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Diagnostic Problems in Surgical Pathology  
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Case 2

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Notice of Faculty Disclosure

I have no relevant financial relationship with commercial interest to disclose.
Case 2

• A 50 year old female presented with a palpable breast mass
• Imaging studies confirmed the presence of a poorly circumscribed 2 cm mass in the upper outer quadrant of the left breast
• A diagnosis of microglandular adenosis was rendered on core needle biopsy
• An excision was performed
Diagnosis....

Additional Information

- Myoepithelial immunostains negative
- ER, PR and HER2 negative
- S100 strongly positive
Weird Tumors in the Breast

• Carcinomas arising in association with microglandular adenosis
• Adenoid Cystic Carcinoma
• Secretory Carcinoma
• Metastasis
Microglandular Adenosis

- Considered to be a benign proliferative glandular lesion
- Wide age range (28-82 years)
- Presents as mass or thickening
- May be an incidental finding in a biopsy for another lesion
Microglandular Adenosis

- Mammographically appears as a density or microcalcifications
- May be “suspicious”
- Grossly ill-defined lesion

Microglandular Adenosis

- Infiltration of small glands in fibrous and/or fatty stroma
- Disorderly arrangement of the glands
- Round glands with single layer of flat to cuboidal epithelial cells
- Round nucleus with inconspicuous nucleolus
Microglandular Adenosis

- Clear to amphophilic cytoplasm
- Absent myoepithelial cells
- Basement membrane present
- Inspissated secretions present in lumens
Microglandular Adenosis

• Cells are strongly immunoreactive for cytokeratin, S100 and cathepsin D
• EMA and GCDFP negative
• ER and PR negative
• MEC markers are negative
Atypical Microglandular Adenosis

- Occurs in association with typical MGA
- Glands become more complex
- Interconnected glands with luminal bridging and microcribriform nests
- Stratification of epithelium forming solid nests of cells
- Cytologic atypia
- Loss of intraluminal secretions
Lesions associated with MGA

- Adenoid Cystic Carcinoma
- Invasive ductal carcinomas with clear cell features
- Metaplastic carcinoma

Acs, 2003
Albores-Saavedra, 2005
Khalifeh, 2008
Da Silva, 2009
Shin, 2009
Geyer, 2009
Microglandular Adenosis as a Precursor Lesion

- MGA can be seen in association with invasive carcinoma (18-28% of a consultation population)
- Progression from typical MGA through atypical MGA and DCIS
- Invasive carcinomas may have some cytologic similarity to MGA – e.g. Clear cells

- Invasive carcinomas tend to retain alveolar growth pattern of MGA
- Predominance of high grade tumors
Microglandular Adenosis as a Precursor Lesion

- Patterns of carcinoma seen include:
  - Infiltrating ductal carcinoma
  - Tumors with basaloid/squamoid differentiation
  - Adenoid cystic carcinomas
  - Metaplastic carcinomas (chondroid differentiation may be seen)

Microglandular Adenosis as a Precursor Lesion

- Similar immunophenotypic profile
  - S100 positive
  - Cathepsin D positive
  - MEC marker negative
  - ER/PR negative
  - HER2 variable

- Recent genetic evidence....
Microglandular Adenosis as a Precursor Lesion

- Genetic evidence indicates that MGA is, at least in some cases, a clonal proliferation that may represent a non-obligate precursor lesion to TNBC
- Studies used microdissection and aCGH on MGA, AMGA and associated IDC

Shin, AJSP, 2009
Geyer, Histopathology, 2012
Wen, Histol and Histopathol, 2013
### Table 2. Summary of immunohistochemical analysis

<table>
<thead>
<tr>
<th>Marker</th>
<th>Malignant glandular adenosis</th>
<th>Atypical malignant glandular adenosis</th>
<th>Invasive ductal carcinoma of no special type</th>
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<tbody>
<tr>
<td>ER</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>PR</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>HER-2</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>S100</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>p53</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CK8/18</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>CK5/6</td>
<td>+/−</td>
<td>+/−</td>
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</tr>
<tr>
<td>CK14</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
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<tr>
<td>CK17</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
</tr>
<tr>
<td>EGFR</td>
<td>1+</td>
<td>3+</td>
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</tr>
<tr>
<td>CAV1</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CAV2</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nestin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ki67</td>
<td>5%</td>
<td>25%</td>
<td>65%</td>
</tr>
<tr>
<td>p53</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

**Geyer, 2009**
**Geyer, 2012**

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**MGA**

**Atypical MGA**

**Invasive ductal carcinoma**
Management of MGA and atypical MGA

- Local excision with clear margins
- Careful follow-up

Management of carcinoma arising in MGA

- Treatment based on stage of individual patient
- Wide local excision and SLN biopsy
- Radiation therapy
- +/- Chemotherapy
Weird Tumors in the Breast

