SURPRISE!

BREAST TUMORS WITH UNEXPECTED FINAL PATHOLOGY

Rachel Factor, MD
28th Annual Park City Pathology Update
Tuesday, Feb 10th, 2015
OBJECTIVES

- **Part I**
  - Review Lobular carcinoma and variants
  - Mimics of lobular carcinoma
  - W/u of primary vs metastatic disease

- **Part II**
  - Review classification of neuroendocrine tumors of the breast
  - Review primary vs metastatic
  - Rare tumors of the breast: Small cell carcinoma and Adenoid cystic carcinoma
PART 1

- Two cases with similar morphology but different origins
FIRST CASE

- 29 yo woman, pregnant
- Palpable breast mass
- U/S: 1.6cm mass at 9:00, 8cm from nipple
- Biopsy performed
SECOND CASE

- 70 year old woman
- 2 masses in the right breast
- Biopsy-proven malignancy
- Excision performed
SIMILAR MORPHOLOGY
SURPRISE!

- One case is invasive lobular breast carcinoma
- One is a metastatic tumor
INVASIVE LOBULAR CARCINOMA AND ITS MIMICS

- Lobular carcinoma and variants
- Mimics of lobular carcinoma
- Review w/u primary vs metastatic disease
5-15% of invasive breast carcinomas
Frequently multifocal in ipsilateral breast
Some reports of increased incidence of breast cancer in contralateral breast
Palpable mass or mammographic or u/s abnormality, but may be subtle
Mass may not be identifiable grossly
INVASIVE LOBULAR HISTOLOGY

- Classic type + variants:
  - Loosely cohesive cells
  - Intracytoplasmic lumina with eosinophilic mucin and eccentrically placed nuclei
  - Linear growth
  - Concentric growth pattern around ducts
LOBULAR VS DUCTAL

Lobular
- Shows loss of E-cadherin
- Usually ER/PR+
- Rarely HER2+
- Less likely to show lymphovascular invasion
- Poor response to chemotherapy
- Negative margin status difficult to achieve
- Mets: bone, GI, meninges, ovary, serosa
LOBULAR VS DUCTAL

Ductal
- ER/PR/HER2 varies
- Variable response to chemotherapy
- Margin status varies
- Mets: more likely to lung

Ultimate question:
- Is there is a prognostic difference?
- It’s complicated!
Retrospective

Patients enrolled in the International Breast Cancer Study Group Clinical Trial 1978-2002

9,374 patients with either pure IDC or ILC

Median follow-up of 13 years
Disease Free Survival (DFS) and Overall Survival (OS)

- Within the first 10 years, risk of death was 16% lower for ILC than IDC.
- After 10 years, risk of death was 50% higher for ILC than IDC.
Epithelial Breast Cancer

In situ

- Lobular
  - Classic
  - Pleomorphic

- Ductal
  - Cribriform
  - Solid
  - Micropapillary
  - Papillary
  - Clinging
  - Comedo

GRADE: Low, Intermediate, High

Invasive

- Lobular
  - Classic
  - Alveolar
  - Solid
  - Trabecular
  - Apocrine
  - Signet ring
  - Histiocytoid
  - Pleomorphic

- Ductal
  - Ductal, NOS
  - Tubular
  - Mucinous
  - Micropapillary
  - Papillary
  - Cribriform
  - Apocrine
  - Secretory
  - Medullary
  - Metaplastic
  - Adenoid cystic
  - Neuroendocrine

GRADE: Well, Moderate, Poor

EXPRESSION:

- ER
- PR
- HER2/NEU
INVASIVE LOBULAR VARIANTS

- Based on architecture and cytology

- Architecture:
  - Classic
  - Solid
  - Alveolar
  - Trabecular

- Cytology:
  - Signet ring
  - Apocrine
  - Histiocytoid
  - Pleomorphic
Studied prognosis of classic ILC vs variants

- 981 patients with pure ILC
- Classified as classic (including alveolar, solid, trabecular) or mixed non-classic (including pleomorphic, signet ring, histiocytoid and apocrine)
- Median follow up 6.4 years for DFS and 7.4 years for OS
RESULTS

- Classic (55.8%), alveolar/trabecular (18.8%), solid (10.6%), mixed non-classic (14.8%)

- Classic: >50% grade 1
- Mixed non-classic: 58.6% grade 3
- Solid: 37.5% grade 3

- Overall, 96.5% were ER+
- Overall, Based on IHC, 48.5% were Luminal B
- Multivariate analysis
- Significantly different outcomes between classic vs non-classic and solid types
- Independent prognostic factors: age >70, large tumor size and positive nodes
CONCLUSION

