Ductal Proliferative Lesions of the Breast: From FEA to ADH to DCIS

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Incidence of ductal lesions

- Pre-mammography: DCIS < 3% of breast cancers, large palpable masses, with invasion
- Mammography: DCIS 25% of newly diagnosed breast cancers in US, most non-palpable
- Concurrent prevalence of ADH and FEA:
  - ADH: 2.1% to 10%
  - FEA: < 1% (not recognized) to 3.6%

Outline

- Conventional intraductal proliferative lesions
  - Distinguish UDH from ADH and low-grade DCIS
  - Clinical significance and management
- FEA
  - Distinguish various columnar cell lesions
  - Clinical significance of FEA
  - Management for FEA

Studies addressing benign breast disease (BBD) and breast cancer risk using criteria by Page et al

- Nashville Breast Cohort
- Nurses’ Health Study (NHS)
  - London, Connolly, Schnitt and Colditz: JAMA 1992
- Breast Cancer Detection Demonstration Project (BCDDP)
  - Dupont, Parl, Hartmann, et al: Cancer 1993
- Mayo Clinic
Breast diseases and risk of invasive ca

• Nonproliferative lesions: no increased risk  
  ➢ mild hyperplasia (< 4-cell layers), cysts, apocrine change, duct ectasia, simple FA, mastitis

• Proliferative lesions without atypia: 1.5-2x risk  
  ➢ moderate to florid UDH, sclerosing adenosis, complex FA, papilloma, radial scar

• Atypical hyperplasia (ADH, ALH): 4-5x risk

• Low-grade DCIS and LCIS: 8-10x risk

Diagnosis of ductal proliferative lesions: Architecture and Cytology

Histologic criteria for UDH  
(WHO 2003)

• Architectural features  
  ➢ Irregular, peripheral fenestrations  
  ➢ Stretched or twisted epithelial bridges  
  ➢ Streaming or whirling  
  ➢ Uneven distribution of nuclei and overlapped nuclei

• Cytologic features  
  ➢ Multiple cell types  
  ➢ Variation in size and shape of cells/nuclei  
  ➢ Indistinct cell margins and deviation from a round contour

• Page D, Rogers L. Hum Pathol 1992;23: 1095-7  
• WHO classification of tumors of the breast and female genital organs 2003
Necrosis may rarely be seen in UDH

Histologic criteria for low-grade DCIS (WHO 2003)

• Cytologic features
  - Monomorphic rounded cell population
  - Evenly spaced with distinct cell borders
  - Oval to round nuclei, ± hyperchromasia
  - Equidistant or highly organized nuclear distribution

• Architectural features
  - Arcades, cribriform, solid, and/or micropapillary

Size/extent criteria: 2 ducts or 2 mm

Cytologic features of LG DCIS

Monotonous
Round to oval nuclei
Distinct cell membrane
Cytologic features of LG DCIS

Highly organized nuclear distribution: polarization to lumen

DCIS--architectural pattern
cribriform

DCIS--architectural pattern
Roman arch/bridge

DCIS--architectural pattern
solid
DCIS--architectural pattern
micropapillary

Monotonous
Evenly spaced
Distinct cell membrane

Heterogeneous
Crowded and overlapping
Indistinct cell membrane

Rigid bar
Nuclei perpendicular to bar

Tapering bar
Nuclei parallel to bar

Micropapillary DCIS
Micropapillary hyperplasia

Papillae:
Narrow base
Bulbous tip

Papillae:
Broad base
Pointed or tapering tip
Micropapillary DCIS  Micropapillary hyperplasia

- Monotonous population
- Hyperchromatic
- Organized: nuclei perpendicular to lumen

- Heterogeneous population
- Hyperchromatic at tip, normochromatic at base
- Crowded and overlapping nuclei

Atypical ductal hyperplasia (Page and Rogers, 1992)

- “Partial involvement of the duct by a cell population of the type defined for LG DCIS”
- Diagnostic criteria imperfect, based on exclusion rather than positive criteria

Histologic criteria for ADH--two categories

- Qualitatively insufficient for DCIS: “mimic DCIS”
  - partial involvement of duct by atypical cells; or
  - architectural atypia insufficient

- Quantitatively insufficient for DCIS: “mini DCIS”
  - characteristic cytologic and architectural atypia, but aggregate diameter ≤ 2 mm
Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria
S. Schnitt et al AJSP 16:1133-43, 1992

- Six breast pathologists /c 24 proliferative ductal lesions; classify as UDH, AH, CIS
- Written & diagrammatic summary of diagnostic criteria (D. Page) and a set of 15 teaching slides
- 14 cases (58%): complete agreement
  17 cases (71%): 5 or more agreed
  22 cases (92%): 4 or more agreed

Approach to borderline ductal lesions

- Epithelial proliferation and atypia: morphologic and molecular continuum
- Distinction between ADH and LG DCIS not clear-cut, cut-off arbitrary
- When in doubt (between ADH and DCIS), the more benign diagnosis is appropriate (ADH)
- For borderline lesion, suggest conservative approach, recommend clinical follow-up

Marker: distinguishing UDH from LG DCIS?

