In Situ Lesions of the Breast

Normal Anatomy

**Terminal Duct Lobular Unit (TDLU)**
Increasingly small branching ducts terminate in clusters of acini called lobules.

Milk flow: Acini → ducts → collecting ducts → Nipple

Set in fibrous stroma with varying amounts of adipose tissue

*Two cell layers:*

1) **Inner Epithelial cell**
   - Cuboidal to columnar cells with eosinophilic cytoplasm and oval nuclei.
   - Stain with LMW cytokeratins (e.g., CK7)

2) **Outer myoepithelial cell**
   - Flat (sometimes barely visible) to plump with abundant clear cytoplasm. Stain with Actin, calponin, SMMHC, p63, CK5/6, S100

In Situ Lesions

**Usual Ductal Hyperplasia (UDH)**

Benign epithelial proliferation that is architecturally, cytologically, and molecularly heterogeneous.

**Think: “Polyclonal”**

Cohesive proliferation with *haphazard* architecture

**Irregular, slit-like lumina**, often peripherally located

Streaming, syncytial pattern

**Variably sized cells** with indistinct borders

Overlapping nuclei

Frequent nuclear grooves, some pseudoinclusions

Any bridges are thin and stretched

Any micropapillae have broad bases and narrow tips with small pyknotic nuclei

Cells stain with a mixture of low-molecular weight cytokeratins (e.g., CK7) and high-molecular with CKs (e.g., CK5/6). Heterogeneous ER staining.

~2x Relative Risk of Developing Cancer

Treatment: None needed
<table>
<thead>
<tr>
<th></th>
<th>UDH</th>
<th>Low-grade DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Think: “Polyclonal”</td>
<td></td>
<td>Think: “Monoclonal”</td>
</tr>
<tr>
<td>Irregular, Slit-like lumina, often peripheral</td>
<td></td>
<td>Regular, punched out lumina, often central</td>
</tr>
<tr>
<td>Streaming architecture, minimal polarization</td>
<td></td>
<td>Prominent polarization</td>
</tr>
<tr>
<td>Variation in cell size/shape</td>
<td></td>
<td>Monomorphic cells/shape</td>
</tr>
<tr>
<td>Indistinct cell margins</td>
<td></td>
<td>Distinct cell margins</td>
</tr>
<tr>
<td>Admixture of cell types (epithelial, myoepithelial and/or apocrine): Stain with high and low-molecular weight cytokeratins</td>
<td>Proliferating cells are epithelial. Myoepithelial cells are against the basement membrane: Epithelium stains with low-molecular weight cytokeratins only</td>
<td></td>
</tr>
<tr>
<td>Heterogeneous ER staining</td>
<td></td>
<td>Strong, diffuse ER staining</td>
</tr>
</tbody>
</table>

**UDH**

**Low-grade DCIS**

<table>
<thead>
<tr>
<th>CK5/6</th>
<th><img src="image1.png" alt="CK5/6 UDH" /></th>
<th><img src="image2.png" alt="CK5/6 Low-grade DCIS" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td><img src="image3.png" alt="ER UDH" /></td>
<td><img src="image4.png" alt="ER Low-grade DCIS" /></td>
</tr>
</tbody>
</table>
Ductal Carcinoma In Situ (DCIS)

Non-invasive neoplastic epithelial proliferation

Often detected on mammography (e.g., linear calcifications)

Often limited to one duct system, but can involve lobules (“Cancerization of the lobule”) and/or can “skip” around in duct

Graded based on nuclear morphology, but can be varying grades within one case due to tumor heterogeneity (Grade NOT architecture based)

Low-grade DCIS

Think: “Monoclonal”

Small, monomorphic cells
  - Uniform size and shape
  - Regular chromatin; small nucleoli
  - 1.5-2x size of RBC
  - Few mitoses

Often cribriform or micropapillary growth
  - Often forms microrosettes/glands with polarization around the gland
  - Sometimes solid growth

Calcifications common. Necrosis uncommon.

Size requirement: >2mm and involving more than two complete spaces

High-grade DCIS:

Think: “Pleomorphic, Ugly”

Large, ugly cells
  - Irregular contours, course chromatin
  - Often prominent nucleoli
  - >2.5-3x the size of an RBC
  - Lots of mitoses

Often solid architecture
  - Minimal/no polarization
  - Comedo necrosis common
  - Sometimes single layer of cells (“Clinging carcinoma”). Uncommonly cribriform or micropapillary

Size requirement: None!!

