Columnar Cell Lesions and Flat Epithelial Atypia
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Question 1?
Columnar cell lesions are:

a) Annoying lesions of no clinical relevance
b) Important to recognize because of the high risk of progression to breast cancer
c) Important to recognize because of their association with other clinically important precursor lesions

Question 2
The lesion shown on the next two slides is best categorized as which of the following?

a) Columnar cell change
b) Columnar cell hyperplasia
c) Usual ductal hyperplasia
d) Atypical ductal hyperplasia
e) Flat epithelial atypia
Question 3
The lesion shown on the next slide is best categorized as which of the following?

a) Columnar cell change  
b) Ductal carcinoma in situ  
c) Usual ductal hyperplasia  
d) Atypical ductal hyperplasia  
e) Flat epithelial atypia

Question 4
Which of the following lesions is often seen in association with flat epithelial atypia?

a) Atypical ductal hyperplasia  
b) Ductal carcinoma in situ  
c) Tubular carcinoma  
d) Lobular carcinoma in situ/atypical lobular hyperplasia  
e) All of the above
Question 5
The lesion shown on the next slide is best categorized as which of the following?

a) Columnar cell change
b) Flat epithelial atypia
c) Usual ductal hyperplasia
d) Atypical ductal hyperplasia
e) Ductal carcinoma in situ

Terminology for Columnar Cell Lesions

Columnar cell change

Columnar cell hyperplasia

Flat epithelial atypia
  – (Columnar cell change with atypia)
  – (Columnar cell hyperplasia with atypia)
**Columnar Cell Lesions**

Increasingly seen in an era of mammographic screening due to the identification of microcalcifications

Further increase noted with introduction of digital mammography (Anoek, Mod Pathol, 2011)

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**Columnar Cell Change**

WHO, 2003

Varially distended acini of TDLUs lined by columnar cells arranged perpendicular to basement membrane

Apical snouts

Secretions and microcalcifications in lumens
Columnar Cell Hyperplasia
WHO, 2003

- Variably distended acini of TDLUs lined by columnar cells arranged perpendicular to basement membrane, some multilayer and piling up of nuclei, but no true micropapillations

- Apical snouts

- Secretions and microcalcifications in lumens, may be more pronounced
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

Flat Epithelial Atypia

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

Flat Epithelial Atypia

Given a number of different names
- Clinging carcinoma (monomorphic type)
- Atypical cystic lobules type A
- Columnar cell change/hyperplasia with atypia
- CAPSS with atypia
- DIN of the flat type
Flat Epithelial Atypia
The “missing link” in breast cancer progression?*

*Simpson, Am J Surg Pathol, 2005

Problems in Breast Pathology
Azzopardi, 1979

“Underdiagnosis of Malignancy”
There is a more common form of clinging carcinoma.....the involved structures are lined by a single or a few layers of neoplastic epithelial cells.....the lesion can be missed entirely since the alteration is cytological rather than anatomical (architectural).”

Normal Epithelium

No consistent genetic alterations
UDH

Low Grade Pathway
ER+, HER2-, low profi rate

LG-Invasive Cancer

Low grade breast neoplasia family

Adapted from Ellis, Mod Pathol 2010
Differential Diagnosis of Flat Epithelial Atypia

- Microcysts
- Apocrine metaplasia
- Cystic Hypersecretory Hyperplasia
- LG-DCIS
- ADH
- Columnar Cell Change/Hyperplasia
**Microcysts**
- Single layer of low cuboidal/attenuated epithelial cells
- Small nuclei
- May have secretions

**Apocrine cysts**
- Single layer of low cuboidal cells
- Abundant pink cytoplasm
- Round nuclei with prominent nucleoli
- Calcifications often calcium oxalate

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**Flat Epithelial Atypia vs. Apocrine Epithelium**

<table>
<thead>
<tr>
<th></th>
<th>FEA</th>
<th>Apocrine Epithelium</th>
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<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 calcifications</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>
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</tbody>
</table>
ER and bcl2 Expression

<table>
<thead>
<tr>
<th>FEA</th>
<th>Apocrine met</th>
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<tbody>
<tr>
<td>ER</td>
<td></td>
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<tr>
<td>bcl2</td>
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Columnar cell lesions without atypia