- ER
- Ki67
- Cyclin D1
- HMW-CK

HMW-CK in ductal lesions

- CK5/6, 34βE12, CK14, CK17
- UDH: HMWK +
- ADH/DCIS: HMWK – (rare exception)
Florid usual ductal hyperplasia

Atypical ductal hyperplasia

High grade basal-like DCIS

Problematic DCIS lesions

- Intermediate grade DCIS
- DCIS with spindle cells
- Papillary and solid/papillary DCIS
  - To be discussed in another lecture
Intermediate grade DCIS may mimic UDH

Intermediate grade DCIS

Intermediate grade DCIS

DCIS with spindle cells: mimic of UDH

CK5/6

CK5/6
**DCIS with spindle cells**

- CK5/6

**High grade DCIS**

- Dx of high grade DCIS: based on cytologic features
- No minimal size required

**Clinical significance & management for DCIS**

- Relative risk of cancer: 8-10X
- Subsequent invasive cancer occurs in same area of breast
- Precursor to invasive ca
- Surgical excision with negative margin
  - adjuvant XRT in patients with breast conservation
  - Hormonal therapy if hormone receptor positive

**Clinical significance & management for ADH**

- Relative risk of cancer: 4-5X
- Risk may be further increased in premenopausal women and those with a first-degree relative with breast cancer
- Subsequent cancer bilateral
Clinical significance & management for ADH

• Non-obligate precursor to invasive ca, risk factor for breast ca

• Excision recommended if found on CNB
  ➢ 33-87% upgraded to ca
  ➢ No features reliably predictive of upgrade

• Close follow-up if found on excision

Flat epithelial atypia--outline

• Columnar cell lesions (CCL) and flat epithelial atypia (FEA): classification, diagnostic criteria

• Distinguishing FEA from ADH and other mimics

• Clinical features and biology

• Management

Columnar cell lesions (CCLs)

• A spectrum of lesions with cuboidal to columnar epithelial cells lining variably dilated TDLUs

• Ranging from little or no cytologic or architectural atypia to ADH or DCIS

• Have long been recognized with various names

• Increasingly encountered due to mammographic calcifications

• Consensus terminology by Stuart and WHO

Classification of CCLs--Based on cytologic atypia

• No cytologic atypia
  ➢ Columnar cell change (CCC)
  ➢ Columnar cell hyperplasia (CCH)

• With cytologic atypia
  ➢ Flat epithelial atypia (FEA)
Columnar cell lesions--
Histologic features

- A spectrum of lesions: TDLUs with variably dilated acini
- Acini lined by cuboidal to columnar cells, often with apical snouts
- ± luminal secretions
- ± microcalcifications, may be psamommatous

Columnar cell change/hyperplasia--
Histologic features

- CCC: 1-2 cell layers
- CCH: 3-5 cell layers; may form tufts, but complex architectural patterns are absent
- Ovoid to elongated nuclei oriented perpendicular to basement membrane; nucleoli absent or inconspicuous

Columnar cell change

Columnar cell change
**Flat epithelial atypia--**

**Histologic features (I)**

- TDLUs usually bluer and rounder at low power
- Acini lined by low-grade (monomorphic type) mildly atypical cells, similar to those seen in low grade DCIS and tubular ca
- Round to oval nuclei; nucleoli may or may not be prominent
- Nuclear chromatin either finely dispersed or slightly clumping and margined

(Source: Stuart and Vincent-Salomon 2003)
Flat epithelial atypia--
Histologic features (II)

- Nuclei lack polarity and are not regularly oriented perpendicular to basement membrane
  - some cases: stratified, tall ovoid to fusiform hyperchromatic nuclei perpendicular to basement membrane (colonic adenoma-like or endometrioid appearance)
- Flat growth pattern (no complex architectural patterns)

(Source: Stuart and Vincent-Salomon 2003)
Flat epithelial atypia

Cytologic features in CLL
- CCC
- FEA
- CCH

Diagnosis of FEA
- Subjective evaluation of cytologic features
- Diagnostic challenge
- Problem with lowest threshold

Flat epithelial atypia--adenoma-like or endometrioid
Role of IHC in evaluation of CCL?

