
- Mammary ductal intraepithelial neoplasia-flat type
- “Clinging ductal carcinoma in situ"
- Hyperplastic Unfolded Lobules (HULs)
- Enlarged lobular units with columnar alteration (ELUCA)
- **Columnar cell change / columnar cell hyperplasia**
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 Ca$^{2+}$
Columnar Cell Change with Cytological Atypia / Flat Epithelial Atypia

- TDLUs darker than normal at low power
- One or more layers of monotonous, cuboidal to columnar cells, resembling low grade DCIS
- Rounder nuclei with mild increase in nuclear/cytoplasmic ratio
- Dispersed or marginated chromatin
- Nucleoli sometimes more prominent
- Mitotic figures rare
- MAY BE SUBTLE !

N.B. High grade atypia = flat high grade DCIS NOT columnar cell change with atypia
Reproducibility of Diagnosis of Flat Atypia

- 28 cases Powerpoint tutorial from Stu Schnitt
- 8 pathologists sent images of 30 cases
- Complete agreement re presence or absence of FEA in 24 of the 30 cases (80.0%)
- 7 or more agreed in 26 cases (86.7%)
- 6 or more agreed in 28 cases (93.3%)

Kappa = 0.83

Columnar Cell Hyperplasia

- Similar to CCC, but stratification > 2 cells depth
- Nuclear 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 Ca\(^{2+}\)

N.B. If true micropapillae, bridges, cribriform pattern etc = consider as ADH/DCIS
### Assessment of Columnar Cell Lesions

<table>
<thead>
<tr>
<th>Cytological atypia</th>
<th>Hyperplasia (No)</th>
<th>Hyperplasia (Yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Columnar cell change</td>
<td>Columnar cell hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Columnar cell atypia <em>(Flat epithelial atypia)</em></td>
<td>Columnar cell hyperplasia with cytological atypia*</td>
</tr>
</tbody>
</table>

* If high grade = DCIS
Columnar Cell Lesions

• Often a spectrum - columnar cell change to columnar cell hyperplasia to columnar cell hyperplasia with atypia to low grade DCIS
Sample thoroughly
Columnar Cell Lesions
Immunohistochemistry Unhelpful

- Most cells in columnar cell lesions show luminal cytokeratin (e.g. CK19) positivity
- No expression with cytokeratins 5 and 6
- Strong homogeneous nuclear estrogen receptor & progesterone receptor positivity
Columnar cell lesions of the breast: the missing link in breast cancer progression?

- CCL in context of UEH & DCIS & invasive carcinoma
- 81 lesions from 18 patients
- Morphological review, IHC & CGH
- CCLs were ER & PgR positive, CK5/6 & CK14 negative with low numbers of genetic alterations with recurrent 16q loss, i.e. similar to low grade DCIS & invasive carcinoma
- Overlapping chromosomal alterations between CCL and more advanced lesions within individual TDLUs suggest commonality in molecular evolution

## Practicalities

### Core Biopsy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columnar cell change or Columnar cell hyperplasia</td>
<td>No additional levels, Excision not required</td>
</tr>
<tr>
<td>Columnar change or hyperplasia with atypia / flat epithelial atypia</td>
<td>Diagnostic excision recommended</td>
</tr>
</tbody>
</table>

### Excision

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columnar cell change or Columnar cell hyperplasia</td>
<td>No levels, No treatment required</td>
</tr>
<tr>
<td>Columnar change or hyperplasia with atypia / flat epithelial atypia</td>
<td>Levels, Submit more/all tissue</td>
</tr>
</tbody>
</table>
History of LCIS

- Described by Foote & Stewart in 1941
- Detection increased in recent years, found in approximately 1% (0.5 - 3.6%) of all breast biopsy specimens but true incidence is unclear
- May be widespread, with high rates of multicentricity (60-80%) & bilaterality (23-35%)
Cancer Risk in Lobular Neoplasia

- Follow-up of 39 of 48 patients (from 10,542 benign breast biopsies (0.5%))
- Higher risk of cancer with LCIS, 9x, & lower risk with more subtle examples - ALH, 4-5x
  Page DL. Human Pathology. 1991; 22; 1232-1239
- Meta-analysis of 9 studies of 228 patients
- 15% developed ipsilateral invasive cancer
- 9% developed contralateral carcinoma
- Ipsilateral cancer 3 x more likely than contralateral
LCIS Vs ALH

