Pathology of Lobular & Ductal Preneoplasia

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Proliferative Epithelial Changes in Breast

- A wide range of proliferative epithelial changes occur in the breast
- There is evidence of a relationship between degree of proliferation & likelihood of developing invasive carcinoma
Evidence of Relationship between Proliferative Changes and Carcinoma

- Most carcinomas usually have proliferative changes in their vicinity
- Some women with proliferative changes develop carcinoma
- ↑ proliferation is common in such settings
- Some molecular alterations in proliferative changes parallel those of carcinoma
**Degrees of Epithelial Hyperplasia**

- Usually classified as *Mild, Moderate & Florid*
- Hyperplasia is *Atypical* when it is abnormal, i.e. not of the usual type
- Atypical hyperplasia can occur in ducts, *Atypical Ductal Hyperplasia (ADH)*, or in lobules, *Atypical Lobular Hyperplasia (ALH)*
ADH & ALH have some, but not all, histological features of *in situ* carcinoma

ADH & ALH diagnosed in ~4% of cases, ~10% now

ADH & ALH confer ↑ risk for invasive carcinoma

## Risk Groupings per College of American Pathologists (CAP)

<table>
<thead>
<tr>
<th>Degree of Hyperplasia</th>
<th>Increased Risk</th>
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<tbody>
<tr>
<td>Mild</td>
<td>none</td>
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<tr>
<td>Moderate-Florid</td>
<td>1.5x-2x</td>
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<tr>
<td>ADH</td>
<td>5x</td>
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<tr>
<td>DCIS</td>
<td>8x-10x</td>
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Breast: Microanatomy & Disease Location

- ALH
- ADH
WHO 2012 Definition of Atypical Ductal Hyperplasia

- “ADH is a proliferation of monomorphic, evenly placed, epithelial cells involving terminal duct lobular units”

The increased risk applies to both breasts
Mean age: ~50, Prevalence: ~4%

WHO Classification of Breast Tumours 4e, 2012
Problems with Definition of Atypical Ductal Hyperplasia

- Interobserver variability
- Multiple histological patterns
- Quantitative criteria variably used, e.g.
  - <2 mm: ADH, >2 mm: DCIS
  - <2 ducts: ADH, >2 ducts: DCIS

Routine Microscopy: Gold Standard for Diagnosis of ADH
Special Studies are Unhelpful in the Differential Diagnosis of ADH & DCIS

- Genetic molecular tests: 16q
- DNA ploidy status
- Morphometry
- Immunostains: cytokeratin 5/6, ER, p53
- E-cadherin stain can distinguish ALH & ADH
- ADH & ALH are both typically ER+ and PR+
Molecular Genetics of ADH

- Common genetic alterations in ADH, low-grade DCIS & invasive carcinomas
- Frequent sites of loss of heterozygosity in ADH & invasive carcinoma include chromosomes 16q, 17p & 11q
- 16q is most frequent

Ann Surg Oncol 2010;17:1688
Clinical Significance of ADH

- Page: 12% of ADH cases developed invasive carcinoma at an average of 16 years
- Mayo: 20% of ADH cases developed carcinoma, including DCIS, in 13 years. Risk to both breasts

ADH: Cumulative Risk of Breast Carcinoma, Effect of Extent & Calcifications

J Clin Oncol 2007;25:2671
Management of ADH

- ADH on Core: Excision ~15% upgrade
- ADH on Excision with
  - negative margin: No further surgery
  - involved margin, focal: No further surgery
  - Involved margin, diffuse: ? Manage as DCIS

Kuerer’s Surgical Oncology 2010

- Consider risk-reduction therapy, i.e. tamoxifen, raloxifene, AI, in selected high-risk patients
Atypical Lobular Hyperplasia

- ALH
- ADH

- Intraductal papilloma
- Adenoma
- Paget's disease
- Duct ectasia
- Cyst
- Fibroadenoma
Lobular (Pre) Neoplasia

- Lobular Hyperplasia (LH)
- Atypical Lobular Hyperplasia (ALH)
- Lobular Carcinoma *In Situ* (LCIS)

Mean age: ~49, Prevalence: ~4%
Lobular hyperplasia generally happens physiologically: in pregnancy, puerperium or pharmacologically: pills

- Uncommon diagnosis
Key Features:
Atypical Lobular Hyperplasia

- ALH has some, but not all, of the histological features of LCIS
- ALH & LCIS describe the variable extent of lesional proliferation
- Distinction between ALH & LCIS is as problematic as between ADH & DCIS
Diagnostic Criteria:
ALH & LCIS

- ALH: Less than half of the spaces in a given lobule is distended by the characteristic cells
- LCIS: More than half of the spaces in a given lobule is distended by the characteristic cells
- Criteria is quantitative, not qualitative
Routine Microscopy: Gold Standard for Diagnosis of ALH
## Risk Groupings per CAP

**ALH & LCIS**

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WHO 2012: Clinical Implication
Atypical Lobular Hyperplasia

“While ALH & LCIS represent a morphological & biological continuum, the diagnostic separation is useful...because the risk of subsequent development of invasive carcinoma associated with ALH is half that of LCIS”
Atypical Lobular Hyperplasia
Risk: Ipsilateral, Contralateral or Both?

- Early studies suggested that both breasts were at equal risk for later carcinoma development; however, recent studies show that ~2/3 of subsequent carcinomas occur in the ipsilateral breast.
“ALH & LCIS are precursors (albeit non-obligate) as well as risk factors”
Management of ALH

- ALH on Core: Correlate with Radiology Excision, if appropriate
- ALH on Excision: No further surgery

Kuerer’s Surgical Oncology 2010
Other Commonly Diagnosed Lesions Related to ADH

Columnar Cell Change
Columnar Cell Hyperplasia
&
Atypical Columnar Cell hyperplasia,
i.e. Flat Epithelial Atypia
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Normal
Columnar Cell Hyperplasia

Calcifications

Normal
Atypical Columnar Hyperplasia
i.e. Flat Epithelial Atypia

Calcifications

Normal
Flat Epithelial Atypia

- The biological significance of FEA is unclear, but may be similar to ADH, but has been associated with LCIS and tubular carcinoma
- FEA, LCIS & tubular carcinoma form The Rosen’s Triad- the 3 lesions may occur synchronously or metachronously
Women with ADH & ALH are at increased risk for development of breast carcinoma
Level of risk differs somewhat for ADH & ALH
Most ADH & ALH cases suffer no consequences
In general, clinical & radiological followup suffices
Consider risk-reduction therapy: i.e. tamoxifen, raloxifene, AI, in selected high-risk patients
Scientists Seek to Rein In Diagnoses of Cancer

“Some of the top scientists in cancer research, suggested that many lesions detected during breast…and other cancer screenings should not be called cancer at all but should instead be reclassified as IDLE conditions ‘indolent lesions of epithelial origin’ ”
“The word ‘cancer’ often invokes the specter of an inexorably lethal process; however, cancers are heterogeneous & can follow multiple paths, not all of which progress to metastases and death, and include indolent disease that causes no harm. Better biology alone can explain better outcomes”
‘Indolent Lesions of Epithelial Origin’