Low-Grade Cytologic Atypia

- Monomorphic
- Round or oval nuclei
- Hyperchromatic, fine, even chromatin
- Smooth nuclear contours
- Inconspicuous nucleoli
- Increased cytoplasm
- Evenly spaced nuclei
Architectural Atypia

• Cribriform spaces
• Trabecular bars
• Roman arches
• Micropapillae
• Uniform solid growth

Defined by cellular polarization
Low-Grade Nuclear Atypia + Architectural Atypia = ductal carcinoma in-situ

Low-Grade Nuclear Atypia + LIMITED Architectural Atypia = atypical ductal hyperplasia
ADH = “Mini” DCIS

- Cytologic atypia REQUIRED
- Monomorphic low-grade
- Occ. intermediate grade
- What constitutes “mini”? 
  - Limited in size (usually ≤2mm)
  - Limited duct distension
  - NOT a proliferation with features b/w UDH and DCIS
  - Those are either UDH or DCIS
  - Lesions with unusual architecture but without cytologic atypia are usually variant UDH
Line between ADH and DCIS is arbitrary
DCIS: Minimum Quantitative Criteria
- Developed for use in excisions
- Arbitrary cutoffs
  - 2 duct profiles
  - >2 mm
- Limited 2-D assessment of 3-D structure
- “Guideposts”

DCIS: Qualitative Criteria
- Cytologic atypia
- Well-developed architectural atypia
- Robust proliferation within individual glands
- Notable duct distension/expansion compared to background

Severe ADH bordering on LG-DCIS or small focus of LG-DCIS?
High grade!

Distinguishing atypia from benign without atypia is also problematic

B-Path Study: Atypia
Concordant = 48%
Underinterpretation = 35%
Overinterpretation = 17%

Diagnostic
Concordance across 19 institutions:
Benign
Atypia
Malignant

0.1 cm
HMWCK and ER do not distinguish ADH from DCIS

<table>
<thead>
<tr>
<th>HMWCK</th>
<th>ER</th>
<th>CK5/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Heterogeneous</td>
<td>UDH</td>
</tr>
<tr>
<td>Negative</td>
<td>Diffuse positive</td>
<td>ADH</td>
</tr>
<tr>
<td>Negative</td>
<td>Diffuse positive</td>
<td>DCIS</td>
</tr>
</tbody>
</table>

ADH stains like DCIS
Clinical Management: Core Biopsy

- **ADH as most significant lesion on CORE BIOPSY**
  - <10% of core biopsies
  - Examine levels to exclude DCIS or invasive cancer

- **Follow-up excision recommended**
  - R/O cancer missed due to sampling error
  - DCIS or invasive cancer found on excision in 15% to 31%

  **Upgrade rate increases with:**
  - 1 number of foci
  - Size of foci
  - Suspicion for DCIS (severe ADH bordering on DCIS)
  - Indication for biopsy = mass
  - High-risk patient factors

Risk for Subsequent Breast Cancer

- Atypical hyperplasia (ADH or ALH) has a relative risk of ~4X for subsequent breast cancer (consistent finding of multiple studies)

    - Mayo Clinic cohort (1967-2001)
    - N = 698
    - Standardized Incidence Ratio:
      - ADH: 3.93
      - ALH: 4.76
      - Increased risk
      - Younger women with atypia
      - 1 number of foci of atypia
      - Less lobular involution
Chemoprevention Significantly ↓ CA Risk

MGH / BWH / NWH Experience

<table>
<thead>
<tr>
<th>CPx</th>
<th>5-yr risk</th>
<th>10-yr risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CPx</td>
<td>8.3%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Yes CPx</td>
<td>4.1%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

CHEMOPREVENTION TRIALS
- Subgroup analysis of patients with atypical hyperplasia
  - 4 trials: NSABP P-1, MAP.3, IBIS-I, and IBIS-II
  - 2009 women randomly assigned to placebo or active agent (tamoxifen or exemestane)
  - Relative risk reductions in atypical hyperplasia subgroup ranged from 41% to 79%

Clinical Management: Excision

- **SURGICAL**
  - Re-excision not necessary for ADH at margins
  - No need to report distance of ADH to margins
  - **Exception**: Severe ADH present at or <0.1 cm from margin → may consider re-excision to exclude DCIS in adjacent tissue
- **SCREENING**
  - Annual mammography & clinical follow-up
  - Insufficient evidence for or against MRI screening
- **MEDICAL**
  - Patients at increased risk for subsequent breast cancer
    - 4X RR (~1% per year develop breast cancer
    - Long term risk
  - Chemoprevention reduces risk of subsequent breast cancer
    - Overall rates of chemoprevention use very low (<5%)

Low-Grade Nuclear Atypia
+ NO Architectural Atypia = FLAT EPITHELIAL ATYPIA
**Flat Epithelial Atypia**

**WHO Definition**
A neoplastic alteration of the terminal duct lobular units characterized by replacement of the native epithelial cells by one to several layers of a single epithelial cell type showing low-grade (monomorphic) cytologic atypia.

