Flat Epithelial Atypia

Diagnostic criteria and Clinical significance

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Introduction

• Ongoing area of controversy
  – Diagnostic criteria not well understood
  – Pathologists reluctant
  – Interobserver variability
  – Significance debated
  – Management unclear
Objectives

• Historical perspective
• Histologic criteria
• Differential diagnosis
• Histologic associations
• Long-term significance
• Suggestions for diagnosis and management
History

- Stewart and Foote “unfolded lobular units”
- Azzopardi’s clinging carcinoma monomorphic type
- Atypical cystic lobules
- Columnar alteration with prominent snouts and secretions
- Columnar cell atypia
- Flat epithelial atypia
PROBLEMS IN BREAST PATHOLOGY

Photograph of Professor John G. Azzopardi (2003)
Histologic Criteria

LOBULOCENTRIC

FLAT

MILDLY ATYPICAL

COLUMNAR CELLS
Low-Power Features
Dilated circular acini

Intraluminal secretions

Thick and Pink epithelial layer
Dilated circular acini

Intraluminal secretions

Thick and Pink epithelial layer
Dilated circular acini

Intraluminal secretions

Thick and Pink epithelial layer
High-Power Features
Uniform enlarged cells
Uniform enlarged cells

Loss of picket-fence polarity
Uniform enlarged cells
Loss of picket-fence polarity
Apical snouts
Uniform enlarged cells

Loss of picket-fence polarity

Apical snouts

Attenuated myoepithelial cells
Differential Diagnosis

Columnar Cell Lesions WITHOUT atypia
Usual Ductal Hyperplasia
Apocrine Change
Is the Diagnosis Reproducible?

Theoretically yes.
Interobserver reproducibility in the diagnosis of flat epithelial atypia of the breast

O’Malley et al., Modern Pathology, 19, 172–179, 2006

30 cases, 8 pathologists, 91.8% agreement
How common is FEA?

It depends...
Isolated FEA

Not common...
Pre-Mammographic Era

_Eusebi et al. (1989):_

25 patients (1965-1971) with “clinging carcinoma” out of 4397 “benign” breast biopsies (0.5%)
Post-Mammographic Era

- Noske et al. (2010): 43 FEA out of 1845 core biopsies (2.3%)
- Graesslin et al. (2010): 1 FEA out of 68 core biopsies (1.4%)
- Ingegnoli et al. (2009): 18 FEA out of 476 core biopsies (3.8%)
- Piubello et al. (2009): 33 FEA out of 875 core biopsies (3.7%)
- De Mascarel et al. (2007): 101 FEA out of 2833 surgical biopsies (3.5%)
- Martel et al. (2007): 63 FEA out of 1751 core biopsies (3.6%)
FEA + AH/DCIS/IBC..

More Common!
Earlier

• Fraser et al. (1999):
  “CAPSS and DCIS commonly coexisted in the same or adjacent TDLUs”

• Rosen PP (1999):
  “Columnar cell hyperplasia is associated with lobular carcinoma in situ and tubular carcinoma”

• Oyama et al. (1999):
  “We discovered atypical cystic lobules in 36% of specimens containing ductal carcinoma in situ and 29% of cases showing lobular neoplasia”
Later

- Abdel Fattah et al. AJSP 2007:
  FEA was present in 104 out of 147 TC, TLC, and ILC (70.7%) and was similarly associated with ADH/DCIS
- Collins et al. AJSP 2007:
  FEA was present in 103 (19%) of the 543 cases with DCIS
- Abdel Fattah et al. AJSP 2008:
  FEA was present in 40 out of 255 cases with IBC+ Precursor (16%) and 20 out of 120 cases of precursors (16%)
Histologic Associations

- ADH
- ALH
- *Low-Grade* DCIS
- Tubular carcinoma
Molecular Associations

- ADH
- ALH
- *Low-Grade* DCIS
- Tubular carcinoma
<table>
<thead>
<tr>
<th>Lesions</th>
<th>Reported Genetic Changes</th>
<th>Reference</th>
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<tbody>
<tr>
<td>CCC</td>
<td>-16q</td>
<td>26</td>
</tr>
<tr>
<td>CCC with atypia</td>
<td>-16q, -19q, +11q</td>
<td>25</td>
</tr>
<tr>
<td>CCH with atypia</td>
<td>-16q, -19q, +11q, +18q</td>
<td>26</td>
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<tr>
<td>CCH complex architectural &amp; atypia</td>
<td>-16q, -9q, +6q</td>
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<tr>
<td>ADH</td>
<td>-16q, -8q, +6q, +8p, -8q</td>
<td>13</td>
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<tr>
<td>Low grade DCIS</td>
<td>-16q, -8q, -19q, -12q, +17q</td>
<td>16, 36</td>
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<tr>
<td>Tubular Carcinoma</td>
<td>-16q, -8q, +8p</td>
<td>34</td>
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Abdel Fattah et al. AJSP 2007
Invasive tubular carcinoma of the breast frequently is clonally related to flat epithelial atypia and low-grade ductal carcinoma in situ.


