When (Lack of) Ancillary Tests Lead You Astray

An Instructive Case

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Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2018:

Name of the enterprise / Nature of the interest

Enterprise | Interest
Consultant for PAIGE.AI
The Breast Pathology Team at MSKCC
Case

- 76-year-old male with palpable right breast mass
- No personal or family history of breast disease
- Diagnostic mammogram and ultrasound performed
Mammogram

Ultrasound: 3.2 cm irregular hypoechoic mass
Breast core biopsy
Necrosis

High-grade nuclei

Mitotic figures

ER
Diagnosis:

Invasive ductal carcinoma, poorly-differentiated

ER: Negative (0%)
PR: Negative (0%)
HER2: Negative (0)
Staging PET/CT prior to planned mastectomy:

1. Right breast mass, 4.1 cm, SUV 9.8

2. Right lower lobe lung mass, 3.1 cm, SUV 13.9

Core biopsy, FNA
Lung biopsy

**Diagnosis:** Small cell carcinoma of lung

**Immunohistochemistry:**
- **TTF-1:** Positive
- **Chromo:** Focally positive
- **RB:** Lost
- **P40:** Negative
- **GATA3:** Negative
- **SOX10:** Negative
Let’s go back and look at the breast tumor...
Necrosis

Spindle cells
Immunohistochemistry in breast carcinoma:
TTF-1: Positive
INSM1: Positive
Chromo: Positive
RB: Lost

GATA3: Negative
SOX10: Negative

Metastatic small cell carcinoma
For this session…

1. Pathology of breast carcinoma in males
2. Metastasis to and from the breast and use of immunohistochemical stains
3. Small cell carcinoma and neuroendocrine tumors of the breast
Breast carcinoma in men

- < 1% of breast cancers
- < 1% of all cancers in men
- High proportion of papillary carcinomas
- 10% occur in *BRCA2* pts, less in *BRCA1*
- Similar prognosis to breast cancer in females with equivalent stage
Triple-negative breast carcinoma is rare in males.

- 0.3% were triple-negative (3 of 1054)
  - 99.3% ER-positive
  - 81.9% PR-positive
  - 8.6% HER2-positive

Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program
A triple-negative breast carcinoma in a man should prompt consideration of metastasis.
Non-mammary metastases to the breast and axilla: a study of 85 cases

Deborah F DeLair, Adriana D Corben, Jeffrey P Catalano, Christina E Vallejo, Edi Brogi and Lee K Tan

Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

- 11 years: 85 patients (72 women, 13 men)
- Breast: 1st presentation of disease in 11%
- 75% were solitary lesions

Metastatic tumors:
1. **Carcinoma**: 58% (49): Ovary + lung most common
2. Melanoma: 21% (18)
3. Sarcoma: 21% (18)
Immunostains can help show that a tumor is from the breast (or from somewhere else)

**IHC markers we may use:**
- CK7, CK20
- ER, PR, HER2
- GATA3
- SOX10

Mammaglobin – sensitive, not specific
GCDFP-15 (BRST2) – specific, not sensitive
Liver biopsy

Is this from the breast?
What can we do to determine if carcinoma of unknown origin is from the breast?

Did the patient have breast cancer and what do we know about the original tumor?

- Morphology, morphology, morphology
- ER/PR/HER2
- Size/stage

Immunostains can be helpful, but are not entirely sensitive or specific
What do we know about the original tumor?