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**Columnar Cell Change/Hyperplasia**

- Columnar cell change
- Columnar cell change with atypia
- Columnar cell hyperplasia
- Columnar cell hyperplasia with atypia

---

**Flat Epithelial Atypia**

[Diagram showing the relationship between Flat Epithelial Atypia and Columnar Cell Change/Hyperplasia]
Flat Epithelial Atypia: Main Histologic Features

1. Enlarged and dilated TDLUs
2. Low-grade cytologic atypia of ductal cells
3. Flat layer of ductal cells lining glands
4. Myoepithelial cells often attenuated

Flat Epithelial Atypia
A step in the development of low-grade ductal carcinoma

FEA is often present in the background of low- and intermediate-grade DCIS

<table>
<thead>
<tr>
<th>DCIS</th>
<th>FEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low *</td>
<td>34-36%</td>
</tr>
<tr>
<td>Intermed</td>
<td>23%</td>
</tr>
<tr>
<td>High</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

* Especially micropapillary and cribriform DCIS
FEA is frequently associated with lobular neoplasia (ALH/LCIS)

<table>
<thead>
<tr>
<th>Index Diagnosis</th>
<th>Associated With:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALH/LCIS</td>
<td>FEA in 60-85%</td>
</tr>
<tr>
<td>FEA</td>
<td>ALH/LCIS in 25-30%</td>
</tr>
</tbody>
</table>

"The Rosen Triad"
Flat Epithelial Atypia: Differential Diagnosis

- Fibrocystic changes
- Blunt duct adenosis
- Early usual ductal hyperplasia
- Atypical ductal hyperplasia
- Ductal carcinoma in situ
Blunt Duct Adenosis

- Ductular and branching shapes
- Expanded intralobular stroma
- Prominent myoepithelial cells
- Columnar luminal cells have cytologic characteristics of usual hyperplasia
It's more likely NOT FEA if there is either:

- Proliferative Stroma
- Prominent MEC Layer

HMWCK/ER immunoprofiles of FEA and non-atypical columnar cells show overlap.

Therefore, it’s not possible to definitively differentiate between the two categories.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Low-Grade Cytologic Atypia</th>
<th>Architectural Atypia</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>✓</td>
<td>Well Developed</td>
</tr>
<tr>
<td>ADH</td>
<td>✓</td>
<td>Limited</td>
</tr>
<tr>
<td>FEA</td>
<td>✓</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**Diagnosis:**
- Low-Grade Cytologic Atypia
- Architectural Atypia

**Notes:**
- DCIS: Well Developed
- ADH: Limited
- FEA: Absent

**Images:**
- DCIS
- ADH
- FEA
Summary of data from published studies 2006-2016

<table>
<thead>
<tr>
<th>N*</th>
<th>Excision Rate</th>
<th>DCIS</th>
<th>Inv CA</th>
<th>Upgrade Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1886</td>
<td>61%</td>
<td>5%</td>
<td>3%</td>
<td>8%</td>
</tr>
</tbody>
</table>

- **ADH** or **ALH/LCIS**: 19% 12% 28%
- Not DCIS data not provided for all studies

*Summary of data from published studies 2006-2016*
Clinical Management: Core Biopsy

- FEA as most significant lesion on CORE BIOPSY
- Questions to ask yourself:
  - Levels examined?
    - Look for any associated ADH, LN, DCIS, invasive CA
  - Clinical and radiographic findings explained?
    - Ca^2+ ≥200 µ to be reliably detected on mammogram
    - FEA does not explain a mass lesion
- No consensus on next step:
  - Follow-up excision to exclude DCIS or invasive carcinoma is recommended by some (8% overall upgrade rate)
  - Careful radiological-pathological correlation: If all calcifications have been removed, clinical follow-up is suggested by others.

Clinical Management: Excision

- FEA as most significant lesion on SURGICAL EXCISION
- Questions to ask yourself:
  - Any associated ADH, LN, DCIS, invasive CA?
  - Clinical and radiographic findings explained?
    - Ca^2+ ≥200 µ to be reliably detected on mammogram
  - FEA does not explain a mass lesion
  - Re-excision not necessary for FEA at margins
  - FEA appears to have a limited risk for progression to CA
  - Risk for subsequent CA in Mayo 2015 study (n=282)
    - AH +/- FEA: Similar risk (4.74 vs 4.31)
    - PDWA +/- FEA: Similar risk (2.04 vs 1.90)
  - No additional therapy
  - No data regarding chemoprevention for risk reduction

thank you