- HMW-CK: negative in CCL irrespective of cytologic atypia
- ER: diffuse and intense + in CCL cells
- Mib-1: low in all CCL

Limited value of IHC in diagnosis of FEA

Reproducibility in diagnosis of FEA


- 30 columnar lesions, 8 breast pathologists
- Powerpoint tutorial with written criteria and images
- Classified as atypia or no atypia
- 91.8% agreement (25 cases unanimous agreement)
  Better agreement on determining no atypia

Differential diagnosis for FEA

- Atypical ductal hyperplasia
- Apocrine metaplasia
- Focal secretory change
- Clinging type DCIS, pleomorphic type (high-grade)
**FEA versus ADH**

- Both with low-grade cytologic atypia
- Distinction based on architectural atypia
  - FEA: flat, lack architectural complexity
  - ADH: with architectural atypia

**Apocrine metaplasia**

- Brightly eosinophilic granular cytoplasm
- Low N/C ratio
- Calcium oxalate

**FEA**

- Eosinophilic or amphophilic cytoplasm
- High N/C ratio
- Psammoma calcification

Both with apical snouts and uniform round nuclei
Apocrine metaplasia

Secretory change

- Bubbly or vacuolated cytoplasm
- Prominent hobnail cells
- Nuclei not monotonous
- ± smudging degenerating chromatin
Clinging DCIS, high-grade

Clinical features of FEA

- Risk factor for concomitant cancer?
- Risk factor for long-term cancer development?

FEA

- Risk factor for concomitant cancer?
  - FEA is frequently associated with ADH, DCIS, lobular neoplasia and invasive cancer in adjacent breast
- Risk factor for long-term cancer development?
FEA with low-grade DCIS and tubular carcinoma

FEA with tubular carcinoma

FEA with ductal carcinoma in situ

FEA with lobular neoplasia
**FEA is frequently associated with cancer**

2833 surgical excisions for microcalcifications

<table>
<thead>
<tr>
<th>Type of atypia</th>
<th>FEA (3.6%)</th>
<th>ADH (12.1%)</th>
<th>LN (7.9%)</th>
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</thead>
<tbody>
<tr>
<td>Without cancer</td>
<td>83%</td>
<td>64%</td>
<td>62%</td>
</tr>
<tr>
<td>Cancer*</td>
<td>17%</td>
<td>36%</td>
<td>38%</td>
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</tbody>
</table>

*Cancer defined as DCIS or invasive ca
#Invasive cancer often as tubular ca or ILC

Modified from Abdel-Fatah et al: 2008 AJSP

**DCIS associated with FEA**

- Low nuclear grade
- Micropapillary and cribriform patterns
- Absence of comedo necrosis

Collins L et al. Mod Pathol 2007

**CCL is associated with low-grade invasive ca**

<table>
<thead>
<tr>
<th></th>
<th>CCL</th>
<th>Lobular neoplasia</th>
<th>ADH/non HG DCIS</th>
<th>HG DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular ca (n=135)</td>
<td>93%</td>
<td>35%</td>
<td>92%</td>
<td>1%</td>
</tr>
<tr>
<td>Inv lobular ca (n=180)</td>
<td>60%</td>
<td>90%</td>
<td>34%</td>
<td>10%</td>
</tr>
<tr>
<td>LG IDC (n=60)</td>
<td>82%</td>
<td>23%</td>
<td>87%</td>
<td>15%</td>
</tr>
<tr>
<td>HG IDC (n=100)</td>
<td>8%</td>
<td>10%</td>
<td>15%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Modified from Abdel-Fatah et al: 2008 AJSP

**Concomitant lesions with FEA**

- Atypical ductal hyperplasia
- Lobular neoplasia
- Non high-grade DCIS
- Low-grade invasive ca: tubular ca, ILC

**FEA: a high risk factor (red flag) for a concomitant worse lesion**
Clinical features of FEA

• Risk factor for concomitant cancer?
  ➢ FEA is a high risk factor for a concomitant worse lesion in the adjacent breast

• Risk factor for long-term cancer development?

Long-term cancer risk in FEA—Clinical outcome of FEA on excision

• Retrospective studies on patients diagnosed with clinging DCIS, mornomorphic type

  • Low recurrence rate (0-4%)

  • Low rate of progression to invasive ca (0-2.6%)

  • Eusebi V et al: 1994 Semin Diagn Pathol
  • Bijker N et al: 2001 J Clin Oncol
  • de Mascare et al: 2007 Virchows Arch 2007

Long-term cancer risk in FEA--Columnar cell lesions and breast cancer risk

• Nashville Breast Cohort
  ➢ RR= 1.47 at 17 years
  ➢ 2-3x increase in prevalence of atypical hyperplasia
  ➢ No differences among 3 categories of CCL
  ➢ Subsequent cancer risk bilateral

• Nurses’ Health Study
  ➢ OR= 1.44
  ➢ Risk attenuated (OR= 1.20) when adjusted for BBD

  Mild increase in long-term cancer risk

  • Boulos et al: 2008 Cancer;113:2415-21
  • Simpson et al: 2010 Mod Pathol;72A (abstr)
  • Collins et al: 2010 Mod Pathol;42A (abstr)

Long-term cancer risk in FEA--Clinical outcome of FEA on excision

• Low recurrence rate (0-4%)

• Low rate of progression to invasive ca (2.6%)

• Mild increase in cancer risk

FEA is a marker of slightly increased risk for subsequent cancer. The risk is bilateral.