LCIS
- More than half acini filled & distended by characteristic cells with no central lumen
- Practically, 8 or more cells within cross-section of acinus

ALH
- Partly fill acinus with minimal or no distension and lumina may still remain
- Number of acini involved < half
- May have admixed myoepithelial cells
LCIS
LCIS Vs. Low Grade Solid DCIS

- Both processes - filling of membrane-bound spaces by uniform, regularly-placed cells with clear cytoplasm
- DCIS more sharply defined cell membranes
- LCIS more discohesion
- Intracytoplasmic lumina more often in LCIS
- Low power view shows lobulo-centricity of LCIS, more haphazard lobular & duct distortion in DCIS – not always available in core biopsy

- If features of both present then classify as LCIS & DCIS because of bilateral & precursor risk
Distinguishing LCIS from DCIS
Distinguishing LCIS from DCIS

Any additional features/tests?
E-cadherin
E-Cadherin

• 28 cases of indeterminate CIS:
  • Group 1 (6) - all cytological & architectural features of LCIS but with comedo necrosis
  • Group 2 (17) - small, uniform cells, either growing in solid pattern with focal microacinar-like structures but with discohesion, or growing in a cohesive pattern but with intracytoplasmic vacuoles
  • Group 3 (5) - marked pleomorphism & nuclear atypia but discohesive growth
  • All group 1 & group 3 cases E-cadherin negative
  • Group 2 heterogeneous E-cadherin staining

Pleomorphic LCIS

- Lack E-cadherin & beta-catenin
- Gain of 1q & loss of 16q = typical of lobular ca.
- Amplification of c-myc and HER2
- Same precursor or same genetic pathway as classic lobular carcinomas

- Lobular IHC profile & genetics
- More “aggressive” re proliferation, HER2 etc
- Very limited data on clinical behaviour
## Histological Features – Ductal Hyperplasia and DCIS

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>UEH</th>
<th>ADH</th>
<th>LG DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Variable</td>
<td>&lt;2-3mm</td>
<td>Usually &gt;3mm</td>
</tr>
<tr>
<td>Cellular</td>
<td>Mixed</td>
<td>Uniform and mixed</td>
<td>Single cell population</td>
</tr>
<tr>
<td>Composition</td>
<td>Variable</td>
<td>Micropap, cribriform, solid</td>
<td>Micropap, cribriform solid</td>
</tr>
<tr>
<td>Architectural</td>
<td>Variable</td>
<td>Distinct/irregular</td>
<td>Punched out</td>
</tr>
<tr>
<td>Luminal</td>
<td>Irregular, slit-like</td>
<td>Distinct/irregular</td>
<td>Punched out</td>
</tr>
<tr>
<td>FEATURE</td>
<td>UEH</td>
<td>ADH</td>
<td>LG DCIS</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Cell Orientation</td>
<td>Streaming, tapering bridges</td>
<td>Nuclei at right angles to bridges, rigid structures</td>
<td>Micropap. structures – no cores or smooth well-delineated geometric spaces. Cell bridges rigid cribriform DCIS</td>
</tr>
<tr>
<td>Nuclear spacing</td>
<td>Uneven</td>
<td>Even/uneven</td>
<td>Even</td>
</tr>
<tr>
<td>FEATURE</td>
<td>UEH</td>
<td>ADH</td>
<td>LG DCIS</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td>---------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Cell Character</td>
<td>Small ovoid, shape variation</td>
<td>Small uniform or medium-sized monotonous cells</td>
<td>Small uniform monotonous cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>monotonous nuclei (focally)</td>
<td></td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Indistinct</td>
<td>Single small</td>
<td>Single small</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Infrequent</td>
<td>Infrequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Rare</td>
<td>Rare</td>
<td>If present, small particulate debris in spaces</td>
</tr>
</tbody>
</table>
Intraductal Epithelial Proliferations
Atypical Ductal Hyperplasia

Architectural features
- Some features of UEH & some features of low grade DCIS

Cytological features
- Cells similar to those seen in low grade DCIS present in a portion of the space
- Second population of cells typical of florid hyperplasia also present

Size/extent
- Less than 2 duct spaces with complete involvement (2mm)
### NHS BSP EQA Scheme