- Columnar cells
- Nuclei elongated
- Polarization maintained
- May stratify

Columnar Cell Change  Flat Epithelial Atypia  Columnar Cell Hyperplasia

Irregular contours  Smooth contours  Irregular contours
Cystic Hypersecretory Hyperplasia

- FEA
- CCL

Atypical Ductal Hyperplasia

- Cells with low grade cytologic atypia
- Architectural atypia also present
Low Grade DCIS

Cells with low grade cytologic atypia

Architectural atypia also present, completely filling a ductal unit
Flat Epithelial Atypia vs.
ADH or DCIS

<table>
<thead>
<tr>
<th></th>
<th>FEA</th>
<th>ADH/DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade cytologic atypia</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Complex architectural patterns</td>
<td>X</td>
<td>√</td>
</tr>
</tbody>
</table>

High Grade DCIS

Clinging carcinoma may present as dilated spaces with single layer of atypical epithelial cells

Differential Diagnosis of Flat Epithelial Atypia

- Microcysts
- Apocrine metaplasia
- Cystic Hypersecretory Hyperplasia
- Columnar Cell Change/Hyperplasia

ARCHITECTURE:
- ADH
- LG-DCIS

CYTOLOGY:
- FEA
Immunophenotype

Immunophenotype studies not helpful for separating FEA and CCC/CCH

- 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
Genetic Alterations

- FEA is a clonal proliferation
- Genetic changes relatively few in number
- Recurrent loss of 16q reported
- Similar alterations in associated DCIS or invasive carcinoma

Lesions often associated with FEA

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

Fraser, 1998; Rosen, 1999; Brogi, 2001; Collins, 2007; Abdel-Fatah, 2007
Clinical Significance
Clinical Significance of FEA

Morphologic evidence to support relationship to ADH, LG-DCIS, tubular carcinoma

- Cytologic similarities
- Coexistence and geographic proximity
- Immunophenotypic similarities

Based on observations of association with other lesions and genetic data, FEA appears to be a precursor to, or the earliest manifestation of LG DCIS.

Relationship between DCIS and FEA

Collins, Mod Pathol, 2007

FEA is preferentially associated with DCIS with particular features
- Low nuclear grade
- Micropapillary pattern
- Absence of comedo necrosis
- Absence of stromal inflammation/desmoplasia

Implications

Our observations provide further evidence for a precursor-product relationship between FEA and DCIS that exhibit such features.
“Rosen Triad”
Brandt et al., Adv Anat Pathol, 2008

• 86 cases of tubular carcinoma
• 100% of cases with associated CCLs
• 53% of cases with associated LCIS

(Rosen, Am J Surg Pathol, 1999)

Proposed Evolutionary Pathway for LG Neoplasia
Abdel-Fatah et al, AJSP, 2007
Clinical Follow-up Studies

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<tr>
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<tbody>
<tr>
<td># of patients</td>
<td>25</td>
<td>59</td>
<td>115</td>
</tr>
<tr>
<td>Type of study</td>
<td>Retrospective review, biopsies originally considered benign</td>
<td>Prospective, randomized clinical trial</td>
<td>Retrospective review, “clinging carcinoma of the monomorphic type”</td>
</tr>
<tr>
<td>Treatment</td>
<td>Diagnostic biopsy: no attempt at excision</td>
<td>Excision alone or Excision and radiation</td>
<td>Biopsy alone (n=70) Biopsy and radiation (n=45)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>19.2 years (mean)</td>
<td>5.4 years (median)</td>
<td>13.3 years (median)</td>
</tr>
<tr>
<td># (%) with LR</td>
<td>1 (4%)</td>
<td>0</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td># with subsequent IBC</td>
<td>0</td>
<td>0</td>
<td>3 (2.6%)</td>
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Histologic Associations and Long-term Cancer Risk in Columnar Cell Lesions of the Breast
A Retrospective Cohort and a Nested Case-Control Study

- Evaluated overall cancer risk in 1,261 CCLs
- Mild increase in overall cancer risk
- RR=1.47 with 17 years of follow-up
- No difference among 3 categories of CCL with regard to future breast cancer risk
- 2-3 fold increase in AH in presence of CCLs
- May indicate the presence of a concomitant worse lesion

