Benign Breast Changes and Clinical Significance

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Harvard Medical School
Boston, MA
BENIGN BREAST BIOPSYIES

• Since 1984, four large studies have been published utilizing standardized criteria and pathologists addressing the issue of benign breast changes and the subsequent risk of breast cancer.
Nashville
Dupont and Page
Nurses Health Study (NHS)
London, Connolly, Schnitt and Colditz
Breast Cancer Detection Demonstration Project (BCDDP)
Dupont, Parl, W. Hartmann, et al.
Mayo Clinic
L. Hartmann, D. Visscher, et al.
• **Case** – A woman with a benign biopsy who subsequently develops carcinoma
Studies of BBD and Breast Cancer Risk Using Criteria of Page, et al

<table>
<thead>
<tr>
<th>Design</th>
<th>Nashville</th>
<th>BCDDDP</th>
<th>MAYO C.</th>
<th>NHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Cohort</td>
<td>Case-Control</td>
<td>Cohort</td>
<td>Case-Control</td>
</tr>
<tr>
<td>Cases</td>
<td>134</td>
<td>95</td>
<td>707</td>
<td>395</td>
</tr>
<tr>
<td>Controls</td>
<td>-</td>
<td>190</td>
<td>-</td>
<td>1610</td>
</tr>
<tr>
<td>Total Pop.</td>
<td>3303</td>
<td>&gt;280,000</td>
<td>9087</td>
<td>&gt;240,000</td>
</tr>
</tbody>
</table>
CATEGORIZATION OF BENIGN BREAST LESIONS

- NON-PROLIFERATIVE
- PROLIFERATIVE WITHOUT ATYPIA
- ATYPICAL HYPERPLASIA
Non-proliferative Lesions
(No increased risk)

- Cysts
- Apocrine metaplasia
- Mild hyperplasia
Proliferative Lesions without Atypia (Slightly increased risk, 1.5-2x)

- Moderate or florid ductal hyperplasia
- Sclerosing adenosis
- Fibroadenoma
Assessment of Ductal Proliferative Lesions: Based on Cytology and Architecture

- Usual ductal hyperplasia (UDH)
- Atypical ductal hyperplasia (ADH)
- Ductal carcinoma in situ (DCIS)
Usual Ductal Hyperplasia
WHO, 2003

• Architectural features
  - Irregular fenestrations
  - Peripheral fenestrations
  - Stretched or twisted epithelial bridges
  - Uneven distribution and overlapping of nuclei

• Cellular features
  - Multiple cell types
  - Variation in appearance of epithelial cells
  - Indistinct cell margins and deviation from round contour
  - Variation in appearance of nuclei

• (HMW-CK positive)
Atypical Ductal Hyperplasia

• Architectural features:
  – Some features of usual ductal hyperplasia and some features of low grade DCIS

• Cytologic 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

• HMW-CK reduced or absent
• (Size/extent)
Low Grade DCIS

• Architectural features:
  – Spaces round, regular, “punched out”
  – Rigid bars
  – Club-shaped micropapillae

• Cytologic features:
  – Nuclei uniform, evenly spaced
Classification of Ductal Lesions of the Breast (hyperplasia, ADH, and DCIS)


This program put together by Dr Susan Lester Brigham and Womens Hospital
Written criteria:

1. **Florid hyperplasia without atypia** has swirling of cells, variable nuclear shape and placement, and irregular intercellular spaces that are most marked centrally.

2. **DCIS (noncomedo type)** has a population of evenly spaced, uniform cells with uniform nuclear features, comprising without doubt the entire population of cells throughout two membrane-bound spaces.

3. ADH has the presence of the cell population defined above for noncomedo DCIS present in part of the space. Usually the second cell population consists of polarized cells as seen in the breast in the luminal position immediately above the basement membrane.
4. When in doubt between ADH and DCIS, use the more benign diagnosis.

5. To qualify as ADH (as opposed to florid H without atypia), the bothersome cell population usually, but not always, has hyperchromatic nuclei.

