Immunostain Update: Diagnosis of metastatic breast carcinoma, emphasizing distinction from GYN primary

Yunn-Yi Chen, MD, PhD
Director of Immunohistochemistry Laboratory
Department of Pathology, UCSF

Metastatic breast cancer

• 1/3 of breast cancer patients will show metastasis
• 1st presentation or 20-30 years after dx of breast ca
• ↑ risk of second new primary, esp. BRCA carriers
• Second new primary vs distant metastasis: different treatment and prognosis

Outline

• Immunophenotype of breast cancer
• Distinction of breast from other primary
  ➢ Breast vs lung
  ➢ Breast vs GYN
  ➢ Malignant effusion

Workup for metastatic breast cancer

• Clinical history
  ➢ History of chemotherapy
• Image findings
• Review of prior slides
• Panel of antibodies
**Immunophenotype of breast cancer**

- CK7+/CK20-
- ER, PR
- GCDFP-15 (BRST-2)
  - Sensitivity dependent on antibody clone
  - Cell Marque, clone 23A3
- Mammaglobin

**Mammaglobin vs GCDFP-15 for breast cancer**

- Mammaglobin: more sensitive (>60-70%) than GCDFP-15 (~50%); more diffuse and intense staining
- Mammaglobin: slightly less specific, also stain some endometrioid and endocervical ca
- Both:
  - More sensitive for ER+ and HER2+ than triple negative tumors
  - More sensitive for lobular than ductal type
  - Positive in salivary and sweat gland tumors
- Complement each other, increase sensitivity

**Mammaglobin and GCDFP-15 may be differentially expressed**

- Mammaglobin
- GCDFP-15
Mammaglobin and GCDFP-15 may be differentially expressed

**Immunophenotype: primary vs met**

- **CK pattern:** stable
- **ER, PR, HER2:** significantly more change
  - ER 20%, PR 40%: bidirectional
  - HER2 15%
  - ↑ with treatment: HER2 32% on trastuzumab
- **GCDFP-15, mammaglobin:** stable

**IHC markers for metastatic breast cancer**

- **Basic panel:** ER, GCDFP-15, mammaglobin
- **Additional markers based on site, morphology, history**

**Adenocarcinoma: breast vs lung?**

70 y/o F with h/o breast ca, now presenting with a lung nodule
ER and TTF-1 expression in breast and lung cancers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Total Cases</th>
<th>Number (%) of Positive Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung adenocarcinoma</td>
<td>55</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>50</td>
<td>36 (72)</td>
</tr>
</tbody>
</table>

Most lung ca: <25% cells ER +; some: 51-75% tumor cells ER +
All ER+ lung ca also + for TTF-1


Adenocarcinoma: breast vs lung?

Case 1: 62 y/o F with h/o a 1 cm, node negative breast ca 12 years ago. She now presents with bilateral lung nodules. Please r/o a lung primary.
Adenocarcinoma: breast vs lung?

Case 2: 54 y/o F without h/o cancer, presenting with an eye mass

TTF-1 expression in breast carcinoma

- Nuclear TTF-1 expression in 2.6% (12/466) of primary breast ca
- 10/12: focal and/or weak; 2/12: diffuse and strong
- 2/12: strong TTF-1 in both invasive and in situ ca
- Expression not associated with particular histologic features or ER/PR/HER2 profile

Robens JN et al. Mod Pathol 2010;23(Suppl 1) Meeting Abstract

Dx: most compatible with metastatic breast ca
Case 2

**Dx:** most compatible with metastatic breast ca

**TTF-1**

**ER**

**MGB1**

Additional work-up: ovarian mass and left breast mass
Core needle biopsy of left breast mass performed

Invasive lobular carcinoma

**The presence of TTF-1 reactivity cannot by itself be used to rule out a breast origin in a carcinoma of unknown primary site**
Distinguishing breast from GYN primary

- Patients with BRCA mutations and other hereditary breast/ovarian carcinoma: increased lifetime risk for breast and gynecologic tumors
- Shared ER+ and PR+ immunophenotypes

Distinguishing breast from GYN primary--three clinical settings

- In lymph nodes
- In malignant effusion
- Metastatic breast cancer to ovary

Adenocarcinoma: breast vs ovary?