• 27 TC (22 FEA, 10 LGDCIS, 3LN)
• Mitochondrial DNA sequencing
  – 50% identical mutation patterns Between TC and adjacent LGDCIS
  – 57% identical mutation patterns Between TC and adjacent FEA
• LOH with high degree of homology in allelic losses between TC, FEA and DCIS
Immunohistochemistry

- ER (+)
- PR (+)
- Her2/neu (−)

- P53
- Cyclin D1

Abdel Fattah et al. AJSP 2008
What is the Significance of FEA?

LONG-TERM?
• Does the association with ADH/ALH, DCIS, and Low grade invasive cancer mean that FEA is a precursor?

• Is FEA a marker of increased risk?
Long-term follow-up of in situ carcinoma of the breast with special emphasis on clinging carcinoma

Eusebi et al, Semin Diagn Pathol, 6: 165-73, 1989

- 25 patients with “clinging carcinoma”
- 19.2 years follow-up
- Single recurrence with same histology
Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853


- 59 patients with “clinging carcinoma”
- 5.4 years follow-up
- No recurrences
Epithelial atypia in biopsies performed for microcalcifications. Practical considerations about 2,833 serially sectioned surgical biopsies with a long follow-up


• 101 patients with isolated FEA
• 10 years follow-up
• No malignant recurrences
Histologic Associations and Long-term Cancer Risk in Columnar Cell Lesions of the Breast: A Retrospective Cohort and a Nested Case Control Study

Boulos et al, Cancer, 113(9):2415-21, 2008

- Columnar cell lesions carry a mildly increased risk (RR=1.46)
- Association between CCLs in general and AH is highly statistically significant
- No statistically significant difference between different CCL subtypes and subsequent cancer risk
Flat DIN 1 (flat epithelial atypia) on core needle biopsy: 63 cases identified retrospectively among 1,751 core biopsies performed over an 8-year period (1992-1999)


- 63 cases of FEA
- 7 ipsilateral cancers from 2-9 years
Simpson et al. USCAP 2010 platform presentation (unpublished)

<table>
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<tr>
<th>CCL Type</th>
<th>Histologic Grade</th>
<th>Size</th>
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<td></td>
<td>1 2 3</td>
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<tr>
<td>CCC</td>
<td>1 8 3</td>
<td>1.8 (1.2-3.0)</td>
<td>4/12 (1-22)</td>
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<td>8 12 3</td>
<td>1.7 (0.5-3.5)</td>
<td>6/23 (1-16)</td>
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<td>FEA</td>
<td>4 2 3</td>
<td>2.9 (0.9-9.0)</td>
<td>4/9 (2-12)</td>
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<td>CCL</td>
<td>13 20 9 (13)</td>
<td>14/41 (1-22)</td>
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4 cases indeterminate for atypia all showed grade 3 subsequent carcinomas

1/3 pure tubular carcinomas arose following FEA and 2/3 arose following CCH
• Carcinoma following CCL is delayed by one decade on average
• The majority of carcinomas are of intermediate grade and no special type
• Among the grade 1 cancers, only 3 pure tubular cancers were present (5%)
• The relative proportion of grade 3 was highest with FEA, but numbers too small
What is the Significance of FEA?

LONG-TERM? Probably not much...
What is the Significance of FEA?
What we don’t know...

“A conservative excision [...] MAY BE warranted for FEA alone.” Lee

“The presence of flat epithelial atypia [...] requires careful consideration, and surgical excision should be SUGGESTED.” Ingegnoli

“...pure FEA, especially if related to a small radiologic target, completely or almost completely removed by the needle biopsy procedure, could be SPARED surgical excision...” Piubello

“Flat epithelial atypia shows a risk of upgrade to carcinoma similar to that of ADH and, hence, should be recognized and WARRANTS a follow-up excision.” Kunju

“...excision is NOT MANDATORY when flat epithelial atypia is found as the most advanced lesion.” Senetta
FEA is upgraded upon surgical excision in 0-62% of cases
What we DO know!

- FEA turns into ADH on deeper sections
- We are likely to find ADH/DCIS/TC in the vicinity of FEA
What is the Significance of FEA?

IMMEDIATE-TERM? May be significant...
What should we do?

We should be careful..
The link and frequent merging between FEA and ADH/DCIS is certain, and it is imperative to ensure that a diagnosis of isolated FEA on core biopsy is accurate, and that no ADH or DCIS is present on deeper levels.
The adequacy of the needle core biopsy, the extent of FEA in tissue cores, and the correlation with pre and post-biopsy mammographic findings are instrumental in deciding whether to proceed with excision or observation.
When in doubt, **err on the conservative side** in order to avoid unnecessary surgical procedures prompted by surgeons uncomfortable with the concept of atypia on a needle core biopsy.
Nomenclature is not yet standardized and any of the currently available terms may be used as long as communication with the clinician is addressed and an explanatory comment is included to minimize confusion.
Train yourselves!
To Conclude

Remember the (relatively gentle) nature of the beast