- ILC is a heterogeneous disease
- Different histologic subtypes with different grades, different behaviors and different response to treatment
- Selected subgroups may benefit from tailored therapy
First described by Page in 1987
Growth pattern of classic ILC
Nuclei 4x the size of a lymphocyte
Hyperchromasia
Nuclear irregularity
Prominent nucleoli
Increased mitotic activity
Clinicopathologic and biomarker analysis of invasive pleomorphic lobular carcinoma as compared with invasive classic lobular carcinoma: an experience in our institution and review of the literature

Melissa Jacobs, MD, Fang Fan, MD, PhD*, Ossama Tawfiq, MD, PhD
Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, Kansas 66160, USA

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and tumor characteristics (PLC vs ILC)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>PLC (n = 7)</td>
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<tr>
<td>Age (y)</td>
<td>35-69</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0/7</td>
</tr>
<tr>
<td>II</td>
<td>5/7</td>
</tr>
<tr>
<td>III</td>
<td>2/7</td>
</tr>
<tr>
<td>LVI present</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2/7</td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>4/7</td>
</tr>
<tr>
<td>N1a</td>
<td>1/7</td>
</tr>
<tr>
<td>N2a</td>
<td>0/7</td>
</tr>
<tr>
<td>N3a</td>
<td>2/7</td>
</tr>
<tr>
<td>ER ≥ 1%</td>
<td>4/7</td>
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<tr>
<td>Her-2</td>
<td>All negative</td>
</tr>
<tr>
<td>Ki-67 ≥ 10%</td>
<td>5/7</td>
</tr>
<tr>
<td>Follow-up</td>
<td>None</td>
</tr>
<tr>
<td>(median, 29 mo)</td>
<td>NED</td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
</tr>
<tr>
<td></td>
<td>Deceased</td>
</tr>
</tbody>
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LVI indicates lymphovascular invasion; NED, no evidence of disease.
Pleomorphic invasive lobular carcinoma is a distinct entity

- E-cadherin negative
- Often higher grade, higher Ki67
- May be ER-
- Has implications for anti-estrogen therapy and chemotherapy
OTHER IMPLICATIONS

- Non-classical morphology
- Fairly rare occurrence
- Need to consider other tumors
MIMICS OF INVASIVE LOBULAR

- **Breast**
  - Apocrine carcinoma
  - Acinic cell carcinoma
  - Secretory carcinoma

- **Metastatic**
  - Melanoma
  - Gastric carcinoma
  - Renal cell carcinoma
  - Hepatocellular carcinoma
  - Alveolar soft part sarcoma
OUR CASE

- Patient had a known history 10 years before
- Alveolar soft part sarcoma of the leg
- Now with widely metastatic disease
- Brain, lungs, breast
PRIMAry vS MEtASTATIC

- Clinical history
- Have a low threshold for “other”
- ER can be positive in metastatic lesions
- ER can be negative in breast tumors
## USEFUL IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th></th>
<th>GCDFP15 (BRST2)</th>
<th>Estrogen Receptor</th>
<th>Progesterone Receptor</th>
<th>PAX8</th>
<th>Gata 3</th>
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</thead>
<tbody>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>60-70%</td>
<td>75%</td>
<td>50-60%</td>
<td>0%</td>
<td>92%</td>
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<tr>
<td>Infiltrating lobular carcinoma</td>
<td>60-70%</td>
<td>&gt;95%</td>
<td>80%</td>
<td>0%</td>
<td>100%</td>
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<tr>
<td>Lung adenocarcinoma</td>
<td>0-1%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>0%</td>
<td>8%</td>
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<td>Ovarian adenocarcinoma</td>
<td>1-5%</td>
<td>50-100%</td>
<td>40-90%</td>
<td>90-100%</td>
<td>6%</td>
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<tr>
<td>Endometrioid adenocarcinoma</td>
<td>negative</td>
<td>70%</td>
<td>70%</td>
<td></td>
<td>7%</td>
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<tr>
<td>GI adenocarcinoma</td>
<td>negative</td>
<td>&lt;5%</td>
<td>1-10%</td>
<td>0%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>negative</td>
<td>negative</td>
<td>0-5%</td>
<td>0%</td>
<td>37%</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>negative</td>
<td>negative</td>
<td>30%</td>
<td></td>
<td>9%</td>
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<tr>
<td>Thyroid carcinoma</td>
<td>negative</td>
<td>20%</td>
<td>30%</td>
<td>100%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-100%</td>
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<tr>
<td>Urothelial carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84-100%</td>
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<tr>
<td>Mesothelioma</td>
<td></td>
<td></td>
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<td>58%</td>
</tr>
</tbody>
</table>