6. To qualify as ADH (as opposed to florid H without atypia), the bothersome cells need to constitute an entire bar crossing a space or at least a cell population of six or seven cells across so as to avoid calling ADH when there is a population of cells less than the numbers indicated. This is an indication of the lower level of definition for ADH.
Diagram

DCIS features smooth, punched-out luminal borders within involved, basement membrane-bound spaces. The cytologic features are regular and present throughout the entire population of at least two basement-membrane bound spaces. Florid hyperplasia without atypia (FHWA) is the most densely cellular and extensive of the proliferative disease without atypia lesions, also called "papillomatosis". There are ragged, often slit-like luminal borders. The nuclei throughout the involved area show the variability and tendency to a swirling pattern, as illustrated. ADH has features predominantly of noncomedo, cribriform DCIS, but also some features of proliferative disease without atypia or normally polarized cells within the same basement-membrane bound space.
Teaching Set - Case 1: Hyperplasia
Teaching Set - Case 2: Hyperplasia
Teaching Set - Case 3: Hyperplasia
Teaching Set - Case 4: Hyperplasia
Teaching Set - Case 5: Hyperplasia
Teaching Set - Case 6: DCIS
Teaching Set - Case 7: DCIS
Teaching Set - Case 8: DCIS
Teaching Set - Case 9: DCIS
Teaching Set - Case 10: DCIS
Teaching Set - Case 11: ADH
Teaching Set - Case 13: ADH
Teaching Set - Case 15: ADH
Atypical Hyperplasia
(Moderately increased risk, 4-5x)

- Atypical ductal hyperplasia (ADH)
- Atypical lobular hyperplasia (ALH)
ALH vs LCIS

• Criteria for distinction differ among “experts”
• Page: Expansion and or distortion of $\geq 50\%$ of acini in lobule=LCIS
• Probably not important to differentiate
• Very important to recognize ALH or LCIS
Lobular Carcinoma in situ
ALH

LCIS
Relative Risk of Breast Cancer Related to the Type of Benign Breast Disease

<table>
<thead>
<tr>
<th>Type of Benign Breast Disease</th>
<th>Nashville</th>
<th>NHS</th>
<th>BCDDP</th>
<th>Mayo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Prolif</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolif</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atyp-Hyperplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Magnitude and Laterality of Breast Cancer Risk in Women with Atypical Hyperplasia of Ductal and Lobular Types: NHS Data
# Breast Cancer Risk According to Category of Benign Breast Disease

<table>
<thead>
<tr>
<th>BBD Category</th>
<th># Cases</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-proliferative</td>
<td>77</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Proliferative without atypia</td>
<td>164</td>
<td>1.6 (1.2-2.2)</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>75</td>
<td>4.0 (2.8-5.9)</td>
</tr>
</tbody>
</table>
Breast Cancer Risk Related to Histologic Type of AH

<table>
<thead>
<tr>
<th>BBD Category</th>
<th># Cases</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>75</td>
<td>4.0 (2.8-5.9)</td>
</tr>
<tr>
<td>ADH</td>
<td>33</td>
<td>2.8 (1.8-4.6)</td>
</tr>
<tr>
<td>ALH</td>
<td>28</td>
<td>5.5 (3.1-9.5)</td>
</tr>
</tbody>
</table>

p for heterogeneity (ADH vs. ALH) = 0.08
Breast Cancer Risk Related to Histologic Type of AH