50 y/o BRCA2 F with h/o breast ca, now with an enlarged axillary LN

WT1
CA125
GCDFP-15 and mammaglobin negative
Dx: most compatible with ovarian primary
IHC markers for GYN tumors

- **Old markers**
  - **WT-1**
    - Positive in ovarian serous ca
    - Negative in endometrial serous ca, other epithelial ca
  - **CA125**
    - Low specificity

- **New marker**
  - **PAX8**

PAX8

- Nuclear transcription factor, expressed in Müllerian system, thyroid and kidney, B cells
- Sensitive marker for tumors derived from Müllerian system, thyroid glands, and kidney
- Positive in most GYN non-mucinous epithelial tumors
  - Distinction between GYN and breast primary
  - Distinction between GYN serous tumors from mesothelioma

Ovarian serous carcinoma

Metastatic carcinoma with micropapillary features
Invasive micropapillary carcinoma

- Small clusters of tumor cells floating in clear stromal spaces
- Seen in various primary sites: breast, ovary, bladder, lung
- Aggressive behavior, risk of LVI and metastasis

IHC panel for metastatic micropapillary carcinoma

- ER, mammaglobin
- WT1, PAX8
- CK20, uroplakin
- TTF-1

Lotan et al: 2009 AJSP 33;1037-41
Malignant effusion

- Primary mesothelioma
- Metastasis: breast, ovary and lung

IHC markers for mesothelioma

- WT1
  - Positive in <10% breast ca (focal, weak)
- Calretinin
  - Positive in ~20% breast ca
- CK5/6
  - Positive in basal-like breast ca
- D2-40
  - Negative in breast ca

D2-40

- Fixation-resistant epitope on podoplanin
- Lymphatic endothelial cells, myoepithelial cells, mesothelial cells
- Clinical utility
  - Lymphovascular invasion
  - Lymphatic-derived vascular tumor
  - Mesothelial cell-derived tumor
  - Skin adnexal tumor

mesothelioma
**IHC markers for malignant effusion**

<table>
<thead>
<tr>
<th></th>
<th>mesothelioma</th>
<th>Breast cancer</th>
<th>Ovarian serous cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WT1</strong></td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td><strong>D2-40</strong></td>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td><strong>Calretinin</strong></td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>Ber-EP4 or MOC-31</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>PAX8</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>ER</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Mammaglobin</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**Metastatic breast cancer to ovary**

- Clinically detected
  - Distinction from primary ovarian ca

- Clinically occult, identified at risk-reducing salpingo-oophorectomy (RRSO)
  - Distinction from primary ovarian ca
  - Distinction from benign ovarian lesions

**Metastatic breast cancer in non-RRSO**

- Larger size (> 2 cm)
- Grossly visible tumor
- Cytologic atypia with mitosis

**Metastatic breast cancer to ovary--**
Clinically detected ovarian mass

**Invasive lobular ca**
Metastatic breast cancer to ovary--
Clinically detected ovarian mass

Invasive ductal ca

Papillary Solid Tubuloglandular

Primary ovarian serous carcinoma
WT-1, PAX8, CA125
Mammaglobin GCDFP-15

Mammaglobin expression may be seen in up to 40% of endometrioid carcinoma

Metastatic breast cancer or primary ovarian cancer?

56 y/o F with h/o breast cancer, on Tamoxifen, now with an ovarian mass

Immunohistochemistry
Metastatic breast or ovarian endometrioid ca?

Features favoring endometrioid ca--
- Squamous differentiation
- Evidence of endometriosis
- PAX8 +, GCDFP -

Dx: Primary endometrioid ca in ovary

Metastatic breast cancer to RRSO

- Majority of RRSO patients already have breast cancer
- Many patients have received chemotherapy
- Clinically occult, chemotherapy effect
  - Distinction from primary ovarian ca
  - Distinction from benign ovarian lesions

45 y/o F with breast ca, who underwent bilateral mastectomy and RRSO following neoadjuvant chemotherapy
A 3 mm focus of foamy cells identified in one ovary

Diagnosis?
Metastatic breast cancer in RRSO

- Chemotherapy effect: foamy cytoplasm, bland cytology, lack of mitosis

- Mimic benign ovarian lesions → underdiagnosis
  - Hilus cell rests
  - Stromal hyperthecosis
  - Steroid cell nodule
Hilus cells

- Keratin
- Inhibin/calretinin

Metastatic breast cancer

- Keratin
- Calretinin/Inhibin
- GCDFP
- PAX8/WT1/CA125

**Take home message**

- Clinical history, imaging findings and review of prior slides: critical
- Use a panel of antibodies
- Understand the limitation of the antibodies

**Rely on the results of a single immunostain to establish the site of origin of a carcinoma in a patient without a known primary site.**