Benign Mimics of Malignancy in Breast Pathology

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Many Benign Lesions of the Breast Can Mimic Malignant Lesions
<table>
<thead>
<tr>
<th>BENIGN</th>
<th>MALIGNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerosing adenosis</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Tubular adenosis</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Microglandular adenosis</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Radial scar</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Complex sclerosing lesion</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Sclerosing papilloma</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Displaced epithelium s/p core needle biopsy</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Nipple adenoma</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Granular cell tumor</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Myofibroblastoma, epithelioid</td>
<td>Invasive carcinoma</td>
</tr>
<tr>
<td>Mucocele-like lesions</td>
<td>Mucinous carcinoma</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>Papillary carcinoma</td>
</tr>
<tr>
<td>BENIGN</td>
<td>MALIGNANT</td>
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<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
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<tr>
<td>Collagenous spherulosis</td>
<td>Adenoid cystic carcinoma</td>
</tr>
<tr>
<td>Benign/reactive spindle cell lesions</td>
<td>Metaplastic carcinoma, sarcoma</td>
</tr>
<tr>
<td>Squamous metaplasia</td>
<td>Metaplastic carcinoma</td>
</tr>
<tr>
<td>Chondroid metaplasia</td>
<td>Metaplastic carcinoma</td>
</tr>
<tr>
<td>Toker cells/hyperplasia</td>
<td>Paget disease</td>
</tr>
<tr>
<td>Pseudoangiomatosous stromal hyperplasia</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Benign vascular lesions</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Angiolipoma (esp. cellular var.)</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Treatment effects (RT, chemo) on normal epithelium</td>
<td>DCIS, invasive carcinoma</td>
</tr>
<tr>
<td>Benign inclusions in axillary lymph nodes</td>
<td>Metastatic carcinoma</td>
</tr>
</tbody>
</table>
Factors Contributing to the Difficulty In Distinguishing Benign Mimics from Malignancy in Breast Pathology

- Lack of awareness of, or familiarity with, the benign entity
- Failure to recognize key (and sometimes subtle) histologic or cytologic features of value in the differential diagnosis
- Criteria to distinguish between benign and malignant lesions poorly-defined
- Failure to use appropriate immunostains
- Failure to understand the limitations and pitfalls of immunostains that are used
- Limited sampling (core needle biopsy)
Topics to be Discussed
(Emphasizing Recent Information)

• Benign sclerosing lesions vs invasive carcinoma
• Mucocele-like lesions vs mucinous carcinoma
• Benign inclusions in lymph nodes vs metastatic carcinoma
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(Emphasizing Recent Information)

• Benign sclerosing lesions vs invasive carcinoma
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A Variety of Benign Sclerosing Lesions Can Mimic Invasive Breast Cancer
A Variety of Benign Sclerosing Lesions Can Mimic Invasive Breast Cancer

Sclerosing Adenosis
A Variety of Benign Sclerosing Lesions Can Mimic Invasive Breast Cancer

Radial Scar
A Variety of Benign Sclerosing Lesions Can Mimic Invasive Breast Cancer

Complex Sclerosing Lesion
A Variety of Benign Sclerosing Lesions Can Mimic Invasive Breast Cancer

Sclerosing Papilloma
Common Theme

- Presence within fibrous stroma of epithelial/glandular elements; produce patterns mimicking invasive carcinoma (especially low grade carcinomas)
Even More Problematic When Sclerosing Lesion Colonized by in situ Carcinoma

LCIS involving Sclerosing Adenosis
Even More Problematic When Sclerosing Lesion Colonized by in situ Carcinoma

DCIS involving Sclerosing Adenosis
Distinguishing Sclerosing Lesions from Invasive Carcinoma

- Histologic features
- Immunostains for myoepithelial cells (not basement membrane)
Histologic Features

• Favor sclerosing lesion:
  – Lobulocentricity (sclerosing adenosis)
  – Zonation (radial scar, CSL)
  – Dense, hyalinized, fibroelastotic stroma (radial scar, CSL)
  – Myoepithelial cells around glands/cell nests
  – Associated UDH
Histologic Features

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• Favor invasive carcinoma:
  – Haphazard, non-lobulocentric pattern; glands in fat
  – Desmoplastic/cellular stroma
  – No myoepithelial cells around glands/cell nests
  – Associated CIS
Low Power is KEY!!

Sclerosing Adenosis
Low Power is KEY!!

Radial Scar
Low Power is KEY!!

Tubular Carcinoma
Myoepithelial Cells
Myoepithelial Cells May Be Difficult to Identify on H&E-Stained Sections No Matter How Good Your Eyes Are

Sclerosing Adenosis

Complex Sclerosing Lesion
Distinguishing Sclerosing Lesions from Invasive Carcinoma

• Histologic features

• Immunostains for myoepithelial cells
Invasive Cancer

No Myoepithelial Cells

Notable Exception: Microglandular Adenosis
Myoepithelial Cell Markers in the 1980’s

Yasmine M. Hijazi, M.D.
James L. Lessard, Ph.D.
Mark A. Weiss, M.D.

