Workshop on Intraductal Proliferations of the Breast

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Goals and Objectives

• Review diagnostic criteria for intraductal lesions (UDH, ADH, DCIS, FEA)
• Understand the biology and clinical implications of these diagnoses
• Review challenging cases/borderline lesions
• Develop practical approaches to cases that take into account clinical considerations
Interobserver Reproducibility in the Diagnosis of Ductal Proliferative Breast Lesions Using Standardized Criteria

Stuart J. Schnitt, M.D., James L. Connolly, M.D., Fattaneh A. Tavassoli, M.D., Robert E. Fechner, M.D., Richard L. Kempson, M.D., Rebecca Gelman, Ph.D., and David L. Page, M.D.

<table>
<thead>
<tr>
<th>TABLE 1. Guidelines for evaluation of proliferative ductal breast lesions as provided by Dr. Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Florid hyperplasia without atypia has swirling of cells, variable nuclear shape and placement, and irregular intercellular spaces that are most marked centrally.</td>
</tr>
<tr>
<td>2. Ductal carcinoma in situ (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.</td>
</tr>
<tr>
<td>3. Atypical ductal hyperplasia has the presence of the cell population defined above for noncomedo ductal carcinoma in situ 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.</td>
</tr>
<tr>
<td>4. When in doubt between atypical ductal hyperplasia and ductal carcinoma in situ, use the more benign designation.</td>
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<tr>
<td>5. To qualify as atypical ductal hyperplasia (as opposed to florid hyperplasia without atypia), the bothersome cell population usually, but not always, has hyperchromatic nuclei.</td>
</tr>
<tr>
<td>6. To qualify as atypical ductal hyperplasia (as opposed to florid hyperplasia 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 atypical ductal hyperplasia when there is a population of cells less than the numbers indicated. This is an indication of the lower level of definition for atypical ductal hyperplasia.</td>
</tr>
</tbody>
</table>

The American Journal of Surgical Pathology 16(12): 1133–1143, 1992
Definition of ADH

• Some but not all of the features of LG DCIS:
  – Cytology: Low grade monotonous cells
  – Architecture: Bridging, polarized spaces, micropapillae

• Size criteria:
  – Developed for use in excisions only
  – Two duct spaces or 2.0 mm
Case #1

• 65 year old with 1.5 cm of suspicious calcifications
Clinical Impact of Core Biopsy Diagnosis

- UDH $\rightarrow$ No further management

- ADH $\rightarrow$ Surgical consultation with excisional biopsy to rule out adjacent DCIS or invasion

- DCIS $\rightarrow$ Surgical excision to negative margins (lumpectomy+XRT or mastectomy) +/- hormonal therapy if ER+

Borderline lesion not definite DCIS – get more tissue!

Need to be 100% certain = a “cancer” diagnosis with major treatment implications!
Diagnosis:

• Left breast calcifications at 2:00, stereotactic core needle biopsy:
  – Atypical ductal hyperplasia
  – Calcifications present, associated with atypical and non-atypical ducts

Sent for excisional biopsy
EXCISIONAL BIOPSY:
Focal (2 mm) Nottingham grade 1 invasive ductal carcinoma
Upgrade Rates of ADH on Core

• Wide range depending on study 3-60% (most between 10-20%) – will depend on study population used
• At Stanford:
  – ADH in 9% of breast cores
  – Upgrade rate of 13% to DCIS or invasion
• What does it upgrade to?
  – Low-intermediate grade DCIS
  – Low grade invasive carcinomas
CASE #2:

- 45 year old with 0.2 cm focus of clustered calcifications
Diagnosis:

• Right breast calcifications at 10:00, stereotactic core needle biopsy:
  – Minimal atypical ductal hyperplasia with associated calcifications

COMMENT: There is a single (< 1 mm) focus of atypical ductal hyperplasia present. Dr Atypia has reviewed selected slides form this case and agrees. Levels were performed in the evaluation of this case.
Minimal ADH

- Studies on # of foci of ADH = can stratify risk some
- What upgrade rate is considered acceptable?
- Agreement is worse with focal lesions
- Correlation with radiology findings

GET A SECOND REVIEW

All 3 upgraded to 1-3 mm foci of Grade 1 IDC
BPATH study
Why do we disagree?