Intermediate-grade DCIS:

In between low and high-grade
Moderate variability, size, polarization
May have necrosis and/or calcifications

~10x Relative Risk of Cancer in ipsilateral breast

Treatment: Excision with “wide” negative margins
Possibly +/- radiation and/or hormone therapy
### Low-grade DCIS vs. High-grade DCIS

<table>
<thead>
<tr>
<th>Low-grade DCIS</th>
<th>High-grade DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small, monomorphic cells</td>
<td>Large, pleomorphic cells</td>
</tr>
<tr>
<td>1.5-2x size of RBC</td>
<td>&gt;2.5x size of RBC</td>
</tr>
<tr>
<td>Regular nuclear contours</td>
<td>Irregular nuclear contours</td>
</tr>
<tr>
<td>Even chromatin</td>
<td>Course chromatin</td>
</tr>
<tr>
<td>Inconspicuous nucleoli</td>
<td>Prominent nucleoli</td>
</tr>
<tr>
<td>Usually cribriform or micropapillary growth</td>
<td>Usually solid growth, but any architecture can be present</td>
</tr>
<tr>
<td>Polarization around lumina</td>
<td>No polarization around lumina</td>
</tr>
<tr>
<td>Necrosis uncommon</td>
<td>Necrosis common</td>
</tr>
<tr>
<td>Must be &gt;2mm</td>
<td>No size requirement</td>
</tr>
<tr>
<td>ER and PR positive frequently</td>
<td>ER and PR negative more frequently</td>
</tr>
<tr>
<td>HER2 negative frequently</td>
<td>HER2 positive frequently</td>
</tr>
<tr>
<td>Few mitoses</td>
<td>Many mitoses</td>
</tr>
<tr>
<td>Low-grade associated cancers</td>
<td>High-grade associated cancers</td>
</tr>
</tbody>
</table>

### Atypical Ductal Hyperplasia (ADH)

Non-invasive neoplastic epithelial proliferation resembling DCIS (similar cytology and architecture), **BUT** less developed in architecture or extent

Similarly genetically to low-grade DCIS → clonally related, just smaller or questionable architecture

**Size: ≤2mm and <2 duct spaces**

**Cells (same as low-grade DCIS):**
- Evenly spaced monotonous cells
- Round nuclei with dense chromatin

**Architecture:**
- **Cribriform**
- Rigid bridges, arcades, and bars
- **Bulbous micropapillae** (with narrow bases and wide tips)

~4-5x relative risk of breast cancer

Treatment: if on Bx → surgical excision to exclude DCIS/carcinoma; On excision → Nothing more
Step-wise Diagnosis

**Evaluate Cytology:** Is it High-grade or Intermediate-grade?

- No
- Unsure
- Yes

**Cytology low-grade (bland)**

- Is the cytology monotonous/clonal appearing?
  - No
  - Unsure
  - Yes

  - Polymorphous/polygonal appearing
  - Unsure if cytology is clonal
  - Monotonous/Clonal appearing

  **Evaluate Architecture:** Are there neoplastic architectural features present?

- No or Unsure
- Cytology Polyclonal
- Cytology Monotonous/Clonal cytology

- UDH vs ADH
- Solid or Subtle architecture
- Flat process
- FEA

- ADH or ALH/LCIS
- < 2 mm
- 2-3 mm
- > 3mm

**Evaluate Extent**

- Non-uniform
- Uniform Throughout Lesion

**Distinguishing DCIS from LCIS:**

<table>
<thead>
<tr>
<th>Feature</th>
<th>LCIS</th>
<th>DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of cohesion</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Intracytoplasmic vacuoles</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Pagetoid ductal involvement</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Microacini</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Polarization at duct periphery</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
**Columnar Cell Change**

Clonal alterations of the TDLU characterized by enlarged, variably dilated acini lined by **columnar epithelial cells arranged perpendicular to the basement membrane**; 1-2 cells thick

**Apical snouts**, secretions and calcification are often present

Earliest step in low-grade carcinoma pathway

Not infrequently associated with ADH, low grade DCIS, or invasive carcinoma, but risk of developing a subsequent carcinoma is negligible, so excision is **not** indicated

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**Flat Epithelial Atypia (FEA)**

Similar to columnar cell change (in dilated TDLUs), but lined by **1-2 layers of cells with enlarged round to oval nuclei**

(same cells as in ADH/low grade DCIS!)

Complex architecture of the type seen in ADH/low grade DCIS is **not** allowed

Apical snouts, secretions and calcification may be present

Frequently associated with DCIS/cancer, so if found on core biopsy, it is an indication for excision (to exclude a worse lesion nearby). No further treatment on excision.

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**Radial Scar / Complex Sclerosing Lesion**

Benign lesion with **fibroelastosis with entrapped glandular structures**, ± Proliferative epithelial lesions (e.g., UDH)

**Radial scar** → smaller with stellate configuration

**Complex sclerosing lesion** → larger and more disorganized

Dense, hyalinized, elastotic stroma

Two cell layers maintained throughout

Excision somewhat controversial, often excised

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*Often may want to do myoepithelial stains to confirm no invasive component given complexity*
Epithelial proliferations originating in the TDLU characterized by:

- Small, discohesive monomorphic cells
- E-cadherin inactivation → Loss of membranous E-cadherin staining → cellular discohesion
  - Note: Up to 15% of lobular lesions retain E-cad, but with an aberrant staining pattern
- CDH1 mutations common (same gene as hereditary diffuse gastric cancer)

**Atypical Lobular Hyperplasia (ALH)**
Solid proliferation of discohesive, monomorphic epithelial cells expanding <50% of the acini in a TDLU
If incidental on a biopsy, no need to excise