- Multifocal microinvasive carcinoma
- ER-neg, PR-neg, HER2-pos
Metastatic carcinoma from breast
CK7+/CK20- tumors

- Breast
- Lung
- Upper GI
- Mesothelial
- Endometrial
- Endocervical
- Thyroid

7.5% of breast carcinomas were CK7- in one study

1.7% were CK20+

May be helpful to stain both metastatic tumor and primary tumor (if available)

Virchos Arch 2012;461(3)
ER staining can be seen in a variety of tumors

Diffuse and strong expression usually indicates breast or gyn

- Was the patient’s breast tumor ER positive?
- ER-positive tumors retain expression in >90% of cases

Other tumors may show weak ER expression:
- Lung, bladder, thyroid
Lung adenocarcinoma

Napsin

TTF1

ER
GATA3

Transcription factor (nuclear) involved in differentiation in variety of tissue types:

- Breast
- Urothelium
- Renal tubules
- Adipose tissue
- Skin adnexa
- Others…
GATA3 is a **sensitive** marker for breast carcinoma

**ER+** breast carcinomas: **90-100%**

**ER-** breast carcinomas:
- Variable in literature: **40-70%**

Also expressed in special types to variable degrees:
- Apocrine ca
- Metaplastic ca
- Medullary-like

Highly concordant between primary and metastatic tumors

*Human Pathol* 2013; 44(7): 1341-1349
*Human Pathol* 2016; 48: 37-47
GATA3 expression is seen other tumor types

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Positive Cases (%)</th>
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<tbody>
<tr>
<td>Breast</td>
<td>80-100</td>
</tr>
<tr>
<td>Bladder: urothelial carcinoma</td>
<td>60-90</td>
</tr>
<tr>
<td>Bladder: adenocarcinoma</td>
<td>30-50</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>80-100</td>
</tr>
<tr>
<td>Skin: squamous cell</td>
<td>90</td>
</tr>
<tr>
<td>Skin: basal cell</td>
<td>90-100</td>
</tr>
<tr>
<td>Skin: adnexal</td>
<td>80-100</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>30-60</td>
</tr>
<tr>
<td>Renal: chromophobe</td>
<td>40-50</td>
</tr>
<tr>
<td>Renal: others</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Cervical: squamous cell carcinoma</td>
<td>30-60</td>
</tr>
<tr>
<td>Cervical: adenocarcinoma</td>
<td>10-20</td>
</tr>
<tr>
<td>Pancreatic/biliary</td>
<td>10-35</td>
</tr>
<tr>
<td>Colorectal</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Gastroesophageal</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Ovarian</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Prostatic</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Endometrial</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Thyroid</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>
GATA3 is more sensitive than mammaglobin and GCDFP-15

Particularly helpful with ER-, poorly-differentiated tumors, which usually lack mammaglobin and GCDFP-15 expression
GATA3 expressed in 66% of TNBC (clone L50-823)

Mammaglobin: 26%
GCDFP-15: 16%

GATA3 expressed in 56% of TNBC that were negative for mammaglobin and GCDFP-15
SOX10 is helpful in establishing breast site of origin in a triple-negative tumor, especially when GATA3 is negative
SOX10

- Transcription factor involved with neural crest differentiation
- Positive in melanoma, nerve sheath tumors
- In breast: myoepithelial cells
SOX10 in breast carcinoma

- Expressed in 40-70% TNBC, less than 5% of ER+ breast carcinomas
- Positive in metaplastic ca, adenoid cystic ca
- Negative in malignant phyllodes

*Human Pathol* 2013;44(6):959-65
*Hum Pathol* 2017;67:205-210
*Hum Pathol* 2018;80:163-169
*Hum Pathol* 2019;85:221-227
57 metastatic TNBCs

- GATA3+ in 82%
- SOX10+ in 58%
- Among GATA3 neg cases, 70% were SOX10 positive
- 95% were positive for either GATA3 or SOX10

*Human Pathol 2013;44(6):959-65*
SOX10, GATA3, GCDFP15, Androgen Receptor, and Mammaglobin for the Differential Diagnosis Between Triple-negative Breast Cancer and TTF1-negative Lung Adenocarcinoma

Elodie Laurent, MBBS,§† Hugues Begueret, MD, PhD,‡ Benjamin Bonhomme, MD,* Rémi Veillon, MD,§ Matthieu Thamerel, MD, PhD,‖ Valérie Velasco, BS,§ Veronique Brouste, MSc,§ Stéphanie Happe, MD,¶ Marion Fourrier, MD,# Thomas Grellety, MD, PhD,††∥ and Gaetan MacGrogan, MD††