Understanding diagnostic variability in breast pathology: lessons learned from an expert consensus review panel

Kimberly H Allison, Lisa M Reisch, Patricia A Carney, Donald L Weaver, Stuart J Schnitt, Frances P O'Malley, Berta M Geller & Joann G Elmore

*Histopathology* 2014, 65, 240–251. DOI: 10.1111/his.12387

<table>
<thead>
<tr>
<th>Pathologist-related</th>
<th>Discussion focused on subtle differences of professional opinion about whether the features present met the criteria for a specific diagnosis</th>
<th>1st</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional differences of opinion on features meeting diagnostic criteria</td>
<td>Discussion focused on whether the features present met the criteria for a specific diagnosis</td>
<td>1st</td>
</tr>
<tr>
<td>Not noting a focal diagnostic finding</td>
<td>Pathologist verbally acknowledged not noting the diagnostic area of the slide (all of these were focal findings)</td>
<td>2nd</td>
</tr>
<tr>
<td>Different diagnostic philosophy (clinical impact versus morphology)</td>
<td>Discussion focused on differences in taking into account the potential clinical relevance of a diagnosis versus utilizing strictly morphological features</td>
<td>3rd</td>
</tr>
<tr>
<td>Different diagnostic criteria</td>
<td>Discussion focused on pathologists' use of different diagnostic criteria for a specific diagnosis in a given case</td>
<td>4th</td>
</tr>
<tr>
<td>Different diagnostic features noted</td>
<td>Discussion focused on disagreement about the specific morphological features present</td>
<td>4th</td>
</tr>
</tbody>
</table>
Figure 2. (A,B) (H&E): Two of the three expert breast pathologists independently classified this case as ADH, and one classified it as DCIS. During consensus review discussion, there was agreement about the cytological monotony and early architecture of low-grade DCIS, but it was agreed that the architectural changes present were not sufficient for a diagnosis of low-grade DCIS. The consensus diagnosis was ADH. (C) (H&E): Two of three

(C) (H&E): Two of three expert breast pathologists independently classified this case as ADH, and one classified it as usual ductal hyperplasia (UDH). Consensus review discussion focused on how the features were borderline between UDH and ADH, and the predictability of their disagreement about subtle features meeting diagnostic criteria. At the consensus conference, it was agreed that there was enough architectural atypia present for a diagnosis of ADH.
Reality Check on Intraductal Proliferative Lesions

• It’s a spectrum and there are grey zones
• Specialists and non-specialists both have poor agreement on atypia
• Clinical context matters
• Second reviews!!
Second Review Policies

Gellar BM, et al. Second opinion in breast pathology: Policy, practice and perception. Archives of Pathology, IN PRESS
Case #3

- 85 year old with poor performance status found to have a 0.3 cm cluster of suspicious calcifications on screening mammogram
Diagnosis?

A. Atypical ductal hyperplasia
B. At least ADH, bordering on low grade DCIS
C. Severely atypical intraductal proliferation, suspicious for DCIS
D. Low grade DCIS
Excision

- Biopsy site changes only
- Review original biopsy knowing it is the entire extent of disease (< 2 mm lesion)
- Great case for a second review or specialist opinion!
- Clinical context discussion as well! (85 y/o with co-morbidities)
Excision Diagnosis Report:

- Left breast, excisional biopsy:
  - Biopsy site changes with no residual atypia or calcifications, see comment

COMMENT:
We have reviewed the prior needle core biopsy and agree that there is a 2 mm focus in that sample that borders on a diagnosis of low grade ductal carcinoma in situ. This lesion appears to have been entirely removed with core biopsy sampling. Given the limited extent and borderline histologic findings we favor classification and treatment as atypical ductal hyperplasia. Drs X and Y have also reviewed these findings and agree. The case was discussed with Dr C on 7-14-14 at 3pm.
Case #4

- 67 year old with prior core biopsy diagnosis of atypical ductal hyperplasia and a 2.5 cm area of calcifications
Diagnosis:

