Hyperplasia, FEA, ADH, and Lobular neoplasia

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Consultant Pathologist
Queen Elizabeth Hospital Birmingham
Intraductal Epithelial proliferation

- Ductal or lobular
- Atypical or not
- Extent of atypia
Epithelial proliferation

Lobular
- High grade
  - PLCIS
  - Extent
    - LCIS
    - ALH

Ductal
- Non high grade
  - Atypia
    - ADH
    - DCIS
- High grade
  - No atypia
    - HUT

Extent
Non atypical ductal hyperplasia

(Epithelial hyperplasia of usual type, Usual ductal hyperplasia)
- Architecture: solid with peripheral slit like spaces, streaming of nuclei.

- Cytological: mixed population
  - Rounded and ovoid cells
  - Variation in size and shape
Epithelial hyperplasia

- Papilloma
- Columnar cell change
- Radial scar
- Fibroadenoma
- Apocrine metaplasia
- Nipple adenoma
- Gynaecomastia
ADH

- Quantitative diagnosis
- Not high grade
- If on core biopsy: designate as AIDEP
- B-coding B3
Architectural atypia
Fauna-form changes in the breast
ADH vs DCIS

- Extent of atypia: 2mm or 2 fully involved ductal spaces = DCIS (NOT FOR HIGH GRADE LESIONS)

- Atypia in papillomas: 3mm
Useful Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>Hyperplasia</th>
<th>ADH/DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK5</td>
<td>mixed</td>
<td>Negative</td>
</tr>
<tr>
<td>ER</td>
<td>Patchy positive</td>
<td>Uniformly positive</td>
</tr>
</tbody>
</table>
DCIS

Ck5/6

ER
HER2 IHC can be helpful in confirming the diagnosis of DCIS
IHC Pitfalls

1. Apocrine lesions
Apocrine metaplasia

CK5
Atypical apocrine proliferation

CK5
2. Basal phenotype DCIS
3. Hyperplasia in the male breast

Male breast
CK14

### Table 1  \( \kappa \) Values for overall diagnosis (all participants)

<table>
<thead>
<tr>
<th>Circulation group</th>
<th>Benign</th>
<th>Atypical hyperplasia</th>
<th>In situ/micro-invasive</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 902–20 002</td>
<td>60</td>
<td>5</td>
<td>62</td>
<td>125</td>
</tr>
<tr>
<td>20 011–20 141</td>
<td>112</td>
<td>6</td>
<td>36</td>
<td>170</td>
</tr>
<tr>
<td>Total</td>
<td>172</td>
<td>11</td>
<td>98</td>
<td>295</td>
</tr>
<tr>
<td>Circulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 902–20 002</td>
<td>0.79</td>
<td>0.18</td>
<td>0.76</td>
<td>0.88</td>
</tr>
<tr>
<td>20 011–20 021</td>
<td>0.83</td>
<td>0.15</td>
<td>0.83</td>
<td>0.96</td>
</tr>
<tr>
<td>20 022–20 032</td>
<td>0.79</td>
<td>0.18</td>
<td>0.75</td>
<td>0.90</td>
</tr>
<tr>
<td>20 041–20 051</td>
<td>0.70</td>
<td>0.20</td>
<td>0.65</td>
<td>0.90</td>
</tr>
<tr>
<td>20 052–200 62</td>
<td>0.87</td>
<td>0.19</td>
<td>0.78</td>
<td>0.96</td>
</tr>
<tr>
<td>20 071–20 081</td>
<td>0.82</td>
<td>0.10</td>
<td>0.70</td>
<td>0.92</td>
</tr>
<tr>
<td>20 082–20 092</td>
<td>0.76</td>
<td>0.17</td>
<td>0.23</td>
<td>0.89</td>
</tr>
<tr>
<td>20 101–20 111</td>
<td>0.83</td>
<td>0.14</td>
<td>0.44</td>
<td>0.92</td>
</tr>
<tr>
<td>20 112–20 122</td>
<td>0.79</td>
<td>0.18</td>
<td>0.75</td>
<td>0.90</td>
</tr>
<tr>
<td>20 131–20 141</td>
<td>0.81</td>
<td>0.13</td>
<td>0.83</td>
<td>0.95</td>
</tr>
<tr>
<td>20 011–20 141</td>
<td>0.81</td>
<td>0.17</td>
<td>0.72</td>
<td>0.92</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 902–20 141</td>
<td>0.80</td>
<td>0.17*</td>
<td>0.75</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Rakha et al 2016
Flat epithelial atypia
Columnar cell lesions