- Carcinomas arising in association with Microglandular Adenosis
- Adenoid Cystic Carcinoma
- Secretory Carcinoma
- Metastasis

Adenoid Cystic Carcinoma

- Histologic features similar to ACC seen elsewhere
- Growth patterns
  - Cribriform
  - Tubular
  - Trabecular
  - Solid
  - *Not* microglandular or microcystic
Adenoid Cystic Carcinoma

**Cellular Constituents**

- **Epithelial cells**
  - Eosinophilic cytoplasm
  - Polarized around true lumens
  - Sebaceous, squamous differentiation (?)
- **Basaloid/Myoepithelial cells**
  - Scant cytoplasm
  - Pseudo-lumens that contain acellular, eosinophilic, basement membrane material or basophilic, myxoid material

Adenoid Cystic Carcinoma

**Immunophenotype**

- Typically ER/PR/HER2 negative (triple negative)
  - Rare cases ER+, usually focal
- **Epithelial cells**
  - Positive for CK7, CAM5.2
  - Variably positive for CK5/6
  - Variably positive for CD117
- **Basaloid/Myoepithelial cells**
  - Positive for p63
  - Variably positive for CK5/6
  - Variably positive for other myoepithelial markers: SMA, calponin, SMMHC
  - Variably positive for CD117
Expression of luminal epithelial cell markers and basal/myoepithelial markers may be variable, unpredictable, and different from that of their normal cellular counterparts.

Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck

Marta Persson², Yvonne Andrén⁻¹, Joachim Mark¹, Hugo M. Horlings⁵, Fredrik Persson⁴, and Göran Stenman²

PNAS 2009

- ACC of head and neck and breast:
  - t(6;9)(q22-23;p23-24) translocation found in 4/4 breast lesions
  - MYB-NFIB fusion
  - Deregulation of MYB and its target genes is a key oncogenic event in pathogenesis of adenoid cystic carcinomas regardless of site of origin
MYB-NFIB translocation/fusion in Mammary ACC

<table>
<thead>
<tr>
<th>Study</th>
<th>MYB-NFIB translocation/fusion</th>
</tr>
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<tbody>
<tr>
<td>Brill, 2011</td>
<td>2/4 (50%)</td>
</tr>
<tr>
<td>Zhu, 2012</td>
<td>3/8 (38%)</td>
</tr>
<tr>
<td>Wetterskog, 2012</td>
<td>12/13 (92%)</td>
</tr>
<tr>
<td>Hudson, 2014</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>D’Alfonso, 2014</td>
<td>7/31 (23%)*</td>
</tr>
<tr>
<td>Martelotto, 2015</td>
<td>10/12 (83%)</td>
</tr>
</tbody>
</table>

*including 5/15 with conventional growth patterns and 2/16 solid/basaloid

Adenoid Cystic Carcinoma

- *MYB-NFIB* translocation/fusion in mammary ACC reported in ~50% of cases, including all subtypes
- Relationship to outcome not established
- Unlike other TNBC, ACCs have low mutation rates and lack mutations in *TP53* and *PIK3CA* (Martelotto, Histopathol, 2015)
Weird Tumors in the Breast

• Carcinomas arising in association with Microglandular Adenosis
• Adenoid Cystic Carcinoma
• Secretory Carcinoma
• Metastasis
Secretory Carcinoma

- Rare: <0.15% of breast cancers
- Median age 25; can occur at any age
- Typically well circumscribed, mobile masses; subareolar location, especially in children and males
- Border often circumscribed but may be infiltrative
- Microcystic, solid, tubular patterns; usually combined
- May show central sclerosis

Secretory Carcinoma

- Polygonal cells with plentiful granular eosinophilic to foamy/vacuolated cytoplasm
- Nuclei regular; inconspicuous nucleoli
- Intracellular and extracellular, PAS+ secretory material
- Associated DCIS with similar cytology may be present
- Outcome
  - Favorable, especially in children and young adults
  - More aggressive in older patients
  - Clinical course may be protracted; late recurrences (after 20 years) may occur
Secretory Carcinoma

• Immunophenotype
  – Usually ER-, PR-, HER2- (triple negative)
  – Typically positive for EMA, S100, CEA, α-lactalbumin

Secretory Carcinoma

• Genetics
  – t(12;15)(p13;q25) balanced translocation leading to ETV6-NTRK3 fusion gene
  – Identical translocation seen in other lesions (congenital cellular mesoblastic nephroma, infantile fibrosarcoma)
Back to Our Case....