• Spectrum of low grade intraductal neoplasia including the following:
  – 0.5 cm focus of low-intermediate grade DCIS
  – Background atypical ductal hyperplasia over a 2.5 cm area
  – Calcifications present associated with DCIS and ADH
  – Prior biopsy site present
  – Margins:
    • DCIS is greater than 0.5 cm to margin
Risk vs Precursor Breast Lesions: Traditional Thinking

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Relative Risk of Invasive Cancer</th>
<th>Location of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical Ductal Hyperplasia (ADH)</td>
<td>4-5 x</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Atypical Lobular Hyperplasia (ALH)</td>
<td>4-5 x</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Lobular Carcinoma in Situ (LCIS)</td>
<td>8-10 x</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Ductal Carcinoma in Situ (DCIS)</td>
<td>8-10 x</td>
<td><strong>Unilateral</strong></td>
</tr>
</tbody>
</table>
Anatomic Distribution: Traditional Thinking

Risk Lesion

Non-surgical

Precursor Lesion

Remove Surgically
Biology of ADH

- PCR-based clonality assay

### Analysis of the progression of intraductal proliferative lesions in the breast by PCR-based clonal assay

<table>
<thead>
<tr>
<th>Sample types</th>
<th>Monoclonal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal breast tissue (30)</td>
<td>0</td>
</tr>
<tr>
<td>UDH (40)</td>
<td>2.9</td>
</tr>
<tr>
<td>FEA (29)</td>
<td>23.1</td>
</tr>
<tr>
<td>ADH (40)</td>
<td>51.3</td>
</tr>
<tr>
<td>DCIS (40)</td>
<td>100</td>
</tr>
</tbody>
</table>

Qi Yu · Yun Niu · Yong Yu · XiuMin Ding · YuRong Shi
Risk Lesions Can Also Be Neoplastic!

- Newer molecular evidence indicates that risk lesions ADH, ALH and LCIS are:
  - Clonal proliferations (neoplastic)
  - Very similar alterations to low grade DCIS
  - Frequent molecular alterations shared with invasive disease

→ ADH, ALH/LCIS are Non-Obligate Precursors with a distribution pattern that warrants treatment as Risk Lesions
Natural History of DCIS: Traditional Thinking

Table 1. Natural history of untreated DCIS

<table>
<thead>
<tr>
<th>Reference</th>
<th>n of patients</th>
<th>Patients developing IBC (%)</th>
<th>Follow-up (years)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Page et al. (1982) [69]</td>
<td>28</td>
<td>32</td>
<td>3–31</td>
<td>9.1</td>
</tr>
<tr>
<td>Eusebi et al. (1994) [70]</td>
<td>80</td>
<td>14</td>
<td>1–14</td>
<td>NC</td>
</tr>
<tr>
<td>Collins et al. (2005) [16]</td>
<td>13</td>
<td>46</td>
<td>4–18</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; IBC, invasive breast cancer; NC, not calculated.

The Oncologist 2007;12:1276–1287

Sounds Bad! Treat aggressively!?  

Problem: Mixing biologically different High Grade/Comedo DCIS with Low Grade DCIS

Question: Does all DCIS behave the same?
DCIS is not one disease

Luminal (ER positive)

HER2

Basal (Triple Negative)
Breast cancer precursors revisited: molecular features and progression pathways

Maria A Lopez-Garcia,² Felipe C Geyer,¹ Magali Lacroix-Triki,¹,³ Caterina Marchio⁴ & Jorge S Reis-Filho³

Historical perspective of breast cancer evolution

- HUT
- ADH
- DCIS
- IDC

Lobules
Ducts

Progression

- ALH
- LCIS
- ILC
Biology of DCIS: Current Thinking Simplified

Low-Intermediate Grade DCIS:
- ER positive
- Frequent 16q and 1q abnormalities
- Detection: Screening mammography
- Risk of invasion: Extends over decades
- Type of invasion: Low –intermediate grade, ER positive

High Grade DCIS:
- More frequently ER negative
- Frequent HER2 amplification, p53 mutations
- Detection: Mass or screening mammography
- Risk of invasion: Typically within a decade
- Type of invasion: High grade, HER2 positive
The Natural History of Low-Grade Ductal Carcinoma in Situ of the Breast in Women Treated by Biopsy Only Revealed Over 30 Years of Long-Term Follow-Up

Melinda E. Sanders, M.D.\textsuperscript{1}  
Peggy A. Schuyler, R.N.\textsuperscript{2}  
William D. Dupont, Ph.D.\textsuperscript{2}  
David L. Page, M.D.\textsuperscript{1}


- 28 women with low grade DCIS treated with excisional biopsy alone
- 57% with no additional events
- 3.5% with DCIS recurrence at 27 years
- 39% developed invasion
  - 7 within 5-10 years, 3 > 15
  - 5 with distant mets and died 1-7 years after invasive diagnosis

\textbf{FIGURE 1.} This chart illustrates the cumulative incidence of invasive breast carcinoma (using the Kaplan–Meier method) for women with small, noncomedo ductal carcinoma in situ (DCIS) at biopsy who were followed without further therapy. Deaths from breast carcinoma are noted by crosses.
DCIS has changed with screening

<table>
<thead>
<tr>
<th></th>
<th>Pre-Screening Era</th>
<th>Screening Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Low (1-2% of breast cancers)</td>
<td>High (20-30% of breast cancers)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Palpable Mass</td>
<td>Non-palpable</td>
</tr>
<tr>
<td>Biopsy sampling</td>
<td>Excision</td>
<td>Core</td>
</tr>
<tr>
<td>Treatment</td>
<td>Mastectomy</td>
<td>Lumpectomy, XRT, HRT</td>
</tr>
</tbody>
</table>

Getting more of the low end of the spectrum!
Most “natural history” studies were done on samples from the pre-screening era.

Overdiagnosis?
ADH vs DCIS Biology Summary

- ADH is often neoplastic and can result in invasion
  - Non-obligate precursor biologically
- ADH has a scattered rather than locally “excisable” growth pattern
  - Treated as a risk lesion clinically (role for hormonal therapies in some cases)
- DCIS is a surgical disease with a risk of local invasion over time (risk is much higher for HG DCIS)
Case #5

• 39 year old with strong family history of breast cancer undergoing MRI screening with 1.5 cm area of NMLE
Diagnosis?

A. Micropapillary usual ductal hyperplasia
B. Micropapillary atypical ductal hyperplasia
C. Micropapillary DCIS
Micropapillary DCIS
Case #6

- 55 year old with 2.0 cm of clustered calcifications on screening mammogram and prior core biopsy of ADH
Case #7

- 43 year old with 0.6 cm of clustered calcifications on screening mammogram
FEA

- Diagnostic agreement issues similar to ADH
- Present most often in association with other risk lesions (ADH, ALH, LCIS) **DO LEVELS!!**
- Associated with similar molecular abnormalities as concurrent ADH, low grade DCIS and invasion (very early step in neoplastic progression) **LOOK NEXT TO ADH AND LG DCIS TO RECOGNIZE FEA**
- Upgrade rates on excision 5-20% with most recent studies suggesting 0-3% for pure FEA
Summary of Intraductal Proliferative Lesions

- Minimal LG DCIS vs ADH:
  - Poor diagnostic agreement
  - Not biologically distinct (spectrum) but have different growth patterns, risks and treatments (currently)
  - Often occur intermixed together (estimation of size and margin status a challenge)
  - Remember core biopsy samples are just initial sampling (don’t overcall)
What to do?

• Need for practice policies to address issues
  – Second reviews (within practice or from specialist)
  – Consensus conferences
  – Test set/consensus set circulation
  – Commenting on specific extent/limitations of sample
  – Radiology and clinical correlation
  – How to treat may be what needs to change
THANK YOU

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Case #8

- 37 year old with a 6 cm area of abnormal enhancement on MRI with lumpectomy
Tips in DCIS Grossing, Examination and Reporting

- Correct estimation of size requires adequate grossing
- Not missing invasion (esp in HG DCIS)- using panCK in addition to myoepithelial markers
- Margin inking and reporting
THANK YOU