#### Kappa’s for overall diagnosis (all participants)

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Atypical hyperplasia</th>
<th>In situ / Micro-invasive</th>
<th>Invasive</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>902, 911, 912</td>
<td>0.72</td>
<td>0.19</td>
<td>0.71</td>
<td>0.81</td>
<td>0.68</td>
</tr>
<tr>
<td>921, 922, 931</td>
<td>0.75</td>
<td>0.16</td>
<td>0.71</td>
<td>0.86</td>
<td>0.72</td>
</tr>
<tr>
<td>932, 941, 942</td>
<td>0.81</td>
<td>0.15</td>
<td>0.75</td>
<td>0.88</td>
<td>0.77</td>
</tr>
<tr>
<td>951, 952, 961</td>
<td>0.75</td>
<td>0.17</td>
<td>0.77</td>
<td>0.86</td>
<td>0.77</td>
</tr>
<tr>
<td>962, 971, 972</td>
<td>0.79</td>
<td>0.26</td>
<td>0.81</td>
<td>0.91</td>
<td>0.82</td>
</tr>
<tr>
<td>981, 982, 991</td>
<td>0.84</td>
<td>0.13</td>
<td>0.69</td>
<td>0.90</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>0.79</strong></td>
<td><strong>0.18</strong></td>
<td><strong>0.75</strong></td>
<td><strong>0.88</strong></td>
<td><strong>0.77</strong></td>
</tr>
</tbody>
</table>
**Study Case 6**

Panel Results:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Your Score</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>H</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ADH</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>DCIS</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Inter-observer Variability in Diagnosis of ADH

- Is real problem for very small % of cases
- Beth Israel Deaconess Medical Center, < 2% of breast biopsies in borderline category
Common adult stem cells in the breast - biological concept

“cells differentiate toward glandular or myoepithelial cells, passing through either Ck5/Ck8/18/19 or Ck5/SMA-positive intermediates” Bocker et al. Lab Invest 2002;82; 737-745
Cytokeratins in Intraductal Hyperplasia

Luminal epithelial cytokeratins (CK 8, 18, 19) & basal intermediate epithelial cytokeratins (CK 5, 6, 14) may be helpful in difficult intraductal proliferations - identify a mixed cell population in UEH

Bocker W. Pathologe 1997;18:3-18
Diagnosis of (low grade) DCIS/ADH with CK 5/6
Gynaecomastoid Hyperplasia

- Small, papillary-like clusters of epithelial cells
- No fibrovascular stalks
- 2 - 3 cells above basement membrane
- Papillary clusters taper towards lumen
- Small, pyknotic nuclei arranged around outer edge of papillary structures
- Variable nuclear features - not regular, evenly spaced, c.f. DCIS

Gynaecomastoid Hyperplasia
Gynaecomastoid Hyperplasia
ER in Diagnosis of Intraductal Epithelial Proliferations

- % of ER +ve cells slightly increased in UEH
- ER +ve surrounded by ER -ve cells or contiguous groups of +ve cells (sometimes >90% cells)
- In ADH, LCIS & low grade DCIS contiguous +ve cells

Shoker BS et al. J Pathol 1999;188;237-244
## Diagnosis of DCIS - NHS BSP EQA Scheme

### Kappa - Overall Diagnosis

<table>
<thead>
<tr>
<th>Circulation</th>
<th>Benign</th>
<th>In situ / MI</th>
<th>Inv.</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>902,911,912</td>
<td>0.72</td>
<td>0.71</td>
<td>0.81</td>
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<td>981,982,991</td>
<td>0.84</td>
<td>0.69</td>
<td>0.90</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>0.79</td>
<td><strong>0.75</strong></td>
<td>0.88</td>
<td>0.77</td>
</tr>
</tbody>
</table>

### Kappa Categories

<table>
<thead>
<tr>
<th>Kappa Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 – 0.20</td>
<td>Slight</td>
</tr>
<tr>
<td>0.21 – 0.40</td>
<td>Fair</td>
</tr>
<tr>
<td>0.41 – 0.60</td>
<td>Moderate</td>
</tr>
<tr>
<td>0.61 – 0.80</td>
<td>Substantial</td>
</tr>
<tr>
<td>0.81 – 1.00</td>
<td>Almost perfect</td>
</tr>
</tbody>
</table>
## Classification of DCIS

### Extent of DCIS - Relation to Architecture

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Comedo</th>
<th>Solid</th>
<th>Cribriform</th>
<th>Micropapillary</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single quadrant</strong></td>
<td>24</td>
<td>19</td>
<td>20</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td><strong>Multiple quadrant</strong></td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26</td>
<td>23</td>
<td>25</td>
<td>14</td>
<td>88</td>
</tr>
</tbody>
</table>

Bellamy. *Hum Pathol* 1993; 24;16
DCIS - NHS BSP Grade

- High grade
- Intermediate grade
- Low grade

Nuclear size, pleomorphism, nucleoli, mitoses

(Growth pattern, necrosis & polarisation)

*Pathology Reporting of Breast Disease.*
*NHS BSP Publication 58, 2005*
Evidence for Progression of DCIS

<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade</td>
<td>Biopsy alone</td>
<td>Progression 50% in 5 yrs</td>
</tr>
<tr>
<td>Low grade</td>
<td>Biopsy alone</td>
<td>Progression 30% in 15 yrs</td>
</tr>
</tbody>
</table>

**Low grade DCIS**

40% of 28 patients with ‘missed’ lesions on biopsy developed invasion at same site at 30 year follow-up

Page et al, Cancer 1995; 76; 1196-1200
DCIS Genetic studies

- Allelic imbalance analysis suggests that low grade & high grade carcinomas follow different genetic pathways

Roylance et al, J Pathol 2002; 196:32-36
Excision of DCIS

3D Mapping Egans Technique
82 cases

1 quadrant 66%
>1 quadrant 23%
Central 11%

81 cases 1 duct system
1 case Multiple ducts systems
= a unicentric process

Holland. Lancet 1990; 335; 519
An adequate margin of excision in ductal carcinoma in situ

2 mm plus radiotherapy is as good as a bigger margin

On balance there is good evidence that surgical resection margins free of DCIS should be obtained. Current evidence suggests, however, that when radiotherapy is given the results are as good when the margin is at least 2 mm as they are when it is more than 1 cm. Finally it is important to keep in mind the extremely low risk of death due to breast cancer associated with a diagnosis of DCIS.5-12 The intensity of the surgical debate on margins and local recurrence in DCIS has resulted in great confusion among patients about treatment choices and is causing patients to choose mastectomies that are not medically necessary.13

Malcolm R Kell fellow in surgical oncology
(malcolmkell@eircom.net)

Monica Morrow chairman, department of surgical oncology

BMJ 2005; 331; 789-90
Specimen Handling

Serial slicing

Superior

Medial

Lateral

Inferior

Max dimension

Distance to nearest margin

Anterior/Superficial

Posterior/Deep

Inferior

Method 1: serial slicing perpendicular to the medial-lateral plane (Figure 2)
<table>
<thead>
<tr>
<th>Type</th>
<th>Visibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedo / Solid</td>
<td>85% of area visible mammographically</td>
</tr>
<tr>
<td>Micropapillary / Cribriform</td>
<td>50% of area visible mammographically</td>
</tr>
</tbody>
</table>
Excision of DCIS - Margins

• Serial subgross technique
• 181 patients with WLE for DCIS
• Involved = “within 1mm of any inked or dyed margin”
• Residual disease in 43% with apparently clear margins
  Silverstein et al. Cancer 1994;73;2985-89

• 232 patients with lumpectomy for DCIS
• Residual disease in 10 of 73 (14%) with >1mm clearance
  Cheng et al. J Nat Cancer Inst 1997;89;1356-60
**Intraluminal Proliferative Lesions of Terminal Duct Lobular Units.**

### Management

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Core biopsy</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columnar cell change</td>
<td>B2</td>
<td>No further action</td>
</tr>
<tr>
<td>Columnar cell hyperplasia</td>
<td>B2</td>
<td>No further action</td>
</tr>
<tr>
<td>Columnar cell change/ hyperplasia with atypia</td>
<td>B3</td>
<td>Open diagnostic bx</td>
</tr>
<tr>
<td>ALH</td>
<td>B3</td>
<td>? Open diagnostic bx</td>
</tr>
<tr>
<td>LCIS</td>
<td>B3</td>
<td>? Open diagnostic bx</td>
</tr>
<tr>
<td>LCIS (pleomorphic)</td>
<td>B3 or B5a</td>
<td>? Complete excision</td>
</tr>
<tr>
<td>Ductal hyperplasia</td>
<td>B2</td>
<td>No further action</td>
</tr>
<tr>
<td>Ductal hyperplasia with Atypia</td>
<td>B3</td>
<td>Open diagnostic bx</td>
</tr>
<tr>
<td>DCIS</td>
<td>B5a</td>
<td>Complete excision</td>
</tr>
</tbody>
</table>
Thanks to –
Dr. Sarah Pinder,
Addenbrooke’s Hospital,
Cambridge.