- *Columnar cell change (without atypia):* columnar cell change/columnar cell hyperplasia
- *Flat epithelial atypia*

If high grade nuclei = flat DCIS
A neoplastic proliferation of TDLUs characterised by replacement of the native epithelial cells by one to several layers of a single epithelial cell type showing low grade (monomorphic) cytological atypia.
Previous terminology of FEA

- Atypical lobule type A
- Atypical columnar cell metaplasia
- Atypical cystic lobules
- Atypical cystic duct
- Hypersecretory hyperplasia with atypia
- Columnar cell change with atypia
- DIN (DIN1a = FEA)
- Clinging carcinoma (monomorphic type)
- Monomorphic epithelial proliferation
Columnar cell change

- Dilated TDLU (oval/branching)
- Columnar cells with polarity
- Apical snouts
- $\pm$ Calcification
- ER positive, CK5 negative
FEA

- Dilated TDLU, regular/rounded acini
- Round/oval nuclei
- Monotonous nuclei with loss of polarity
- Cytological atypia, often hyperchromasia
- Usually with apical snouts
- May have small nucleoli
- ER positive, CK5 negative

No high grade atypia or complex architecture
FEA Immunohistochemical profile

- ER, PR +, Bcl2+
- CK5 –
- Her 2 negative

Similar to ADH and low grade DCIS

FEA diagnosis is morphological
FEA Reproducibility of Diagnosis

- Poor agreement on assessment of images by a mixed group of pathologists
  

- Excellent agreement among breast pathologists after PowerPoint training session (better for exclusion of atypia)

Tips

- Do not over-diagnose atypia
- Discuss with colleagues!
Rosen’s triad

Columnar cell lesions, lobular neoplasia, tubular carcinoma
FEA and Lobular insitu neoplasia
Associated lesions

Low nuclear grade neoplasia family

- Tubular, cribriform, grade 1 ductal NST, lobular, tubulo-lobular carcinoma

- CCC, FEA, ADH, low grade DCIS, lobular in situ neoplasia

- ER, bcl2, CK8, 18, 19 positive. CK5, 14, p53, HER2 neg

Lobular neoplasia

- Encompasses atypical lobular hyperplasia (ALH) and lobular in situ carcinoma (LCIS).

- LCIS: classical and variants
ALH vs LCIS

- Depends on extent of lesion

- LCIS: more than half of the acini are filled, distended, and distorted by the dyscohesive lobular cells.
Histologically

- A monomorphic proliferation within TDLU of dyscohesive cells with uniform round nuclei, indistinct nucleoli and scant cytoplasm.

- Intracytoplastic lumina are often present

- Pagetoid spread can be seen.
■ **Type A cells:** small uniform cells with bland nuclei and scant cytoplasm

■ **Type B cells:** cells are larger, with more cytoplasm and mild to moderate atypia
Immunohistochemistry

- E-cadherin: negative (but not always)
- CK5, CK14: negative
- ER: positive
- Her2: negative
- Loss of β-catenin
- Cytoplasmic catenin p120: indicates e-cadherin complex is dysfunctional
E-cadherin
E-cadherin
The diagnosis of lobular neoplasia is morphological.

- E-cadherin is often negative (but not always) in invasive lobular carcinoma.

- Expression may be diminished, aberrant or heterogeneous.

- B-catenin (neg) and p120 (cytoplasmic) may be helpful in difficult cases.
E-cadherin immunohistochemistry in breast pathology: uses and pitfalls

Rita Canas-Marques & Stuart J Schnitt

Department of Pathology, Champalimaud Foundation, Lisboa, Portugal, and 1Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Table 2. Frequency of aberrant E-cadherin expression in invasive lobular carcinomas in series with at least 20 cases

<table>
<thead>
<tr>
<th>First author</th>
<th>No. (%) E-cadherin-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwaida 12b</td>
<td>0 of 20 (0%)</td>
</tr>
<tr>
<td>Sutonen 20</td>
<td>0 of 55 (0%)</td>
</tr>
<tr>
<td>Acs 21</td>
<td>1 of 42 (2.4%)</td>
</tr>
<tr>
<td>Goldstein 22</td>
<td>5 of 143 (3.5%)</td>
</tr>
<tr>
<td>Qureshi 23</td>
<td>5 of 44 (11.4%)</td>
</tr>
<tr>
<td>Da Silva 17</td>
<td>4 of 25 (16%)</td>
</tr>
<tr>
<td>Rakha 18</td>
<td>38 of 239 (15.9%)</td>
</tr>
<tr>
<td>Sarno 24</td>
<td>12 of 51 (23.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>65 of 619 (10.5%)</td>
</tr>
</tbody>
</table>
Variants of LCIS