Adapted from Surgical Pathology Criteria [http://surgpathcriteria.stanford.edu/](http://surgpathcriteria.stanford.edu/)

PART 2

Two consult cases, similar on first blush and both initially given the wrong diagnoses.
FIRST CASE

- 73 yo woman with a left breast mass
- Core biopsy performed
OUTSIDE HOSPITAL STUDIES

Ancillary studies:

- **POSITIVE:** AE1/AE3, CAM5.2, CK7, ER (weak, 20%), Synaptophysin, Chromogranin
- **NEGATIVE:** CK20

Synaptophysin
Due to positivity for Estrogen receptor, Synaptophysin and Chromogranin, the tumor was called “poorly differentiated invasive ductal carcinoma with neuroendocrine features.”

Our in house oncologist agreed.

To us, the work-up was incomplete.
Patient had lesions in bone, breast and lung. We performed additional stains:

- **POSITIVE**: TTF-1 (diffuse, strong)
- **NEGATIVE**: PR (0), HER2 (0)
Metastatic neuroendocrine tumor, most likely of primary lung origin.
SURPRISE!

IDC of breast with neuroendocrine features

↓

Metastatic NET from lung

Flounder

Sand
DISCUSSION POINTS

- Neuroendocrine tumors of the breast: classification and diagnosis

CATEGORIES (WHO 2003)

- **Common**
  - Tumors with NE differentiation
    - <50% IHC

- **Rare**
  - Poorly differentiated (small cell, large cell)
  - Well differentiated (solid/carcinoid)
    - >50% IHC
TUMORS WITH NEUROENDOCRINE DIFFERENTIATION

- Uncertain how many cases this includes
- Lack cyto-architectural features of true neuroendocrine tumors
- Often post-menopausal
- IDC-NOS, mucinous, solid papillary included
- Show scattered expression of endocrine markers such as Synaptophysin and Chromogranin in <50% of cells (WHO 2003)
Uncertain

Some report no prognostic significance

Others report better prognosis

Most important: Grade, Stage, ER/PR/HER2

Bottom line:

- No need to test every tumor for NE Diff
- Some NE staining does not = NEC
SOLID/CARCINOID-LIKE

- <1% of breast cancers
- Morphologically indistinguishable from carcinoids from other sites
- Presence of DCIS and/or LVI may help
- Majority ER/PR+
- HER2 negative

POORLY DIFFERENTIATED

- Small/large cell neuroendocrine carcinomas
- Morphologically indistinguishable from lung
- TTF-1 does not help: may be positive
- In situ carcinoma may help
- Variable expression of NE markers
- Prognosis?

9 patients diagnosed with primary small cell ca
Treatment: mastectomy or lumpectomy with or without ALDN
Follow-up 3-35 months
All patients alive
Conclusion: Primary small cell carcinoma of the breast is not as aggressive as at other sites
ISSUES WITH NE CLASSIFICATION

- >50% expression is arbitrary
- Most appropriate IHC marker for NET’s?
  - Panel is recommended
  - Synaptophysin and chromogranin
  - Others: NSE, CD56
- Some tumors with cyto-architecture of neuroendocrine tumors are negative for markers of NE differentiation
**Breast Primary Neuroendocrine Tumor**

**Tumors with NE differentiation**

- **Common**
  - Well differentiated (solid/carcinoid)
  - Poorly differentiated (small cell, large cell)

- **Rare**
  - No mention of IHC
  - “IHC characteristic”

- **Well differentiated (solid/carcinoid)**
- **Poorly differentiated (small cell, large cell)**

**CATEGORIES (WHO 2012)**
Breast carcinoma with endocrine differentiation is relatively common.

True primary neuroendocrine carcinoma of the breast is rare (<1%).

Any neuroendocrine tumor of the breast should be distinguished from metastatic neuroendocrine tumors if possible.
4 patients showed dimorphic tumor growth, showing small cell carcinoma co-existing with invasive lobular, ductal NOS, metaplastic and mixed types.

SECOND CASE

- 2010: 71 yo woman, 3cm mass in right breast
- Outside hospital case - excision performed
6 negative lymph nodes.

Stains: Pan-K and NSE (+), ER/PR/HER2 (-), Synaptophysin (-), Chromogranin (-).