- **SOX10 100% specific for breast vs. lung**

Note: Cytokeratin should be performed to exclude metastatic melanoma (CK-neg, SOX10-pos)
Small cell morphology in a breast biopsy (without DCIS) should prompt additional work-up
Papillary and neuroendocrine breast lesions: the WHO stance

Histopathology

1. Well-differentiated (carcinoid-like)

\(~1\%\) of malignant breast tumors

2. Poorly-differentiated/small cell

3. Invasive carcinoma with neuroendocrine differentiation
   - Heterogeneous group
   - Special and non-special types of breast cancer

\(~25\%\) of malignant breast tumors
Neuroendocrine tumor, well-differentiated

- Fibrovascular stroma
- Nests of spindle cells
Neuroendocrine tumor, well-differentiated

- Resembles carcinoid of lung and GI tract
- Solid nests, trabeculae, minimal tubules
- Ovoid, spindle, clear cells
- Low to intermediate nuclear grade
- +/- stippled “salt and pepper” chromatin, nucleoli
- Delicate fibrovascular stroma
Well-differentiated neuroendocrine carcinomas express the “usual” breast markers and are typically ER+ and HER2-
Small cell carcinoma
Mammary small cell carcinoma

- Identical to small cell carcinoma of lung
- Infiltrative, densely-packed cells
- Hyperchromatic, scant cytoplasm
- Crush artifact
- Abundant mitotic figures
- Necrosis
- Frequent LVI
Infiltrative growth
Densely-packed cells

Infiltrative growth
High N/C ratio
Mitoses
DCIS associated with small cell carcinoma:
- High-grade
- Solid, cribriform
- Small cell nuclei
CD56

Ki-67

ER

CD56

Ki-67

TTF-1
Must exclude metastatic small cell carcinoma

Features that support breast primary:
- Clinical
- ER-positivity (seen in 30-50%)
- GATA-3 positivity
- DCIS
- Co-existing invasive carcinoma, no special type

**Caution**
TTF-1 positivity can be seen in small carcinoma from any site, including breast
Invasive carcinoma with NE differentiation

- Up to 25% of invasive breast carcinomas
- Special types and invasive carcinoma, no special type
- No indication for routine use of neuroendocrine markers

Mucinous carcinoma, hypercellular  Solid papillary carcinoma
Comparison of metastatic neuroendocrine neoplasms to the breast and primary invasive mammary carcinomas with neuroendocrine differentiation

Sambit K Mohanty¹, Stacey A Kim¹, Deborah F DeLair², Shikha Bose³, Anna R Laury¹, Shefali Chopra¹, Richard B Mertens¹ and Deepti Dhall¹

Metastatic to the breast: n=22

Well-differentiated: n=15
- 7 small bowel
- 6 lung
- 1 colon, 1 ovary

Poorly-differentiated: n=7
- 5 lung
- 1 endometrium, 1 cervix

7 (32%) had no known history of neuroendocrine tumor

3 (14%) initially diagnosed as primary breast carcinoma
- All well-differentiated from small bowel

Mod Pathol. 2016;29(8):788-98
<table>
<thead>
<tr>
<th></th>
<th><strong>1° Breast NEC</strong></th>
<th><strong>Metastatic NEC</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Nuclei:</strong></td>
<td>Irregular, pleomorphic</td>
<td>Smooth borders, uniform</td>
</tr>
<tr>
<td><strong>In situ:</strong></td>
<td>+/-</td>
<td>Not present</td>
</tr>
<tr>
<td><strong>Coexisting IDC:</strong></td>
<td>+/-</td>
<td>Not present</td>
</tr>
<tr>
<td><strong>ER:</strong></td>
<td>+ (&gt;90%)</td>
<td>- (or weak staining)</td>
</tr>
<tr>
<td><strong>GATA-3:</strong></td>
<td>+ (&gt;90%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>TTF-1:</strong></td>
<td>-</td>
<td>+ in lung</td>
</tr>
<tr>
<td><strong>CDX2:</strong></td>
<td>-</td>
<td>+ in GI tract</td>
</tr>
</tbody>
</table>

Stay tuned.....