<table>
<thead>
<tr>
<th>BBD Category</th>
<th># Cases</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>75</td>
<td>4.0 (2.8-5.9)</td>
</tr>
<tr>
<td>ADH</td>
<td>33</td>
<td>2.8 (1.8-4.6)</td>
</tr>
<tr>
<td>ALH</td>
<td>28</td>
<td>5.5 (3.1-9.5)</td>
</tr>
<tr>
<td>ADH + ALH</td>
<td>14</td>
<td>8.3 (3.8-18.5)</td>
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</table>
Menopausal Status at Time of Benign Breast Biopsy and Breast Cancer Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>3.9 (2.5-6.1)</td>
<td>3.8 (1.7-8.5)</td>
</tr>
<tr>
<td>ADH</td>
<td>2.7 (1.6-4.7)</td>
<td>4.0 (1.7-9.8)</td>
</tr>
<tr>
<td>ALH</td>
<td>7.3 (3.7-14.2)</td>
<td>3.4 (1.1-10.8)</td>
</tr>
</tbody>
</table>

p=0.02

p=0.82
## Menopausal Status at Time of Breast Cancer Diagnosis and Breast Cancer Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>3.6 (1.8-7.0)</td>
<td>3.5 (2.1-5.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>ADH</td>
<td>2.0 (0.9-4.8)</td>
<td>3.1 (1.8-5.5)</td>
<td></td>
</tr>
<tr>
<td>ALH</td>
<td>8.5 (3.1-23.4)</td>
<td>4.2 (2.1-8.4)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

p=0.03 and p=0.50 indicate the statistical significance of the differences between pre-menopausal and post-menopausal groups.
## Time to Development of Breast Cancer and Breast Cancer Risk

<table>
<thead>
<tr>
<th></th>
<th>&lt;10 yrs after benign bx</th>
<th>≥10 yrs after benign bx</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>3.3 (2.1-5.3)</td>
<td>5.1 (2.8-9.4)</td>
</tr>
<tr>
<td>ADH</td>
<td>2.4 (1.4-4.2)</td>
<td>4.8 (2.4-9.8)</td>
</tr>
<tr>
<td>ALH</td>
<td>5.6 (2.9-10.7)</td>
<td>5.8 (2.4-14.2)</td>
</tr>
</tbody>
</table>

\[ p=0.06 \quad p=0.75 \]
Laterality of Breast Cancers

<table>
<thead>
<tr>
<th></th>
<th>% Ipsilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>58.9%</td>
</tr>
<tr>
<td>ADH</td>
<td>56.0%</td>
</tr>
<tr>
<td>ALH</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

ADH vs ALH, p=0.64
Laterality of Breast Cancers According to Time Since Benign Biopsy

% Ipsilateral

<table>
<thead>
<tr>
<th>Years post-biopsy</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>15</td>
</tr>
<tr>
<td>5 to 9</td>
<td>19</td>
</tr>
<tr>
<td>10 to 15</td>
<td>10</td>
</tr>
<tr>
<td>15+</td>
<td>12</td>
</tr>
</tbody>
</table>

p=0.99
Conclusions

• Women with AH in a benign breast biopsy are at increased risk for the development of breast cancer

• However, level of risk differs for ALH and ADH, especially when menopausal status and time to development of breast cancer are considered
Conclusions

• Among pre-menopausal women, breast cancer risk associated with ALH significantly higher than risk associated with ADH (~7x vs 3x)

• ALH is more strongly associated with development of pre-menopausal breast cancer than is ADH (~8x vs 2x)
Conclusions

• The risk of breast cancer within 10 years of the benign breast biopsy is greater for women with ALH than for those with ADH (~6x vs 3x)

• Only about 60% of the subsequent breast cancers in women with AH occur in the ipsilateral breast – frequency of ipsilateral cancers similar for ADH and ALH
Implications

• Our results suggest that combining ADH and ALH into a single “AH” group, as is commonly done in clinical and epidemiologic studies, may obscure potentially important clinical and biological differences between these two lesions.
Implications

• Given that only about 60% of the cancers that develop in women with AH occur in the ipsilateral breast, for the purposes of risk assessment and clinical management, ADH and ALH are best viewed as markers of a generalized (bilateral) increase in breast cancer risk.
Is there a Difference in Risk Between Minimal and Established ALH?

- Minimal: lack of cohesion with little or no proliferation
- Established: easily recognized ALH with proliferation and expansion of up to half a lobular unit
Breast Cancer Risk Related to the Degree of ALH

<table>
<thead>
<tr>
<th>BBD Category</th>
<th># Cases</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>75</td>
<td>4.0 (2.8-5.9)</td>
</tr>
<tr>
<td>Minimal ALH</td>
<td>23</td>
<td>5.03 (2.73-9.28)</td>
</tr>
<tr>
<td>Established ALH</td>
<td>13</td>
<td>6.51 (2.85-14.87)</td>
</tr>
</tbody>
</table>

p for heterogeneity (Minimal vs. Established ALH) = 0.62
Breast Cancer Risk Related to the Degree of ALH

• There is no difference in risk related to the degree of ALH
• Lesions easily overlooked have significant clinical implications
Lobular Type / Involution

- Lobules vary in size and change with menstrual and pregnancy status
- Both the Nurses Health Study and the Mayo Clinic series have seen a decreased risk associated with having only small/involuted lobules across all proliferative categories
Other Factors that May Modify Risk

- Family history
- Post-menopausal hormone use
- Other benign lesions
Influence of Family History on Relative Risk of Breast Cancer in Women With Proliferative Breast Disease
Influence of family History on Relative Risk of Breast Cancer in Women Atypical Hyperplasia
Post Menopausal Hormone Use and RR of Breast Cancer
Radial Scar
### Radial Scars and Breast Cancer Risk

<table>
<thead>
<tr>
<th>Category of BBD</th>
<th>Radial</th>
<th>Scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>absent</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>3.8</td>
<td>5.8</td>
</tr>
</tbody>
</table>

**Note:** BBD stands for Breast Disease.
Radial Scars and Breast Cancer Risk

The topic remains controversial

- Increased risk has been found in a study from London (J Sloane) and the NHS (T Jacobs)
- No increased risk was found in a study from Nashville (M Sanders) or the Mayo Clinic (J Berg)
What is the significance of finding atypia in a papilloma?
Papilloma-Subsequent Breast Carcinoma (Nashville)

- 16 women had papillomas with ADH
- 368 women with papillomas within the Nashville study
- Outcome compared to matched women from the Third National Cancer Survey in Atlanta

Page DL. Cancer 1996; 78:258
# Papilloma-Subsequent Breast Carcinoma (Nashville)

<table>
<thead>
<tr>
<th>Lesion</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma - no atypia</td>
<td>0.78</td>
</tr>
<tr>
<td>Atypical hyperplasia in a papilloma</td>
<td>9.8</td>
</tr>
<tr>
<td>Atypical hyperplasia in papilloma + adjacent tissue</td>
<td>15.8</td>
</tr>
</tbody>
</table>

Page DL. Cancer 1996; 78:258
What was the histologic appearance of the atypia in that study?
Papilloma-Subsequent Breast Carcinoma (Nashville)

• All but one of the subsequent cancers ipsilateral

Page DL. Cancer 1996; 78:258
Papillomas

• Since papillomas are within ducts the epithelial atypia in the papilloma may also be present in adjacent ducts
• Therefore if there is something in a papilloma that otherwise would be DCIS, diagnose it as such
• If there is severe ductal atypia in a papilloma, excise adjacent tissue to rule out DCIS
Papillomas

• In the NHS and the Mayo Clinic series single papillomas (SP) carried the same risk as PDWA
• Atypia associated with a SP carried the same risk as that of atypia alone
• In the Mayo Clinic study multiple papillomas especially those with atypia increased the RR
• 3 to 7 fold
Relative Risk vs Absolute Risk

Relative Risk

# cancers / # in subpopulation

# cancers / # in reference pop.

Absolute Risk

# or % cancers in # years
### Relative Risk vs Absolute Risk

**Dupont and Page**

<table>
<thead>
<tr>
<th>Category</th>
<th>RR</th>
<th>AR (15 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWA</td>
<td>1.9</td>
<td>4%</td>
</tr>
<tr>
<td>AH</td>
<td>5.3</td>
<td>8%</td>
</tr>
<tr>
<td>AH + FH</td>
<td>8.9</td>
<td>20%</td>
</tr>
</tbody>
</table>
# Frequency of Atypical Hyperplasia

<table>
<thead>
<tr>
<th>Indication for Biopsy</th>
<th>% AH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable mass</td>
<td>2 – 4%</td>
</tr>
<tr>
<td>Mammographic abnormality</td>
<td>10 – 15%</td>
</tr>
</tbody>
</table>
Risk of Subsequent Cancer

- Non-proliferative lesions
  - no increased risk
- Proliferative lesions without atypia
  - slightly increased risk (1.5-2x)
- Atypical hyperplasia
  - Moderately increased risk (4-5x)
Epithelial Atypia in serially sectioned biopsies for calcifications

- 2833 biopsies no palpable lesions
- 971 cases of ductal or lobular atypia
- A concomitant small (5mm max) low grade invasive carcinoma was present in 31% (301)
- The remaining patients followed a mean of 13.3 y
- At 5 & 10 y the risk of developing cancer was 2.8 and 5.5% (93% ipsilateral)

Are There Cellular Markers for Atypical Hyperplasias?

- A lack of e-cadherin staining marks lobular lesions
Are There Cellular Markers Ductal Lesions?

- Ductal lesions may differentially mark with different cytokeratins
- The following slides courtesy of Dr Bocker Professor of Pathology at Muenster
Abs to Ck 5/14 can be used as diagnostic tool to differentiate between UDH and DCIS (rare exceptions!)

Nagle et al, 1986
Böcker et al, 1992a, b
Otterbach et al, 2000
Cytokeratins

- May be able to distinguish between UDH and most cases of DCIS (usually not the problem)
- Cannot distinguish between ADH and DCIS
- Currently an interesting research tool
- We are not using it for diagnosis at this time
## Side of Biopsy vs Side of Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>% Ipsilateral</th>
<th>% Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade DCIS</td>
<td>~100</td>
<td>~0</td>
</tr>
<tr>
<td>Size criteria (AIDH)</td>
<td>~75%</td>
<td>~25%</td>
</tr>
<tr>
<td>(Tavassoli &amp; Norris)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH</td>
<td>~50%</td>
<td>~50%</td>
</tr>
<tr>
<td>(NHS, Dupont &amp; Page)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ADH: Size Criteria

• The use of size criteria (eg. 2-5mm) identifies small well differentiated DCIS as well as ADH
• I do not recommend the use of size to differentiate ADH from DCIS
• The data do not support a biologic justification of the proposed DIN classification
Atypical Hyperplasia

- Marker of increased risk of subsequent invasive breast cancer
- Treatment: observation, bilateral mastectomy, ? tamoxifen
**NSABP Breast Cancer Prevention Trial (P-1)**
13,388 women; med FU 54.6 mos

<table>
<thead>
<tr>
<th></th>
<th># Breast</th>
<th>Cancer</th>
<th>% red’n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>175</td>
<td>89</td>
<td>49%</td>
</tr>
<tr>
<td>ER+</td>
<td>130</td>
<td>41</td>
<td>69%</td>
</tr>
<tr>
<td>LCIS</td>
<td>18</td>
<td>8</td>
<td>56%</td>
</tr>
<tr>
<td>AH</td>
<td>23</td>
<td>3</td>
<td>86%</td>
</tr>
</tbody>
</table>
• The ability of pathologists to reproducibly classify a small subset of proliferative breast lesions is a matter of legitimate concern.
## Interobserver Agreement In Proliferative Breast Lesions

<table>
<thead>
<tr>
<th>Standardized Criteria?</th>
<th>Complete Agreement</th>
<th>All But 1 Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Yes</td>
<td>58%</td>
<td>71%</td>
</tr>
</tbody>
</table>
• The use of standardized histologic criteria is an important step toward reducing interobserver variability in the diagnosis of proliferative breast lesions to an acceptable level.
Inter-observer Variability

