Proliferative, Borderline and In-situ Proliferations

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Weekends of Pathology- March 2018
No conflict of interest
Objectives

- To provide an overview of proliferative, borderline and in-situ lesions diagnosed on core needle biopsy (CNB)
- To discuss the importance of the identification of patients with these lesions
- To briefly discuss follow-up options
Each year, approx. 1.6 million breast biopsies are performed in the United States.

Approximately 20% of these biopsies carry a diagnosis of malignancy.

The majority of breast biopsies are classified within the spectrum of benign, atypical and borderline breast disease.
Background

Modified classification (from Dupont and Page 1985)

- **Non-proliferative breast changes**
  - Cysts
  - Mild hyperplasia
  - Simple fibroadenoma
  - Papillary apocrine change
  - Epithelial-related calcifications
  - Ductal ectasia
  - Non-sclerosing adenosis
  - Periductal fibrosis

- **Proliferative breast changes without atypia**
  - Complex fibroadenoma
  - Moderate-florid hyperplasia
  - Sclerosing adenosis
  - Intraductal papillomas
  - Radial scar

- **Proliferative breast changes with atypia**
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia
  - (Any of the above with atypia)
Non-proliferative changes
No elevation in breast cancer risk

Proliferative breast changes without atypia
Relative breast cancer risk: 1.3–1.9

Proliferative breast changes with atypia
Relative breast cancer risk: 3.9–13
Core needle biopsy diagnosis

- Requires multidisciplinary approach
- Availability of only limited material
- Sampling error
- Loss of calcifications during processing
- Association with a more significant lesion at excision
- Inaccurate tumor grading
- Lack of uniform diagnostic criteria and terminology
- Diagnostic difficulties with certain lesions
- Lack of consensus on managing
Core needle biopsy diagnosis
Multidisciplinary approach

- To confirm that the targeted lesion was biopsied
- To confirm that there is pathological/radiological correlation
- To confirm that there is clinical/pathological correlation
- To evaluate management options
## Core needle biopsy

### Sampling error

<table>
<thead>
<tr>
<th><strong>Pathologic Diagnosis</strong></th>
<th><strong>Incidence of malignancy after excision</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal carcinoma in situ</td>
<td>Up to 20%</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia</td>
<td>33 - 87%</td>
</tr>
<tr>
<td>Lobular neoplasia</td>
<td>13 – 28%</td>
</tr>
<tr>
<td>Radial sclerosing lesion</td>
<td>0 – 40%</td>
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<tr>
<td>Papillary lesions</td>
<td>14 – 25%</td>
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</tbody>
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Core needle biopsy

Sampling error/Processing

- Small biopsy size
- Distortion and fragmentation of the tissue samples
- Differences regarding tissue processing
- Available laboratory technology/resources
Core needle biopsy
Lack of uniform diagnostic criteria and terminology

• Variable histologic diagnostic criteria
• Variable terminology
• Confusing or inadequate terminology
• Interobserver variability
• Lack of adequate clinical history and radiologic findings
Core needle biopsy
Diagnostic difficulties

- Papillary lesions
- Mucinous lesions
- Radial sclerosing lesions
- Columnar cell changes
- Atypical proliferative lesions vs. low grade in-situ carcinoma (Borderline lesions)
- Adenosis
- Fibroepithelial lesions with cellular stroma
- Spindle cell lesions
- Residual or recurrent carcinoma after radiation
- Specific tumor types
Papillary lesions

Papillomas: Central vs. Peripheral

Central (large duct papilloma):
- Close to nipple within principal lactiferous ducts
- 90% solitary
- 70% associated with nipple discharge
- No increased risk of subsequent malignancy

Peripheral:
- Multiple
- Clinically occult, discovered by mammographic calcifications
- *Increased risk of subsequent malignancy, particularly if ADH/ALH is present*
Papillary lesions in CNB

Most commonly used terminology:

- Intraductal papilloma/ papillary lesion without atypia
- Papilloma with atypia/ atypical papilloma
- DCIS, papillary type
- In-situ papillary carcinoma
- DCIS with features of solid papillary carcinoma

DCIS: Ductal carcinoma in situ
Papillary lesions in CNB

When to use the terms “atypical papilloma”, “DCIS, papillary type” and “in-situ papillary carcinoma”?