Pleomorphic LCIS (PLCIS)
PLCIS
Definition

Similar to Rosen’s criteria for classic LCIS:

lobular units expanded by dyscohesive, pleomorphic cells with abundant eosinophilic cytoplasm, grade 3 nuclei, and prominent nucleoli (Chivukula et al 2008)
Recently recognized variant of Lobular Carcinoma In Situ (LCIS)

May calcify hence present through breast screening

Biology and natural history uncertain

Histologically: mimics high grade DCIS
Pleomorphic apocrine LCIS PAL-CIS

- Chen et al 2005 (suppl) described 10 cases
- Pleomorphic apocrine LCIS: LCIS with myxoid, apocrine and pleomorphic cytology
- CGH: Loss of 16Q, gain at 1Q
- DD apocrine DCIS with involvement of lobules
Immunohistochemistry of PLCIS

- **E-CADHERIN** NEGATIVE

- **OESTROGEN RECEPTOR** may be POSITIVE OR NEGATIVE

- **GCDFP-15** OFTEN POSITIVE—may be helpful in histological diagnosis

- **HER-2** may be POSITIVE

- **P120 catenin**: cytoplasmic staining in LCIS, membranous in ductal
E-cadherin
PLCIS within background of LCIS

PLCIS (ER neg) with conventional LCIS (ER pos)

Carder et al 2010
E-cadherin

HER2
Rare variant of LCIS

Classical LCIS with comedo necrosis

(Mass forming LCIS, Florid LCIS)
Sapino et al 2000 described 10 cases of LCIS with necrosis, 4 of which associated with invasive carcinoma.


Chin et al 2013 examined the genetic profile of 20 cases of “Florid LCIS”. Lesions showed loss of 16q (all cases) and 1q gain (80%).
UK multicentre series

- 28 cases
- Association with malignancy 53.6%
- Upgrade following core biopsy diagnosis: 35.7%
- Associated invasive: predominantly lobular

Shaaban et al., manuscript in preparation
Diagnostic challenges

Is the proliferation ductal or lobular?

( Low/intermediate grade DCS VS LCIS)
(High grade DCIS VS PLCIS)
Look for:

- Cellular cohesion
- Architectural pattern of DCIS
- E-cadherin IHC can help
Are the nuclei pleomorphic enough to designate as PLCIS?
- Compare size with normal ductal epithelial cell.

- IHC: ER, GCDFP-15, HER2 may help
DCIS,
e-cadherin
Pleomorphic lobular carcinoma in situ of the breast: a single institution experience with clinical follow-up and centralized pathology review

Marina De Brot¹ · Starr Koslow Mautner² · Shirin Muhsen² · Victor P. Andrade¹ · Anita Mantani² · Melissa Murray³ · Dilip Girli³ · Rita S. Sakr² · Edi Brogi³ · Tari A. King⁴,⁵

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New terminology from MSKCC

LCIS-PF: LCIS with pleomorphic features
In situ carcinoma with mixed ductal and lobular features

- E cadherin IHC may show heterogeneous staining (DD positive residual cells)

Clinical relevance
<table>
<thead>
<tr>
<th>Lesion</th>
<th>Relative risk</th>
<th>Upgrade risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEA</td>
<td>X2</td>
<td>13-21%, average 15% (in pure form); if co-existent with AIDEP then higher risk: pooled 29%</td>
</tr>
<tr>
<td>AIDEP</td>
<td>x4.4-5</td>
<td>37-53 %, pooled value 21%</td>
</tr>
<tr>
<td></td>
<td>x8 if FH</td>
<td>after VAB</td>
</tr>
<tr>
<td>ALH</td>
<td>x4-5</td>
<td>0-43%, pooled data 19%</td>
</tr>
<tr>
<td>LCIS</td>
<td>x8-10</td>
<td>0-60, pooled value 27%</td>
</tr>
</tbody>
</table>
B - Categorisation

- Epithelial hyperplasia, no atypia: B2
- FEA, AIDEP, Lobular neoplasia: B3
- DCIS/PLCIS: B5a
- LCIS with necrosis: best coded as B4
Lobular neoplasia on core biopsy

- ALH/Classical LCIS: code as B3 and recommend second line VAB

- PLCIS: code as B5a and manage as DCIS

- Classical LCIS with necrosis: rare, best coded as B4, recommend surgical excision.
PLCIS on excision

- Sample well to exclude invasion
- Assess lesion size, relation to margin
- If associated with invasion: include size in whole tumour size
- If at margin: re-excision
THANK YOU