Diagnosis: poorly differentiated small cell neuroendocrine carcinoma.

Patient received 6 cycles of Carboplatin, Taxol and radiation.

Developed severe neuropathy and recurrence in 2014.
CASE REVIEWED

- Small round blue cell tumor.
- Sheets and clusters.
- Mitotically active (15/10).
- Areas of necrosis and LVI.
- Intervening hyaline and myxoid stroma.
STAINS: RECAP AND NEW

- SMA and p63: Negative
- Synaptophysin, Chromogranin: Negative
- CK7: Positive (patchy)
- NSE: Positive
- CD117: Positive (patchy to diffuse)
New diagnosis:

- Adenoid cystic carcinoma of the breast, solid type with basaloid features
Primary small cell neuroendocrine carcinoma

Primary adenoid cystic carcinoma

Seahorse

Coral
ADENOID CYSTIC CARCINOMA OF THE BREAST

- Rare: 0.1% of breast carcinoma
- Morphologically indistinguishable from Adenoid cystic in salivary gland, lung, cervix
- 6th-7th decade
- Subareolar region common
- Good prognosis
ADENOID CYSTIC CARCINOMA

- Architectural patterns:
  - Trabecular, tubular, cribriform, solid

- Histology triplet:
  - Epithelial cells
  - Myoepithelial cells - bulk of tumor
  - Matrix
ADENOID CYSTIC CARCINOMA

- **Epithelial cells**
  - Eosinophilic cytoplasm, round nuclei
  - Forms real glands
  - CK7, CD117+

- **Myoepithelial cells**
  - Basaloid: small, dark, scant cytoplasm
  - Pseudolumens
  - p63, SMA, Calponin+

- **Matrix**
  - PAS-d+
DIFFERENTIAL

- Malignant
  - Cribriform carcinoma
    - DCIS
    - Invasive

- Benign
  - Collagenous spherulosis
HOW TO DISTINGUISH?

- **Adenoid cystic**
  - Infiltrative with two cell populations
  - ER, PR, HER2 negative
  - *CD117 positive*

- **Invasive Cribriform carcinoma**
  - Usually ER/PR positive
  - Lacks myoepithelial cells

- **Cribriform DCIS**
  - Myoepithelial cell markers around periphery

- **Collagenous spherulosis**
  - Incidental
  - Not infiltrative
  - Lack cytologic atypia
1. Most common
   - Nottingham grade (I-III)

2. Salivary gland method:
     - Grade 1: no solid areas
     - Grade 2: <30% solid
     - Grade 3: at least 30% solid
MORE AGGRESSIVE ADENOID CYSTIC VARIANTS?

Some reports suggest the following:

- Solid type ([Ro, et al. *Hum Pathol* 18: 1276-1281, 1987])
Each >90% solid with basaloid features
Nuclear atypia moderate - marked in 8 cases
Brisk mitotic activity in 50% of tumors
No LVI or PNI
Two cases with one positive axillary lymph node
Management differed (surgical, radiation, endocrine)
Follow-up:
- 6 patients with no evidence of recurrent carcinoma (2-88 mo out)
- 1 patient died of unknown causes; 1 lost to follow-up
Conclusion: may be a worse ACC subtype, but still better than invasive ductal, NOS of similar size
DIFFERENTIAL

- Cribriform carcinoma (in situ, invasive)
- Collagenous spherulosis
- Lymphoma
- Small cell carcinoma
- Solid papillary carcinoma
- Metaplastic carcinoma
TEACHING CASE

Solid variant of mammary “adenoid cystic carcinoma with basaloid features” merging with “small cell carcinoma”

Daniela Cabibi\textsuperscript{a,*}, Calogero Cipolla\textsuperscript{b}, Ada Maria Florena\textsuperscript{a}, Salvatore Frisano\textsuperscript{b}, Elisabetta Barresi\textsuperscript{a}, Salvatore Vieni\textsuperscript{b}, Vito Rodolico\textsuperscript{a}, Liborio Napoli\textsuperscript{b}

Pathology – Research and Practice 201 (2005) 705–711

Small cell
- Keratin and CD117+
- Synaptophysin, NSE+
- MIB-1 >30%

Adenoid cystic
- Keratin and CD117+
- Synaptophysin, NSE-
- MIB-1 10%
OUR CASE: REVISITED

- Solid, basaloid with trabecular components showing matrix production
- Mitotically active
- CD117+, NSE+
- Originally called small cell carcinoma
- Possible collision tumor?
Deer Valley in the summer