Use of anti-actin and S-100 protein antibodies in differentiating benign and malignant sclerosing breast lesions
Myoepithelial Cell Markers in 2013

- Actins
- S-100
- Smooth muscle myosin heavy chain
  - Calponin
    - p63
  - Maspin
    - CD10
    - p75
    - D2-40
    - WT-1
    - HMW-CK
  - P-cadherin
  - 14-3-3 sigma
DCIS involving sclerosing adenosis
Invasive ductal carcinoma, grade 1
Complex sclerosing lesion with invasive ductal carcinoma and DCIS
Antibody Cocktails

- Combinations of MEC markers (e.g., SMMHC+p63)
- Combination of MEC marker(s) and cytokeratin antibody
  - Most useful for identifying microinvasion
- Some commercially available
Potential Pitfalls in the Use of Myoepithelial Cell Markers

- Markers vary in specificity and sensitivity
- Myoepithelial cells may not be uniformly distributed throughout a benign or in situ lesion
- Myoepithelial cells associated with some lesions may have an immunophenotype that differs from that of myoepithelial cells surrounding normal structures
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First and Second Generation Myoepithelial Cell Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-100</td>
<td>Good</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Actin</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>SMMHC</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Calponin</td>
<td>Excellent</td>
<td>Very good</td>
</tr>
<tr>
<td>HMW-CK</td>
<td>Very Good</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Myofibroblast Staining

Actin > Calponin > SMMHC
Antibody to human podoplanin
Used to identify lymphatic spaces
Stains MEC in a pattern similar to calponin but less intense
Less myofibroblast staining
In Situ Carcinoma Mimicking LVI
D2-40 Stain

Rabban and Chen, 2008
LVI Mimicking DCIS
D2-40 Stain

Rabban and Chen, 2008
Potential Pitfalls in the Use of Myoepithelial Cell Markers

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• Myoepithelial cells associated with some lesions may have an immunophenotype that differs from that of myoepithelial cells surrounding normal structures
• DCIS-associated myoepithelial cells show phenotypic differences from normal myoepithelial cells
  – Reduced expression of SMMHC in 3/4 of cases
  – Reduced expression of CD10 and CK 5/6 in 1/3 of cases
• Myoepithelial cells associated with benign sclerosing lesions show phenotypic differences from normal myoepithelial cells
  – Reduced expression of CK5/6 in 1/3 of cases
  – Reduced expression of SMMHC in 16% of cases
Summary

• DCIS-associated MEC and MEC associated with benign sclerosing lesions exhibit immunophenotypic differences from normal MEC

• Biological significance

• Practical implications:
  – sensitivity of MEC markers for DCIS-associated MEC and MEC associated with sclerosing lesions varies and differs from their sensitivity for normal MEC
  – Don’t base diagnosis of invasion on absence of MEC using only one marker
Topics to be Discussed
(Emphasizing Recent Information)

• Benign sclerosing lesions vs invasive carcinoma
• Mucocele-like lesions vs mucinous carcinoma
• Benign inclusions in lymph nodes vs metastatic carcinoma
Mucinous Carcinoma

- Pure form accounts for ~2% of breast cancers
- On average, pts older than those with NST carcinomas (but wide age range)
- Gross: Circumscribed, bosselated; gelatinous cut surface
- Micro:
  - Neoplastic cell nests/glands in mucin pools
  - Cells usually have low or intermediate grade nuclei; rarely high grade
Capella C, Eusebi V, Mann B, Azzopardi JG. Endocrine differentiation in mucoid carcinoma of the breast. Histopathol 1980;4:613
Mucocele-Like Lesion

- Palpable mass, mammographically detected, or incidental
- Gross: Gelatinous cut surface
- Micro:
  - Dilated mucin-filled ducts/cysts
  - Stromal mucin extravasation
  - Ductal epithelium can range from attenuated to UDH to ADH to DCIS
CAUTION!

- Detached strips or fragments of epithelium derived from duct or cyst lining may be present within mucin of mucocele-like lesions
- Should not be viewed as evidence of mucinous carcinoma
But, this may not be so straightforward when the mucocele-like lesion is associated with DCIS
Mucin Pools + Neoplastic Cell Nests = Invasive mucinous carcinoma

Or, does it ????????
Invasive mucinous ca
or
Mucocele-like lesion
with detached fragments of DCIS?
Sometimes you just can’t be sure!
Potentially Helpful in Distinguishing Mucocele-like Lesion with Displaced Epithelial Cells from Mucinous Carcinoma

- Myoepithelial cell immunostains
- Vascularization of mucin
Myoepithelial Stains Only Helpful if Positive
Myoepithelial Stains Only Helpful if Positive
Myoepithelial Stains Only Helpful if Positive

p63
Vascularization of Mucin
Mucocele-Like Lesion
Mucinous Carcinoma
• Vascularization of mucin seen in invasive mucinous carcinomas and mucinous DCIS but not in extravasated mucin of mucocele-like lesions (but only 4 cases of MLL)

• Conclusions:
  – Vascularization of mucin cannot be used by itself to distinguish between invasive mucinous carcinoma and mucinous DCIS
  – Vascularization of mucin can be helpful in distinguishing mucocele-like lesion from invasive mucinous carcinoma, especially in small samples
Mucocele-like Lesion or Stromal Mucin Pools on Core Needle Biopsy

Excision Required in All Cases?
Can Mucocele-Like Lesions Be Reliably Diagnosed on CNB?

