Case 1

Anna Marie Mulligan
University Health Network, Toronto
University of Toronto

Clinical History

• 48 year old female, premenopausal
• PMHx: hypertension
• FHx: non-contributory
• P3 G3
• Non-smoker, non-drinker

Clinical History

• Imaging:
  – 2007: normal mammo
  – 2008: increasing asymmetric density, right UOQ; Suggestion of mass on spot compression
  – Ultrasound: 3 cm mass
  – MRI: enhancing mass and additional smaller foci
• Core needle biopsy: invasive carcinoma
• Lymph node FNA: negative

ACCME/Disclosure

Dr. Mulligan has nothing to disclose
Wire-localisation excision and sentinel lymph node biopsy performed

**Macroscopic**
Tan, ill-defined mass lesion measuring 3 cm x 1.7 cm x 1.4 cm
Lysozyme

Anti-chymotrypsin

Laminin

Reticulin
### IHC Summary

<table>
<thead>
<tr>
<th></th>
<th>MG growth pattern</th>
<th>NST</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>EMA</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Lysosome</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Alpha1-antichymotrypsin</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Anti-trypsin</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hormone Receptor</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HER2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Collagen IV</td>
<td>Focal</td>
<td>-</td>
</tr>
<tr>
<td>Laminin</td>
<td>Focal</td>
<td>-</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SMM-HC</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Diagnosis

Mixed invasive ductal carcinoma no special type and acinic cell carcinoma

Minor component in keeping with atypical microglandular adenosis

Acinic Cell Carcinoma (ACC)

A breast carcinoma similar to the acinic cell carcinoma of the parotid gland that shows (serous) differentiation with zymogen-type cytoplasmic granules

WHO Classification of Tumours of the Breast
Eds Lakhani et al, IARC 2012

Acinic Cell Carcinoma

- Rare
- Average 48.5 years, median 45.5 years (23-80)
- Palpable mass, rarely imaging
- Imaging
- Gross
  - Size range: 1.1 cm to 5.5 cm
  - Mean 3.4 cm, median 2.7 cm

Microscopic

- Infiltrative > circumscribed
- Growth pattern:
  - Microglandular
  - Solid
  - Admixture
- Dense eosinophilic material within the lumen
- Pure or mixed
Microscopic

- Abundant cytoplasm
  - Eosinophilic to amphophilic or clear
  - Granular
  - PAS/DPAS positive
- Nuclei round to oval, +/- coarse chromatin, 1-2 nucleoli
- Variable grade, often admixed

Immunohistochemistry

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low molecular weight cytokeratin</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lysozyme</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Salivary-type amylase</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pancreatic-type amylase</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>α1-antichymotrypsin</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>α1-antitrypsin</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Chromogranin</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>CD68</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Differential Diagnosis

- Eosinophilic Granules
  - Mitochondria Osteocytes
  - Secretory granules Apocrine cells Paneth cells
  - Lysosomes Granular cells
  - Phloxine-tartrazine negative Paneth cell metaplasia
  - Neurosecretory granules Neuroendocrine cells

Eosinophilic Granules

- Intestinal Paneth cells
  - Phloxine-tartrazine stain negative
  - Paneth cell metaplasia prostate
    - represent neuroendocrine differentiation
- Benign breast/lactational change
- ACC and Microglandular Adenosis (MGA)
**ACC vs (Atypical) Microglandular Adenosis**

<table>
<thead>
<tr>
<th></th>
<th>ACC</th>
<th>MGA/AMGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small round glands with luminal eosinophilic secretions</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Haphazard distribution in fat/fibrous stroma</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fine to coarse eosinophilic granules</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>S100</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hormone receptors/HER2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EMA</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Secretory proteins, e.g. lysozyme, amylase, etc.</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Myoepithelial cell layer</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Basement membrane</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Association with high grade triple negative breast cancer</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Complex copy number changes, e.g. 8q gain, 5q loss</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Malignant*</td>
<td>Benign</td>
</tr>
</tbody>
</table>

* Lung metastasis described as showing ACC morphology
Lymph node metastasis described in pure ACC

**Microglandular Adenosis vs Acinic Cell Carcinomas**

- **MGA = 4, Atypical MGA = 3, ACC = 8**
- **Somatic mutations:**
  - ACC = 6 (2-10); MGA = 7 (1-6)
  - TP53 mutation: ACC (88%), 71% (MGA)
  - Additional: BRCA1, FGFR2, ERBB3, INPP4B, PIK3CA
  - ACC: KMT2D, ERBB4, NEB; MGA: PTEN, MED12
- **Complex patterns of copy number alteration**
  - gains 1q, 2q, 8q; losses 3p, 5q, 12q, 13q, 14q, 17p, 17q
- **Same spectrum?**

**Molecular Genetics**

- ACC: somatic mutations Median = 5 (range 2-11)
  - Complex patterns of copy number alteration
    - gains 1q, 2q, 8q; losses 3p, 5q, 12q, 13q, 14q, 17p, 17q
- ACC harbour a high mutational burden akin to high grade TNBC
  Guerini-Rocco et al, J Pathol 2015
- **MGA**
  - Complex patterns of copy number alterations
  - Heterogeneous
  Geyer et al, Histopathology, 2012

**Differential Diagnosis**

**Abundant and/or granular cytoplasm, secretory activity**

- Carcinoma with apocrine differentiation:
  - Fine PAS/DPAS+ granules, apical
  - No colloid-like globules
  - GCDFP-15 +ve
- Glycogen rich carcinoma:
  - Clear cytoplasm > 90% of tumour cells
  - PAS+, diastase-labile
  - Lack electron-dense granules
- Secretory carcinoma:
  - Recurrent balanced chromosomal translocation t(12;15)(p13;q25)
  - ETV6 rearrangements not identified in 6 ACC of the breast => distinct entities
  Reis-Filho et al

