Lesions of the Low Grade Breast Neoplasia Pathway

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**TABLE 3.1** Key Features of Usual Ductal Hyperplasia

<table>
<thead>
<tr>
<th>Cytologic features</th>
<th>Architectural features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneous cell population, Variation in cell size, shape, and orientation, Cell borders poorly defined, Variation in size, shape, and placement of nuclei, with areas of nuclear overlapping and internuclear cytoplasmic inclusions</td>
<td>Solid, fenestrated, or micropapillary, Lumens irregular, variable in size and shape, often slitlike and displaced to periphery without polarization of surrounding cells, Bridges stretched or twisted with central attenuation</td>
</tr>
</tbody>
</table>

* Normal Epithelium
* LCIS
* ADH
* LG-DCIS
* HG-DCIS
* UC
* LG-Invasive Cancer
* IG-Invasive Cancer
* HG-Invasive Cancer
* ILC
* ER+, HER2-, low proliferative rate
* +1q, -16q, -17p
* Apocrine Metaplasia

**No consistent genetic alterations**
Immunophenotype of UDH

• Mixed population of cells that express low and high molecular weight cytokeratins (the latter often in a heterogeneous or mosaic pattern)

UDH: "Triple Stain"
LMW-CK red, HMW-CK brown cytop, p63 brown nuclear

HMW-CK in UDH
**Immunophenotype of UDH**

- Mixed population of cells that express low and high molecular weight cytokeratins (the latter often in a heterogeneous or mosaic pattern)
- Heterogeneous expression of ER

**ER in UDH**

**UDH: Differential Diagnosis**

- ADH
- DCIS
  - Intermediate nuclear grade
  - Solid papillary carcinoma
Lesions of the Low Grade Breast Neoplasia Pathway Often Co-exist

- Flat epithelial atypia
- Atypical ductal hyperplasia
- Low grade ductal carcinoma in situ
- Lobular neoplasia (ALH/LCIS)
- Tubular carcinoma

Fraser, 1998
Rosen, 1999
Brogl, 2001
Collins, 2007
Abdel-Fatah, 2007
Proposed Evolutionary Pathway for LG Neoplasia

Abdel-Fatah et al, AJSP, 2007

Adapted from Ellis, Mod Pathol 2010

Low grade breast neoplasia family
Flat Epithelial Atypia

First Reported Recognition of Flat Epithelial Atypia
Azzopardi, 1979

- Subsequent to development of breast carcinoma in a woman with a prior biopsy misclassified as “fibrocystic changes”
- Re-review demonstrated a few dilated acini lined by atypical epithelial cells
- Involved spaces were lined by 2-4 layers of atypical cells
- Lesion had been overlooked on scanning magnification

First Reported Recognition of Flat Epithelial Atypia
Azzopardi, 1979

- Comparison with conventional DCIS demonstrated striking cytologic similarities
- Azzopardi introduced the term “clinging carcinoma” to describe this type of DCIS characterized by one to a few layers of atypical epithelial cells, lacking significant intraluminal proliferation
European Classification of DCIS
Holland, Semin Diag Pathol, 1994

• Recommended separation of clinging DCIS into:
  – a monomorphic variant with low grade atypia (FEA)
  – a pleomorphic variant with high grade atypia (clinging carcinoma)

Molecular Genetics of “Flat DIN”
Moinfar, Cancer, 2000

• First study of genetic alterations in “flat DIN” (aka FEA)
• LOH identified in 9/13 cases, and found to be the same as that seen in adjacent DCIS and IDC in 4/5 cases
• 16q alterations particularly common

Molecular Alterations

Promoter methylation of tumor suppressor genes seen in CCL (CCND2 and ID4)

Similar alterations identified in associated LG DCIS or invasive carcinoma

Direct transitions from FEA to LG DCIS seen on studies of mDNA

Abdel-Fatah et al, AJSP, 2007
Aulmann, AJSP, 2012
Verschuur-Maes, BCRT, 2012
Go, Human Pathol, 2012
Molecular Alterations in FEA

FEA is a clonal proliferation
Genetic changes relatively few in number
Recurrent loss of 16q reported

Abdel-Fatah et al, AJSP, 2007
Aulmann, AJSP, 2012
Verschoor-Maes, BCRT, 2012
Go, Human Pathol, 2012

Flat Epithelial Atypia

The "missing link" in breast cancer progression?*

*Simpson, Am J Surg Pathol, 2005

Flat Epithelial Atypia

WHO, 2003

• Variably distended acini of TDLUs
• Monotonous proliferation of cuboidal to columnar epithelial cells
• Apical snouts
• Secretions and microcalcifications in lumens
Flat Epithelial Atypia

- Low-grade cytologic atypia
- Nuclei usually round rather than elongated
- Loss of polarization
- Flat growth pattern

Features do not fulfill combined architectural and cytologic criteria for diagnosis of ADH or DCIS
Differential Diagnosis
Differential Diagnosis of FEA

Cytology:
- Microcysts
- Apocrine Metaplasia
- CCC/CCH
- HG DCIS

Architecture:
- ADH
- LG DCIS

Differential Diagnosis of FEA

Microcysts
Apocrine metaplasia

Columnar cell lesions without atypia

- Columnar cells
- Nuclei elongated
- Polarization maintained
- May stratify
Flat Epithelial Atypia
Columnar Cell Change
Columnar Cell Hyperplasia

Flat Epithelial Atypia
Columnar Cell Change
Columnar Cell Hyperplasia
Flat Epithelial Atypia