- Our case was microglandular
- Coarse red granules in cytoplasm
- Lacked MECs
- Triple negative
- S100+
- Lacked *ETV6-NTRK3* rearrangement
A Weird and Really Rare Breast Tumor…

Acinic Cell Carcinoma

- Very rare, incidence unknown
- First report in 1996 (Roncaroli) as a counterpart to the salivary gland tumor
- Mean age 56 yrs (range 35-80 yrs)
- Presents as a palpable nodule (1-5 cm in size)
- Border often infiltrative
Acinic Cell Carcinoma

- Shows the full spectrum of differentiation
- Patterns:
  - Microcystic and microglandular
  - Solid nests +/- comedo necrosis
- Round to ovoid nuclei with single nucleoli
- Mitoses may be prominent
- Abundant cytoplasm (granular, amphophilic to eosinophilic, or clear)
- Coarse red (zymogen) granules
Acinic Cell Carcinoma

• IHC: Positive for
  – Alpha-1-antichymotrypsin
  – Salivary gland amylase
  – Lysozyme
  – EMA
  – S100

• ER, PR and HER2 negative

• Does not show t(12:15)ETV6-NTRK3 rearrangement
Acinic Cell Carcinoma

Genetics

- Negative for t(12:15)ETV6-NTRK3 rearrangement using ETV6 dual-color, break-apart probe
- TP53 and PIK3CA mutations reported (among others, similar to TNBC) in breast AcCC, but not in salivary gland AcCC

Piscuoglio, Histopathol, 2015
Guerini-Rocco, Histopathol, 2015
Acinic Cell Carcinoma

- Interestingly, AcCC has been reported to arise in association with MGA \cite{Huo, Ann Diagn Pathol, 2011}
- Some secretory carcinomas reclassified as AcCC using \textit{ETV6} rearrangement, amylase and $\alpha$-lactalbumin \cite{Osako, Histopathol, 2013}
- Very little information on treatment
- Based on very limited data, prognosis reported to be good \cite{Limite, Int J Surg, 2014}

Differential Diagnosis

- Microglandular adenosis-atypical
- Secretory carcinoma
- Acinic cell carcinoma
- Metastasis-important to consider with any TNBC lacking a clear in situ component
<table>
<thead>
<tr>
<th></th>
<th>MGA</th>
<th>ACC</th>
<th>Secretory</th>
<th>Acinic Cell</th>
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</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Microglandular</td>
<td>Cribiform</td>
<td>Microcystic</td>
<td>Microcystic</td>
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<tr>
<td></td>
<td></td>
<td>Trabecular</td>
<td>Solid Tubular</td>
<td>Microglanular Solid</td>
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<tr>
<td></td>
<td></td>
<td>Solid</td>
<td></td>
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<tr>
<td>Cytoplasm</td>
<td>Clear to</td>
<td>Eosinophilic</td>
<td>Eosinophilic</td>
<td>Clear, eosinophilic,</td>
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<tr>
<td></td>
<td>amphophilic</td>
<td></td>
<td>clear/vacuolated</td>
<td>amphophilic</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coarse eosinophilic granules</td>
</tr>
<tr>
<td>Nuclear features</td>
<td>Bland in MGA</td>
<td>Typically low</td>
<td>Regular with</td>
<td>Round to ovoid, may be high</td>
</tr>
<tr>
<td></td>
<td>Higher grade</td>
<td>grade; can be</td>
<td>inconspicuous</td>
<td>grade</td>
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<tr>
<td></td>
<td>in atypical</td>
<td>high grade in</td>
<td>nucleoli</td>
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<td></td>
<td>MGA and</td>
<td>solid/basaloid</td>
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<tr>
<td></td>
<td>carcinoma</td>
<td>form</td>
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<tr>
<td></td>
<td></td>
<td>MECs bland</td>
<td></td>
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<tr>
<td>Myoepithelial cells</td>
<td>Absent</td>
<td>Present within</td>
<td>Absent</td>
<td>Absent</td>
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<tr>
<td></td>
<td></td>
<td>tumor</td>
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<tr>
<td>ER/PR/HER2</td>
<td>Negative</td>
<td>Usually negative</td>
<td>Usually negative</td>
<td>Negative</td>
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<td></td>
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</tr>
<tr>
<td>S100</td>
<td>Positive</td>
<td>Likely positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Genetics</td>
<td>Many demonstrated; none specific to MGA as yet</td>
<td>MYB-NFIB fusion</td>
<td>ETV6-NTRK3 translocation</td>
<td>TPS3 and PIK3CA mutations demonstrated</td>
</tr>
</tbody>
</table>

**Diagnosis**
**Acinic Cell Carcinoma**