**Lobular Carcinoma In Situ (LCIS)**
>50% of the acini are filled and expanded
Often >8 cells thick
Non-obligate precursor to invasive lobular carcinoma
~8-10x Relative Risk of Cancer
If incidental on a biopsy, no need to excise
On excision, margins don’t matter

**LCIS Subtypes:**

**Pleomorphic LCIS**—composed of large cells (>4x size of a lymphocyte) with marked nuclear pleomorphism

**Florid LCIS**—classic LCIS cells, but forming a confluent mass-like lesion with little to no intervening stroma between distended TDLUs (often ~50 cells in diameter)

Both of these subtypes exhibit greater genomic instability → behave more aggressively → excise with negative margins

<table>
<thead>
<tr>
<th>IHC Stain</th>
<th>Normal Epithelium</th>
<th>Lobular Neoplasia</th>
<th>DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Cadherin</td>
<td>Membrane staining</td>
<td>Negative</td>
<td>Membrane staining</td>
</tr>
<tr>
<td>P120 catenin</td>
<td>Membrane staining</td>
<td>Cytoplasmic</td>
<td>Membrane staining</td>
</tr>
<tr>
<td>β-catenin</td>
<td>Membrane staining</td>
<td>Absence of membrane staining</td>
<td>Membrane staining</td>
</tr>
</tbody>
</table>
Sclerosing Adenosis

Very common
Lobulocentric proliferation of acini and tubules accompanied by compressing fibrosis

Epithelial cells are often cuboidal, small, and bland
Myoepithelial cells have spindled, hyperchromatic nuclei and inconspicuous to prominent clear cytoplasm
Can highlight myoep's with IHC stains if necessary

Microcalcifications are common
Can extend into fat occasionally
Can be involved by epithelial proliferations (e.g., UDH)
Primarily significant as it can be confused with carcinoma

Lactating Adenoma

Benign breast nodule diagnosed during pregnancy or breast feeding, that is composed of an aggregate of glands with lactational change

Well-circumscribed proliferation of closely packed hyperplastic secretory lobules separated by delicate connective tissue
Cuboidal to hobnailed epithelial cells are bland with vacuolated to granular cytoplasm and small, uniform, pinpoint nuclei
Spontaneously regress when done lactating

Microglandular adenosis

Haphazard proliferation of small, round, uniform, tubular glands composed of a single layer of epithelium (without associated myoepithelial cells!)

Luminal spaces are open and often contain an eosinophilic colloid-like secretion
Small bland nuclei with amphophilic cytoplasm
IHC: Cells stain with CKs and S100, Negative for ER, PR, and HER2
Myoepithelial stains negative
Benign, but thought to be a non-obligate precursor to basal-type breast cancer

DDX:
Sclerosing adenosis → S100 Neg, Myoep intact
Tubular carcinoma → ER pos, S100 Neg
**Tubular Adenoma**


Well-circumscribed, sharply demarcated, dense proliferation of closely approximated round to oval tubular structures with little background stroma.

Glands have usual two layers: Epithelium and myoepithelium.

May be related to fibroadenomas histogenetically (but just stroma poor)

**Apocrine Adenosis**

= Apocrine metaplasia + Sclerosing adenosis

Lobulocentric proliferation of benign glandular structures composed of cells with abundant granular cytoplasm distorted by fibrosis.

Enlarged, round nuclei with prominent nucleoli.

Often have apical “snouts”

Intact myoepithelial cells → can highlight with IHC.

Cells typically ER-negative, AR-positive, and positive for GCDFP-15.

If significant cytologic atypia (≥3:1 size variation, mitotic activity) → Atypical Apocrine Adenosis.

If complex architecture (e.g., cribriform growth) or very marked pleomorphism, → Apocrine DCIS.

**Collagenous Spherulosis**

Intraductal deposits of basement membrane: Appear as hyaline, acellular, eosinophilic spherules or fibropapillary, amorphous eosinophilic to mucoid material.

Myoepithelial cells surround the lumina and are often compressed and spindle-shaped.

Can be calcified. Commonly seen with papillomas, UDH, or sclerosing lesions.

Main importance is to recognize that it is benign and NOT DCIS or adenoid cystic carcinoma.
Bilateral, diffuse or discrete retroareolar masses. Most common lesion of the male breast.

Caused by androgen/estrogen imbalance. Physiologic in infants, children, and adolescents. In a minority, often older age, it is pathologic and associated with endocrine abnormalities (Klinefelter syndrome, obesity, cirrhosis) and certain drugs (e.g., spironolactone and marijuana).

**Histologic appearance varies with duration/stage:**

**Early**

- Loose periductal stroma
- Mixed chronic inflammatory infiltrate
- Extensive epithelial hyperplasia with tapering tufts *(pyramid-shaped micropapillae)* and protrusion into lumen (like what is seen in juvenile fibroadenomas), so have a high threshold for calling DCIS/ADH

**Late**

- Fibrosis and hyalinization of periductal stroma
- Atrophy of epithelium
- Can se pseudoangiomatous hyperplasia (PASH)

**Not** associated with any risk of cancer

Usually no treatment necessary

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**Male breast histology:**

Contains fibrous stroma and branching ducts and terminal ductules, but extremely few (if any) acini.