Columnar Cell Change

Irregular contours

Irregular contours

Irregular contours

Columnar Cell Hyperplasia

Smooth contours

Irregular contours

Clinging carcinoma may present as dilated spaces with single layer of atypical epithelial cells
**Columnar Cell Lesions**

**Practical Implications**

- Increasingly seen in an era of mammographic screening due to the identification of microcalcifications
- Important to separate CCC/CCH from FEA on CNB, as some FEA excised

**Columnar Cell Lesions**

**Biological Implications**

- Molecular evidence to suggest CCLs are a non-obligate precursor on the low grade breast neoplasia pathway
- Epidemiological evidence lacking—i.e. very low risk of progression to invasive carcinoma, and subsequent carcinomas are of all grades
- Should not be managed as a “high risk lesion”

**Atypical Ductal Hyperplasia**
Atypical Ductal Hyperplasia

- Defined in terms of its resemblance to low grade DCIS
- Diagnosis of ADH should not be made unless a diagnosis of low grade DCIS is being seriously considered
- If there is uncertainty as to whether to categorize a lesion as UDH or ADH, categorize it as UDH

TABLE 5.2 Key Features of Atypical Ductal Hyperplasia

<table>
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<tr>
<th>Cytologic features</th>
<th>Architectural features</th>
<th>Size/extent</th>
</tr>
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<tbody>
<tr>
<td>Atypical cell population similar to that of low-grade ductal carcinoma in situ (small, uniform cells with generally rounded nuclei that are evenly spaced and have well-defined borders)</td>
<td>In association with atypical cell population: rigid bridges and arcades of uniform thickness, micropapillations with bulbous tips, cribriform pattern with polarization of cells around lumens, solid pattern</td>
<td>Partial involvement of multiple spaces; complete involvement of less than two spaces or ≤2 mm in extent (see text)</td>
</tr>
</tbody>
</table>
Differential Diagnosis of ADH

• Usual ductal hyperplasia
  – Micropapillary pattern (gynecomastoid)
• Collagenous spherulosis
• LG DCIS
Extent Criteria to Distinguish ADH from Low Grade DCIS

- Lesions that possess ALL of the qualitative features of LG-DCIS but are limited in extent are given the diagnosis of ADH:
  - 1985, Page et al: <2 spaces (i.e., 1 space)
  - 1990, Tavassoli and Norris: ≤2mm
Conservative approach recommended, especially in CNB in which the differential diagnosis is between ADH and LG DCIS of limited extent

- Diagnosis of “atypical intraductal proliferative lesion” is sufficient to prompt surgical excision
- Definitive categorization based on evaluation of excision specimen
- If no further lesion, manage as ADH
ADH vs. Low Grade DCIS

- The distinction between ADH and limited examples of low grade DCIS is based primarily on the extent of the lesion
- While this distinction may be problematic in some cases, it is clinically important since ADH and DCIS are managed differently

Ductal Carcinoma in Situ

DCIS is classified according to nuclear grade

Low  Intermediate  High
DCIS can have many architectural patterns
Differential Diagnosis of LG DCIS

- ADH
- Collagenous spherulosis
- LCIS
E-cadherin Staining May Be of Help in Problematic Cases

DCIS: positive  LCIS: negative

Immunophenotype

Immunophenotype

Immunoperoxidase studies not helpful for separating low grade atypical ductal lesions from one another (inc. CCC)

• Express CK 19
• Lack expression of HMW-CK (CK 5/6)
• Strong expression of ER and PR
• Overall higher expression of proliferation and anti-apoptotic markers than normal TDLUs
Molecular Alterations
Genetic Alterations in DCIS

• Quantitative and qualitative differences in genetic alterations according to grade
• More numerous genetic abnormalities with higher grade than with lower grade lesions

Genetic Alterations in DCIS

• Associations between specific genetic changes and DCIS grade
  – Loss of 16q and 17p in low grade DCIS
  – Gains of 11q, 13q and 17q in high grade DCIS
  – Genetic changes in intermediate grade DCIS more heterogeneous

Expression Signatures in DCIS

• Low and high grade lesions exhibit reciprocal expression patterns
• Expression signatures characteristic of lesion grade but not stage of progression
  – e.g., low grade DCIS signature more like that of low grade invasive cancer than high grade DCIS

Ma, et al. PNAS 2003; 100:5974-5979
Clinical Significance

Evidence to support relationship of FEA to ADH, LG-DCIS, tubular carcinoma and lobular neoplasia
- Cytologic similarities
- Coexistence and geographic proximity
- Immunophenotypic similarities
- Molecular similarities

Brandt, Adv Anat Pathol, 2008

Relative Risk of Breast Cancer According to Category of Low Grade Proliferative Lesion

RR

CCL  AH  CIS

~1.5  3-5  8-10

4/5/2017
Management Issues

Core Needle Biopsy
- CCL
  - No further treatment for CCC/CCH
  - Evolving for FEA, but moving toward no excision if there is good rad/path correlation
- ALH and classical LCIS
  - Excision not required for incidental rad/path concordant lesions
- ADH and LG DCIS
  - Excision needed

Excision Specimens
- CCL
  - No further treatment
- ADH and lobular neoplasia
  - Observation
  - +/- Chemoprevention
- LG DCIS
  - Complete local eradication
  - Clear margins
  - +/- Radiation
  - Chemoprevention
Conclusions

• CCL, ADH and DCIS increasingly prevalent in an era of mammographic screening
• FEA may represent the earliest precursor to LG DCIS
• Precursor lesions of the LG neoplasia pathway often associated with one another...if you see one...look for others
• Risk of progression to invasive carcinoma varies by lesion, but low and protracted