Columnar Cell Lesions and Subsequent Breast Cancer Risk
Aroner, Breast Cancer Res Treat, 2010

- Women with CCL had an increased risk of breast cancer compared with those without CCL
  OR=1.44, 95%CI: 1.14–1.83
- However, this increase in risk was attenuated after adjustment for histologic category of BBD
  OR=1.20, 95%CI: 0.94–1.54
**Management Issues**

**Columnar Cell Change/Hyperplasia**

- Found on excision:
  - No further treatment
- Found on CNB:
  - No excision necessary
- No additional levels obtained

**Flat Epithelial Atypia**

- **FEA on core biopsy**
  - Excision required
  - “Upgraded” in 0-30% of cases

References:
- Peres, BCRT, 2011
- De Mascarel, Mod Pathol, 2011
- Lee, Breast Journal, 2010
- Ingegnoli, Breast Journal, 2010
- Tomasino, J Cell Physiol, 2009
- Chivukula, Am J Clin Pathol, 2009
- Senetta, Mod Pathol, 2009
- Kunju, Hum Pathol, 2007

- **FEA on core biopsy**
  - “Upgraded” in 0-30% of cases
  - But need for excision remains uncertain
  - Rad-path correlation required

References:
- Peres, BCRT, 2011
- Lavoue, BCRT, 2011
- Lee, Breast Journal, 2010
- Ingegnoli, Breast Journal, 2010
- Tomasino, J Cell Physiol, 2009
- Chivukula, Am J Clin Pathol, 2009
- Senetta, Mod Pathol, 2009
- Kunju, Hum Pathol, 2007
FEA on excisional biopsy
- Obtain multiple levels looking for areas diagnostic of ADH or LG DCIS
- Submit all tissue

Management Issues
- FEA in association with ADH
  - Manage as ADH
- FEA in association with LG DCIS
  - Manage as DCIS
  - Question as to whether FEA included in extent/size of DCIS
  - Question of how to manage FEA at margins remains unanswered

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d) Atypical ductal hyperplasia
e) Flat epithelial atypia

Answer 2: e) Flat epithelial atypia

This lesion is characterized by terminal duct lobular units with dilated acini that contain flocculent secretions. The acini are lined by several layers of cuboidal epithelial cells with low grade, monomorphic type nuclear atypia and prominent apical cytoplasmic snouts. The features are diagnostic of flat epithelial atypia.

Schnitt SJ and Collins LC. Columnar cell lesions and flat epithelial atypia of the breast. Seminars in Diagnostic Pathology 2005;8:100-111.
Question 3

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Answer 3: a) Columnar cell change

The acini in this terminal duct lobular unit are variably dilated and are lined by a single layer of columnar epithelial cells with ovoid to elongated nuclei oriented perpendicular to the basement membrane imparting a "picket fence"-like appearance. Many of the cells have apical cytoplasmic snouts. These features are diagnostic of columnar cell change.


Question 4

Which of the following lesions is often seen in association with flat epithelial atypia?

a) Atypical ductal hyperplasia  
b) Ductal carcinoma in situ  
c) Tubular carcinoma  
d) Lobular carcinoma in situ/atypical lobular hyperplasia  
e) All of the above
Although the subsequent breast cancer risk associated with flat epithelial atypia is not well-defined, the presence of flat epithelial atypia should serve as a "red flag" for the presence of other lesions with which it frequently co-exists. These include atypical ductal hyperplasia, DCIS, tubular carcinoma and lobular neoplasia. It is for this reason that the diagnosis of flat epithelial atypia on core needle biopsy currently warrants excision.

Schnitt SJ and Collins LC. Columnar cell lesions and flat epithelial atypia of the breast. Seminars in Diagnostic Pathology 2005;8:100-111.

Question 5
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e) Ductal carcinoma in situ
Answer 5: b) Flat epithelial atypia

This lesion is characterized by an acinus containing flocculent secretions, lined by several layers of cuboidal to columnar epithelial cells with low grade, monomorphic type nuclear atypia and prominent apical cytoplasmic snouts. The features are diagnostic of flat epithelial atypia.

Conclusions

CCL and FEA increasingly prevalent in an era of mammographic screening (especially digital mammography)

May represent a precursor to LG DCIS

Risk of progression to invasive carcinoma appears to be very low (with limited data)