- Is a real problem for a very small percentage of cases
- In a study from Beth Israel Deaconess Medical Center, less than 2% of breast biopsies were in the borderline category
In clinical practice, it is sometimes difficult to rigidly separate a highly atypical ductal hyperplasia from low grade DCIS.
• If a lesion such as this is present near a margin, I occasionally diagnose “Highly atypical intraductal proliferation; Excision Recommended”
• In a small series of such patients, re-excisions revealed diagnostic DCIS in 16%
• The two space rule or size criteria should not be applied to core needle biopsy specimens.
• Ductal atypia on CNB should generally be followed by excision.
• Until or unless a more clinically relevant classification system arises, I recommend that the criteria of Page *et al* be utilized.
What is the Relationship Between The Features of Prior BBD and Subsequent DCIS or Invasive Carcinoma

• Low Grade Invasive cancer is associated with Low Grade DCIS and LCIS
• The question is whether Atypical Hyperplasias which resemble Low Grade DCIS or LCIS would be associated With Low Grade DCIS, Low Grade Invasive Cancers or Cancers of Special Types
• In the NHS there was no difference between DCIS or invasive tumors in women with any of the types of prior benign biopsies

• In particular, the frequency of low-grade cancers did not differ among patients with non-proliferative lesions, proliferative lesions without atypia or the atypical hyperplasias

• Therefore it seems that these atypical proliferations are for the most part not behaving as direct precursors
Columnar Cell Lesions and Flat Epithelial Atypia
Classification

Lesions are categorized into one of two groups, either:

– “Not atypical” (this category includes lesions fulfilling the criteria for either columnar cell change or columnar cell hyperplasia, as described subsequently)

OR

– “Flat epithelial atypia”

Lesions with features equivocal for flat epithelial atypia should be categorized as “Not Atypical”
Columnar Cell Change

Histologic Features

- TDLUs with variably dilated acini
- Acini lined by one to two cell layers
- Lining cells columnar in shape, with uniform ovoid to elongated nuclei oriented perpendicular to basement membrane; nucleoli absent or insconspicuous
- Apical snouts may be present; usually not prominent or exaggerated
- Luminal secretions may be present; usually not prominent
- Calcifications may be present
Columnar Cell Change-Not Atypical
Columnar Cell Change-Not Atypical
Columnar Cell Change-Not Atypical
Columnar Cell Change-Not Atypical
Columnar Cell Hyperplasia

Histologic Features

• TDLUs with variably dilated acini
• Acini lined by cells that show stratification (more than 2 cell layers); may form tufts, but complex architectural patterns (rigid bars, bridges, well-formed micropapillations) are absent
• Lining cells columnar in shape with uniform ovoid to elongated nuclei oriented perpendicular to basement membrane; nuclei may appear crowded and overlap; nucleoli absent or inconspicuous; cells similar to those seen in columnar cell change
• Apical snouts often present; may be exaggerated
• Luminal secretions may be present and prominent
• Calcifications often present; may be psamommatous
Columnar Cell Hyperplasia-Not Atypical
Columnar Cell Hyperplasia-Not Atypical
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Columnar Cell Hyperplasia-Not Atypical
Columnar Cell Hyperplasia-Not Atypical
Columnar Cell Hyperplasia-Not Atypical
Flat Epithelial Atypia

- Variably distended TDLUs
- Native epithelial cells replaced by one to several layers of a monotonous, atypical cuboidal to columnar cell population with apical snouts and occasional cellular tufts and mounds
- Many spaces contain secretory or floccular material that often contains microcalcifications

IARC Press, 2003
Histologic Hallmarks of Flat Epithelial Atypia

- TDLUs usually bluer than normal at low power
- Acini lined by cells with low-grade (monomorphic type) cytologic atypia; cells most often resemble those seen in low grade DCIS
- Nuclei typically round, but may be ovoid in some cases; nucleoli may or may not be prominent
Histologic Hallmarks of Flat Epithelial Atypia