New neuroendocrine tumor classification:

1. Neuroendocrine tumour
   - Low to intermediate grade
2. Neuroendocrine carcinoma
   - High grade

5th Edition coming soon
Bonus case:
74-year-old woman with breast mass
Core biopsy performed
Papillary carcinoma?
Diagnosis:
Tissue contaminant from bladder case

“You GATA be careful!”
- Natasha Rekhtman
Take home points:

- Triple-negative breast carcinoma is rare in men. Other diagnoses (metastasis, skin primary) should be considered and excluded.

- GATA3 and SOX10 are sensitive and specific markers for breast carcinoma, but should be interpreted with caution.

- Small cell carcinoma morphology should prompt additional work-up so you are not “lead astray.”
Thank you for your attention
Additional slides
Chromogranin-Reactive Endocrine Cells in Argyrophilic Carcinomas ("Carcinoids") and Normal Tissue of the Breast

Demonstrated chromogranin reactivity in argyrophilic breast carcinomas but not in invasive ductal carcinomas

Clinical significance of neuroendocrine carcinoma of the breast
A. Sapino, M. Papotti, L. Righi, P. Cassoni, L. Chiusa & G. Bussolati

Department of Biomedical Sciences and Human Oncology, University of Turin, Turin, Italy

> 50% positive cells cutoff
35 cases: grade, ER, presence of mucin prognostic

Am J Pathol. 1985;120:186-92
Neuroendocrine tumor, well-differentiated

Rounded nests
Well-differentiated (carcinoid-like)
Neuroendocrine tumor, well-differentiated
Neuroendocrine tumor, well-differentiated

- Round nuclei
- Nucleoli
- Stippled chromatin

- Spindled nuclei
- Fine chromatin
DCIS:

- Seen in 50-70% of neuroendocrine carcinoma
- Cribriform, solid, papillary intermediate nuclear grade, +/- neuroendocrine cytologic features
Neuroendocrine tumor, well-differentiated

**Immunohistochemistry:**

Neuroendocrine markers:
- Synaptophysin, chromogranin most specific
ER+/HER2- neuroendocrine carcinomas (n=18)
- Heterogeneous morphology: ILC, mucinous, IDC with NE diff
- No small cell carcinomas

GATA-3, FOXA1, TBX3, ARID1a (each mutated in 3/18 cases)
PIK3CA, AKT1, CDH1 (each mutated in 2/18)

PIK3CA and TP53 (n=0) mutations less frequent than ER+/HER2- tumors from control groups, whereas ARID1a, FOXA1, TBX3 mutations were more frequent
47 neuroendocrine ca
- 30 well-diff., 7 small cell, 10 IC w/ NE differentiation
- Luminal A (52%) or luminal B (48%)
- 46/47 (98%) GATA-3

PIK3CA: 3/42 (7%) (all well-diff)
TP53: mutations in 3/42 (2 small cell, 1 well diff)
- Both less frequent than ER+/HER2- tumors in TCGA and METABRIC

Outcome:
- NE carcinoma assoc. w/ shorter RFS compared with matched IDC
- No difference in OS
- No survival differences between NE carcinoma groups, however histologic grade prognostic for RFS

Mod Pathol. 2018;31:68-82
Breast tumor in a 71-year-old woman

Is there any history?
2 years earlier...

Small bowel obstruction:
Well-differentiated neuroendocrine tumor
Breast tumor

Small bowel tumor

CDX2

Metastatic neuroendocrine tumor

Breast tumor
- **TP53** mutations seen in 75% of lung and breast
- **PIK3CA** mutations seen in 33% of breast, none in lung