- Reported upgrade rates to DCIS or invasive cancer range from 0 to 30%
- Small numbers
- Not all patients underwent excision
- Includes cases of mucocele-like lesions and without atypia/ADH
## What About Mucocele-Like Lesions Without Atypia on CNB?

<table>
<thead>
<tr>
<th>Study</th>
<th># MLL without atypia</th>
<th># (%) Excised</th>
<th>Upgrade to DCIS or Inv CA</th>
<th>% Upgrade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renshaw, 2002</td>
<td>5</td>
<td>3 (60%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carder, 2004</td>
<td>7</td>
<td>6 (86%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ramsaroop, 2005</td>
<td>9</td>
<td>9 (100%)</td>
<td>2</td>
<td>22%</td>
</tr>
<tr>
<td>Wang, 2007</td>
<td>6</td>
<td>6 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sutton, 2012</td>
<td>22</td>
<td>22 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carkaci, 2011</td>
<td>22</td>
<td>7 (32%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Begum, 2009</td>
<td>21</td>
<td>9 (43%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Jaffer, 2011</td>
<td>61</td>
<td>45 (74%)</td>
<td>1</td>
<td>2%</td>
</tr>
</tbody>
</table>

Modified from Sutton, et al, 2012
Mucinous Lesions on Core Needle Biopsy
(that are not obviously mucinous ca or DCIS with mucin production)

• Excision required if there is
  – pathologic-radiologic discordance
  – epithelial atypia/ADH

• Excision *may not* be required if the findings are unequivocally those of a mucocele-like lesion without atypia/ADH

• Multiple levels to R/O mucinous carcinoma
Topics to be Discussed
(Emphasizing Recent Information)

- Benign sclerosing lesions vs invasive carcinoma
- Mucocele-like lesions vs mucinous carcinoma
- Benign inclusions in lymph nodes vs metastatic carcinoma
Benign Inclusions in Axillary Lymph Nodes

• Nevus cell aggregates
• Epithelial inclusions
• (Displaced epithelium s/p core needle biopsy)
• Must be distinguished from metastatic carcinoma
Nevus Cell Aggregates in Axillary Nodes of Patients with Breast Cancer

• UNCOMMON!

• Ridolfi, et al (1977)
  – 17,504 lymph nodes from over 900 mastectomy specimens
  – Nevus cell aggregates in 3 lymph nodes (0.017%)

• Nodal capsule, fibrous trabeculae

• But, may be seen in parenchyma

• Cells most often polygonal/epithelioid, non-pigmented

• Nodal blue nevi (spindle cells, prominent pigmentation)
S-100 positive
(Keratin negative)
Benign Epithelial Inclusions in Axillary Nodes of Patients with Breast Cancer

- ALSO UNCOMMON!
- Maiorano, 2003:
  - 7 cases identified among >3500 sentinel node biopsies
- Nodal capsule, fibrous trabeculae
- But, may be seen in parenchyma
- Glandular, squamous, mixed
- Some glandular inclusions have the appearance of endosalpingiosis
Ectopic Breast Tissue as a Possible Cause of False-Positive Axillary Sentinel Lymph Node Biopsies

Eugenio Maiorano, M.D., Giovanni M. Mazzarol, M.D., Giancarlo Prunerri, M.D., Mauro G. Mastropasqua, M.D., Stefano Zurrida, M.D., Enrico Orvieto, M.D., and Giuseppe Viale, M.D., F.R.C.Path.

Benign Epithelial Inclusions in Axillary Lymph Nodes: Report of 18 Cases and Review of the Literature

Giovanii Fellegara, MD,* Maria Luisa Carcangi, MD,† and Juan Rosai, MD‡

Endosalpingiosis in Axillary Lymph Nodes: A Possible Pitfall in the Staging of Patients With Breast Carcinoma

Adriana D. Corben, MD, Tatjana Nehhozina, Karuna Garg, MD, Christina E. Vallejo, MD, and Edi Brogi, MD, PhD
Benign Glandular Inclusions in Axillary Lymph Nodes

- May show any changes that occur in mammary epithelium in the breast including:
  - Cysts
  - Apocrine metaplasia
  - Proliferative lesions including UDH, papilloma, sclerosing adenosis, ADH, DCIS
Endosalpingiosis in Axillary Lymph Nodes

- Lymph node capsule or parenchyma
- Ciliated cells, peg cells
- No cytologic atypia
- Immunophenotype
  - No myoepithelial cells
  - Nuclear staining for WT-1 and PAX8
Benign Glandular Inclusion?
Benign Glandular Inclusions vs Metastatic Carcinoma

• Features favoring benign inclusions
  – Location in capsule and fibrous trabeculae
  – Myoepithelial cells
  – Cilia, peg cells
  – Lack of cytologic atypia

• Compare with breast primary (if available)
Many Benign Lesions of the Breast Can Mimic Malignant Lesions