• Cells typically lack polarity and are not regularly oriented perpendicular to basement membrane; however, in some cases, stratified, atypical, ovoid nuclei are arranged perpendicular to basement membrane (resembling pattern seen in colonic adenomas)

• Flat growth pattern (no complex architectural patterns)

• Features do not fulfill combined architectural and cytologic criteria for diagnosis of ADH or DCIS
Flat Epithelial Atypia
Flat Epithelial Atypia
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Flat Epithelial Atypia
Flat Epithelial Atypia
• Flat Epithelial Atypia is often present in association with tubular carcinoma, as illustrated on the next 2 slides.
Flat Epithelial Atypia and Tubular Carcinoma
## FEA vs. Apocrine

<table>
<thead>
<tr>
<th></th>
<th>FEA</th>
<th>Apocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical snouts</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Granular eosinophilic cytoplasm</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Hobnail cells</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Psammomatous calc`s</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>ER expression</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Bcl-2 expression</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
Genetic Alterations

• FEA is a clonal proliferation
• Genetic changes few in number
• Loss of 16q reported
• Loss of 16q is seen in association with lobular neoplasia, low grade DCIS and low grade invasive cancers
Lesions often seen with FEA

- ADH
- Low grade DCIS
- Lobular neoplasia (ALH/LCIS)
- Tubular carcinoma
“Rosen Triad”
Brandt et al., Adv Anat Pathol, 2008

- 86 cases of tubular carcinoma
- 100% of cases associated with CCLs
- 53% of cases associated with LCIS
- “Rosen Triad”
  - Tubular carcinoma
  - LCIS
  - Columnar cell lesions
Clinical Follow-up Studies
<table>
<thead>
<tr>
<th># Pts</th>
<th>Study</th>
<th>RX</th>
<th>FU</th>
<th>LR</th>
<th>INV</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Retro review of “benign”</td>
<td>Biopsy only, no excision</td>
<td>19.2 yrs (mean)</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>59</td>
<td>Randomized trial of DCIS</td>
<td>Excision with or without RT</td>
<td>5.4 yrs (med)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>115</td>
<td>Retro review of LG “Clinging ca”</td>
<td>Excision with (45) or without RT(70)</td>
<td>13.3 (med)</td>
<td>3 (2.6%)</td>
<td>3 (2.6%)</td>
</tr>
</tbody>
</table>
Long Term Cancer Risk
Boulos, Mod Pathol., 2008:98;24A

• 817 CCLs evaluated
• RR of 1.72 at ten years (Slight increase)
• No difference between categories of CCL
• 2-3 fold increase in AH in presence of CCLs
Comparative Cytologic Features

Columnar Cell Change

Flat Epithelial Atypia

Columnar Cell Hyperplasia
Algorithmic Approach to Columnar Cell Lesions and Flat Epithelial Atypia
Columnar Cell Lesion

Cellular stratification

No  Yes

Cytologic atypia*

No  Yes

Simple  Complex

Columnar Cell Change
Flat Epithelial Atypia

Atypical Ductal Hyperplasia or DCIS

One to several layers of atypical cuboidal cells

*most often resembling that seen in low grade DCIS
Management
Columnar Cell Change/Hyperplasia

- Found on excision
  - No further treatment
- Found on CNB
  - No excision necessary
- No additional levels
Flat Epithelial Atypia

- FEA on CNB
  - Management controversial
  - More significant lesion found in ~ 25% of cases in some studies
  - In my experience it is unusual to find a more significant lesion on excision

If all of the calcifications removed from the biopsied area one could argue for follow up
Flat Epithelial Atypia

FEA on excisional biopsy

In order to exclude areas diagnostic of ADH, LG DCIS, LN or tubular carcinoma

• Submit all parenchymal tissue
• Evaluate multiple levels
Flat Epithelial Atypia

**FEA in association with “Worse” lesions**

- Manage as the “Worse” lesions
- Unanswered questions
- What about a case of LG DCIS with FEA?
- Do you include FEA in the size of the lesion?
- Do you include FEA in the margin evaluation?
Questions