  • Eusebi V et al: 1994 Semin Diagn Pathol
  • de Mascare et al: 2006 Mod Pathol (abstr)
  • Boulos et al: 2008 Cancer
  • Simpson et: 2010 Mod Pathol (abstr)
  • Collins et al: 2010 Mod Pathol (abstr)
Breast diseases and risk of invasive ca

- Nonproliferative lesions: no increased risk
  - mild hyperplasia (< 4-cell layers), cysts, apocrine change, duct ectasia, simple FA, mastitis
- Proliferative lesions without atypia: 1.5-2x risk
  - moderate to florid UDH, sclerosing adenosis, complex FA, papilloma, radial scar
- Columnar cell lesion/FEA: ~1.5x risk
- Atypical hyperplasia (ADH, ALH): 4-5x risk
- Low-grade DCIS and LCIS: 10x risk

Biomarker profile of FEA

- CK19 +, CK5/6 –
- Strong ER and PR +
- Bcl-2 +, cyclin D1 +
- HER2 –
- Low Mib-1 proliferation index (mean ~8%)
- Profile Similar to adjacent low-grade invasive ca

Genetic changes in FEA

- Clonal chromosomal alterations
- Share similar, but less, genetic changes when compared with adjacent DCIS and invasive cancer
- Changes different than those seen in HG DCIS and IDC

FEA and LG DCIS/Invasive ca

- Physical proximity in the breast
- Similar biomarker profile
- Similar genetic alterations
- Clinical follow-up studies
  1. Earliest recognizable, but non-obligate precursor of low grade breast cancer pathway
  2. Progression slow

-Simpson et al: 2005 AJSP
-Simpson et al: J Pathol 2005
Management of FEA--
Found on CNB as most advanced lesion

• Additional level sections

• Most: recommend conservative excision
• Some: close follow-up with repeat mammogram

• Follow-up excision: 0-38% upgraded to DCIS and/or invasive ca

*Lee et al: 2010 Breast J
*Chivukula et al: 2009 Am J Clin Pathol
• Piubello et al: 2009 AJSP
• Datrice et al: 2007 Am Surg

Management of FEA--
Found on excision as most advanced lesion

• Levels to look for features diagnostic of ADH or DCIS

• Submit all (parenchymal) tissue

• Regular clinical and mammographic follow-up

Management of FEA--
Found on excision with concomitant DCIS

• Should FEA be taken into consideration in:
  - determining DCIS size?
  - margin evaluation?

• Unanswered questions, however, current recommendation is “No”

FEA: Take-home message (I)

• Diagnosis based on low-grade cytologic atypia

• Distinction from ADH based on architecture

• High risk factor for concomitant cancer, but mildly increased risk for subsequent cancer

• Likely early, but non-obligate precursor for low grade breast ca
FEA: Take-home message (II)

• Excision is generally recommended if found on CNB

• Regular follow-up if found on excision

Apocrine lesions

• A wide spectrum similar to non-apocrine ductal lesions

• Normal apocrine cells have large nuclei and prominent nucleoli, so nuclear size cannot be used to distinguish apocrine change from atypical apocrine lesions

• Criteria: cytologic atypia, size, (architecture, necrosis)

Papillary apocrine change (simple and complex)
Apocrine lesions

• A wide spectrum similar to non-apocrine ductal lesions

• Normal apocrine cells have large nuclei and prominent nucleoli, so nuclear size cannot be used to distinguish apocrine change from atypical apocrine lesions

• Criteria: cytologic atypia, size, (architecture, necrosis)

Diagnosis of apocrine lesions

• Benign apocrine change: lack cytologic atypia

• Apocrine DCIS
  ➢ Most: obvious cytologic atypia, ± necrosis, large
  ➢ Rare: less cytologic atypia, but arranged in cribriform pattern identical to that in cribriform DCIS

• Atypical apocrine lesions: cytologic atypia and limited extent (size cut off?)

Cytologic atypia in apocrine lesions--
Normal apocrine cells as reference point

Apocrine DCIS
• Markedly enlarged (>3x) variable nuclei
• Multiple irregular nucleoli or markedly enlarged single nucleolus
• Irregular nuclear membrane
• Coarse chromatin

Apocrine metaplasia
• Large but uniform nuclei
• Prominent but uniform nucleoli
• Smooth nuclear membrane
• Fine chromatin