Geyer et al., Abstract 160, 2016, Mod Path, 42A
Guerini-Rocco et al, J Pathol 2015
Guerini-Rocco et al, J Pathol 2016
Differential Diagnosis
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Reis-Filho et al
Differential Diagnosis

• Granular cell tumour
  – Can mimic invasive carcinoma
  – Copious PAS/DPAS+ granular cytoplasm
  – Uniform round to oval nuclei, nucleoli discernible
  – S100+, CD68+

• Oncocytic carcinoma:
  – Abundant eosinophilic granular cytoplasm (mitochondria)
  – Antimitochondrial antibody +ve; ER(78%), PR(62%), HER2 (25%)

• Metastatic carcinoma of parotid, pancreatic or renal origin:
  – Clinical history
  – IHC, e.g. vimentin and pancreatic amylase
**ACC of breast vs ACC of salivary glands**

<table>
<thead>
<tr>
<th></th>
<th>ACC Breast</th>
<th>ACC Salivary Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>Rare</td>
<td>10% of malignant</td>
</tr>
<tr>
<td><strong>Tumour edge</strong></td>
<td>Usually infiltrative</td>
<td>Circumscribed</td>
</tr>
<tr>
<td><strong>Growth pattern</strong></td>
<td>MG and solid</td>
<td>Solid, microcystic</td>
</tr>
<tr>
<td><strong>Lymphoid infiltrate</strong></td>
<td>Occasionally described</td>
<td>May be prominent</td>
</tr>
<tr>
<td><strong>Granules</strong></td>
<td>Fine to coarse eosinophilic</td>
<td>Basophilic/fine*</td>
</tr>
<tr>
<td><strong>TPS3 mutations</strong></td>
<td>80%</td>
<td>-</td>
</tr>
<tr>
<td><strong>PIK3CA mutations</strong></td>
<td>10%</td>
<td>-</td>
</tr>
</tbody>
</table>

*Blue dot tumour

**ACC - Genetics**

- **Mixed ACC and high grade TNBC**
  - Components clonally related in two of four cases based on the mutational and copy number profiling
  - Additional somatic mutations in one high grade component
  - In two cases, distinct somatic mutations were identified in the ACC and high grade TNBC components

- **ACC harbour a high mutational burden akin to high grade TNBC**
  - recurrent TPS3 mutations, BRCA1 germline and somatic pathogenic mutations and complex patterns of gene copy number alterations

- **†substrate for the development of TNBC of higher histologic grade or of a more aggressive subtype**

Guerini-Rocco et al, J Pathol 2015
Treatment

- Treatment variable:
  - Lumpectomy vs mastectomy
  - +/- SLN and/or ALN
  - Adjuvant radiation, chemotherapy, anti-oestrogen therapy
  - Neoadjuvant therapy (3 patients)

Outcome (N=29)

<table>
<thead>
<tr>
<th>Lymph node status</th>
<th>Age</th>
<th>Tumour Size</th>
<th>Metastases</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/18</td>
<td>42</td>
<td>3 cm</td>
<td></td>
<td>NED @5 years</td>
</tr>
<tr>
<td>2/20 (post NAT)</td>
<td>35</td>
<td>4 cm</td>
<td></td>
<td>NED @ 1 year</td>
</tr>
<tr>
<td>2/11 (post NAT)</td>
<td>49</td>
<td>N/A</td>
<td>Liver mets @ 12 mos</td>
<td>DOD @ 36 mos</td>
</tr>
<tr>
<td>1/1 (micrometastasis)</td>
<td>39</td>
<td>5.5 cm</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>10/17</td>
<td>36</td>
<td>5 cm</td>
<td></td>
<td>DOD @ 24 mos</td>
</tr>
<tr>
<td>2/22*</td>
<td>35</td>
<td>1.8 cm</td>
<td></td>
<td>DR, 72 mos F-up</td>
</tr>
<tr>
<td>ND</td>
<td>63</td>
<td>5 cm</td>
<td></td>
<td>DR, 48 mos F-up</td>
</tr>
<tr>
<td>6/15</td>
<td>36</td>
<td>3.5 cm</td>
<td>Lung mets @ 8 yrs</td>
<td>NED @ 120 mos</td>
</tr>
<tr>
<td>NA</td>
<td>70</td>
<td>1.4 cm</td>
<td></td>
<td>DR</td>
</tr>
<tr>
<td>Positive</td>
<td>30</td>
<td>2.6 cm</td>
<td>Brain, spinal cord</td>
<td>DOD @ 24 mos</td>
</tr>
</tbody>
</table>

NED: no evidence of disease, DOD: dead of disease, DR: disease recurrence, ND: not done; NA: not available

Lung mets n = 1 @ 8 yrs, NED @ 10 years
*pure ACC, grade 1
Follow-up: 8 - 184 months (average 38 months, median 21 months)

Summary

- Distinctive appearance
- Frequently mixed (usually NST carcinoma)
- Triple negative
  - S100, EMA, secretory protein expression
- ? Special type or variant of MGA-Ca
- Clinical significance: pure vs mixed
Our Patient

- Nottingham grade III/III
- SLN negative
- Revision of margins
- Chemotherapy (FEC-D)
- Radiation therapy
- No evidence of disease (88 mos follow-up)

Thank You