**Papilloma with atypia:**
- Basic lesion is a papilloma
- Morphologic features of atypia/low nuclear grade DCIS
  - Atypia in <33% of the papilloma
  - Atypia in 33-90% of the papilloma = Carcinoma arising in papilloma
  - ADH focus involving <3 mm/Atypical papilloma
  - Atypical focus involving >3 mm = DCIS arising within a papilloma

**DCIS, papillary type:**
- Usually admixed with other morphologic types of DCIS
- Retain a myoepithelial cell layer

**In situ papillary carcinoma:**
- Fragmented biopsy
- Doubtful regarding invasion or type of papillary lesion
Columnar cell changes

- Often associated with microcalcifications detected on mammogram
- Classified as columnar cell change (CCC) and columnar cell hyperplasia
- Each of these categories can have associated atypia
- Atypical columnar cell lesions are also known as flat epithelial atypia

Because CCC has been referred to by several different names in the literature, data on its significance as a risk marker for development of invasive cancer or the risk of finding adjacent associated malignancy are limited
Columnar cell changes

- Columnar cell lesions should be examined at intermediate or high magnification because atypia may be unapparent at low power

- CCC-atypia (low-moderate)
  - Two layers
    - CCC atypia (flat epithelial atypia)
  - More than 2 layers
    - No or minimal architectural changes
      - Columnar cell hyperplasia with atypia
    - Complex architectural changes
      - ADH
  - Flat high-grade DCIS
  - CCC-high grade atypia
Proliferative changes without atypia
Usual ductal hyperplasia

**Architectural features**
- Irregular fenestrations
- Peripheral fenestrations
- Stretched or twisted bridges
- Streaming
- Overlapped nuclei

**Cellular features**
- Multiple cell types (epithelial, myoepithelial, apocrine)
- Variation in appearance of epithelial cells
- Indistinct cell margins
- Variation in nuclear appearance
Ductal proliferations
Ductal hyperplasia of usual type, florid
Borderline breast disease
Atypical ductal hyperplasia

- A neoplastic proliferation of evenly distributed, monomorphutic cells similar to those of low-grade DCIS
- The cells do not fill or distend the entire acini within a lobule
- Architectural atypia does not involve the entire duct
- Lesion is less than 2 mm or 2 contiguous ducts
Ductal proliferations
Atypical ductal hyperplasia

- Size
- Duct involvement
Core needle biopsy

Adenosis

- Adenosis can cause diagnostic problems especially in CNB
- Microglandular adenosis is the only benign lesion with an infiltrative growth pattern and absence of myoepithelial cells
- Use myoepithelial cell markers in difficult cases and be conservative in small biopsies
Sclerosing adenosis

• A benign lobulocentric lesion with significant sclerotic stromal changes

• SA can be associated with perineural and perivascular invasion

• Relative risk for development of invasive carcinoma is approx. 1.7
Core needle biopsy

Adenosis

Microglandular adenosis

- The glands contain deep eosinophilic colloid-like intraluminal secretion
- The glands are round and not angulated as seen in tubular carcinoma
- ER, PR negative
- S-100 positive
Core needle biopsy
To excise or NOT to excise?

- There is current consensus that lesions diagnosed as "atypical" on minimally invasive procedures should be excised
Core needle biopsy
Excise or NOT excise, that is the question!
What to do with some proliferative lesions without atypia diagnosed on CNB?
Core needle biopsy

Diagnostic difficulties
To excise or NOT to excise?

Problems with current studies
- Selection criteria
- Terminology, grading, interobserver variability
- Present of other premalignant/atypical lesions in the same biopsy
- The extent of core needle biopsy sampling
- The way biopsies are processed
Core needle biopsy
To excise or NOT to excise?

- There is radiologic–pathologic disagreement
- Sampling technique:
  - Needle gauge
  - Number of cores
  - Use of vacuum-assisted techniques
- Size of the lesion
- Patient’s age and personal or family history of breast cancer
Core needle biopsy diagnosis

Summary

- Pathologists carry a major responsibility in patient diagnosis, risk stratification and management.
- Despite attempts to refine and improve the diagnostic accuracy of atypia in CNB, there are still substantial differences in the interpretation and management of “borderline” lesions.
- In some cases, excisional biopsy is the only reliable method for establishing the presence of prognostically significant lesions.
References: