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

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
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

Clinical Impact of Core Biopsy Diagnosis

- UDH → No further management
- ADH → Surgical consultation with excisional biopsy to rule out adjacent DCIS or invasion
- Borderline lesion not definite DCIS – get more tissue!
- DCIS → Surgical excision to negative margins (lumpectomy+XRT or mastectomy) +/- hormonal therapy if ER+

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

Excisional biopsy:

Focal 12 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

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

- Pathologist-related:
  - Intraobserver variability in interpreting diagnostic criteria
  - Interobserver variability in applying diagnostic criteria

Figure 2. (A&B): Two of the three experts focused on the same lesion, classified this case as ADH, and one classified it as DCIS. During consensus review discussion, there was agreement about the architectural and cytologic features that support a diagnosis of low-grade DCIS, but there was disagreement about the architectural changes present in the lesion that support a diagnosis of low-grade ADH (C: 195x400). Two of three
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

Of participants reporting no second opinion policy for ADH:
- 83.9% obtained second opinions in at least some cases
- 28.0% in all cases

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>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 Bilateral</td>
</tr>
<tr>
<td>Atypical Lobular Hyperplasia (ALH)</td>
<td>4-5 x Bilateral</td>
</tr>
<tr>
<td>Lobular Carcinoma in Situ (LCIS)</td>
<td>8-10 x Bilateral</td>
</tr>
<tr>
<td>Ductal Carcinoma in Situ (DCIS)</td>
<td>8-10 x Bilateral</td>
</tr>
</tbody>
</table>

Anatomic Distribution: Traditional Thinking

- **Risk Lesion**
- **Precursor Lesion**
- Non-surgical
- Remove Surgically

Biology of ADH

- PCR-based clonality assay

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>References</th>
<th>n of patients</th>
<th>Patients developing</th>
<th>Follow-up (years)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris et al. (1995)</td>
<td>15</td>
<td>51</td>
<td>1.26</td>
<td>NC</td>
</tr>
<tr>
<td>Page et al. (1992)</td>
<td>20</td>
<td>52</td>
<td>0.31</td>
<td>0.1</td>
</tr>
<tr>
<td>Ellis et al. (1986)</td>
<td>80</td>
<td>84</td>
<td>1.14</td>
<td>NC</td>
</tr>
<tr>
<td>Collins et al. (2005)</td>
<td>76</td>
<td>66</td>
<td>0.138</td>
<td>1.3</td>
</tr>
</tbody>
</table>

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

DCIS is not one disease

Sounds Bad! Treat aggressively?

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

Question: Does all DCIS behave the same?
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

Higher Risk Precursor
Lower Risk Precursor

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

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 Mass</td>
</tr>
<tr>
<td>Biopsy sampling</td>
<td>Excision</td>
<td>Core biopsy</td>
</tr>
<tr>
<td>Treatment</td>
<td>Mastectomy</td>
<td>Lumpectomy, XRT, HRT</td>
</tr>
</tbody>
</table>

Most “natural history” studies were done on samples from the pre-screening era.

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
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
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

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

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)

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