Clinical Case
Mammography and ultrasound findings

- 33 yo G1P1 female presented with self-detected right breast mass at 3 months post partum
- Breast imaging showed an 1.9 cm mass at 1 o’clock at 3 cm from the nipple corresponding to the palpable area of concern
- Ultrasound evaluation revealed a mass with posterior acoustic shadowing corresponding to the mammographic findings
- Breast Imaging also showed an enlarged axillary lymph node
- An US guided NCB was performed

Clinical Case
Needle core biopsy findings

- Following the NBC the patient underwent bilateral mastectomies, intraoperative evaluation of the sentinel node and right sided AXLD
- Final Pathology:
  - Right breast mastectomy
    - IDC, grade 3/3, 1.9 cm, with prominent lymphocytic reaction
    - ER/PR/HER2: negative
    - 1/14 lymph nodes with metastatic disease
    - pT1c, N1a, Mx. Stage IIa
  - Left breast mastectomy
    - Benign breast findings

Mastectomy: Breast  Tumor Markers

Disclosure of Relevant Financial Relationships

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Pregnancy Associated Breast Cancer (PABC)

PABC: Definition

- Breast cancer diagnosed during gestation, lactation and within 1 to 5 years postpartum

Epidemiology

- Malignancy in pregnancy
  - 1:2000 in 1964 to 1:1000 deliveries in 2000

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>1:2000 – 10,000</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1:2000 – 10,000</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>1:1000 – 4,000</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 – 5/100,000</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1/75,000 – 100,000</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>4 – 8/100,000</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1:13,000</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>14/100,000</td>
</tr>
</tbody>
</table>

Breast Cancer and Pregnancy

- 6,000,000 pregnancies/year in the US
- 1 in 3,000 to 1 in 10,000 are associated with BC
- PABC constitutes 0.2-3.8% of all breast cancer cases
- PABC constitutes 25-30% of all premenopausal women diagnosed with breast cancer
- Breast cancer is the leading cause of cancer death in US women age 15-29.

Source: SEER data, 2013

Epidemiology (cont’d)
Dual effects of Pregnancy on Breast Cancer Development

- **Protective**
  - Pregnancy induced epithelial cell differentiation
  - Changes in estrogen responsiveness of parous gland
  - Diminution in number of mammary stem cells


- **Promoting**
  - Involutional changes post pregnancy, simulate wound healing/inflammatory environment increasing propensity for metastasis
  - Altered hormone levels in parous women especially GH and prolactin


Involution hypothesis

- Mammary gland involution: fully differentiated milk-producing breast regresses to a pre-pregnant-like state
  - Involves apoptotic cell death of 50-80% of the mammary epithelium
  - Tissue-remodeling programs similar to wound healing and inflammation
  - Wound healing and inflammation → tumor progression, dissemination and metastasis
**PABC: Clinical Presentation**

- Palpable breast mass
  - Physiologic changes of pregnancy
    - increased breast volume
    - palpable nodularity
    - firmness
    - increased parenchymal density
- Usually presents as advanced disease
  - Largest proportion of stages II-IV breast cancers

**Pathologic features of PABC**

- Can be any subtype of BC
  - Invasive ductal carcinoma (75-90%)
  - Larger tumor size
  - Higher grade
  - Higher stage at presentation
  - Higher rates of lymph node involvement (56-89%)

**PABC: Histologic Features**

- Breast mass
- Lymph node

**PABC: IHC**

- High frequency of hormone negative status
  - <70% ER and PR negative with high Ki67
- More frequently triple negative
  - ER, PR and HER2
- If not TN, then often overexpression of HER2

**Prognosis**

- Worse prognosis in a matched case study (stage, age and year of diagnosis)
- 5-year OS 30.7% PABC vs. 48.7% non-PABC ($p < 0.0001$)

**PABC: Genomic Signatures**

- Hormonal milieu of pregnancy contributes to the aggressiveness of PABC
- PABC samples clustered with established breast cancer subtypes
PABC: Genomic Signatures of Tumor Cells

- Hormone-regulated genes differed in PABC vs. non-PABC (malignant epithelium)
  - Cell proliferation
  - Cell migration
  - Lipid metabolism
  - Immune response

PABC: Genomic Signatures of Stroma

- Hormone-regulated genes differed in PABC vs. non-PABC (tumor-associated stroma)
  - immune-related genes (macrophage response)

Hormone-regulated genes differed in PABC vs. non-PABC (malignant epithelium)

- Cell proliferation
- Cell metabolism
- Lipid metabolism
- Immune response

Hormone-regulated genes differed in PABC vs. non-PABC (tumor-associated stroma)

- immune-related genes (macrophage response)

The significant differences in genomic pathways support the involution hypothesis

- Development and prognosis of PABC
- May aid in the identification of unique therapeutic targets

The Inflammatory Microenvironment in Cancer Development and Progression

- Tumor microenvironment:
  - Blood vessels
  - Fibroblasts
  - Signaling molecules
  - Extracellular matrix
  - Inflammatory cells

Inflammatory tumor microenvironment contributes to the biological behavior of cancer

The significant differences in genomic pathways support the involution hypothesis

- Development and prognosis of PABC
- May aid in the identification of unique therapeutic targets

Inflammatory tumor microenvironment contributes to the biological behavior of cancer

PABC diagnosed within 2 years of pregnancy

- grade 3 (76% vs. 26%)
- triple negative (34% vs. 3%)
- positive lymph nodes (61% vs. 45%)

Majority of PABC have tumor associated inflammation (TAI - 50% moderate or severe).

Severe TAI more likely in PABC (1 in 5 cases) and absent in controls.

All 5 cases with severe TAI → grade 3 tumors with positive lymph nodes.

<table>
<thead>
<tr>
<th>TAI 0</th>
<th>TAI 1+</th>
<th>TAI 2+</th>
<th>TAI 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABC</td>
<td>1 (3.8%)</td>
<td>12 (46.2%)</td>
<td>8 (30.8%)</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>6 (27.3%)</td>
<td>13 (59.9%)</td>
<td>3 (13.6%)</td>
</tr>
</tbody>
</table>

- Majority of PABC have tumor associated inflammation (TAI - 50% moderate or severe)
- Severe TAI more likely in PABC (1 in 5 cases) and absent in controls
- All 5 cases with severe TAI → grade 3 tumors with positive lymph nodes

Perilobular inflammation (PLI) away from the tumor

<table>
<thead>
<tr>
<th>PLI 0</th>
<th>PLI 1+</th>
<th>PLI 2+</th>
<th>PLI 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABC</td>
<td>4 (15.4%)</td>
<td>13 (50%)</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>10 (45.5%)</td>
<td>9 (40.9%)</td>
<td>1 (4.5%)</td>
</tr>
</tbody>
</table>

- PABC more likely to have perilobular inflammation (85% vs. 55%)
- TAI and PLI may play an important role in tumor metastasis in PABC and contribute to the poor prognosis in these patients

- Immunohistochemical stains for T cells (CD4 and CD8)
- Similar amounts of CD4+ lymphocytes
- PABC more abundant CD8+ lymphocytes

<table>
<thead>
<tr>
<th>CD4</th>
<th>1+</th>
<th>2+</th>
<th>3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABC</td>
<td>0</td>
<td>7 (35%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>0</td>
<td>6 (40%)</td>
<td>9 (60%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD8</th>
<th>1+</th>
<th>2+</th>
<th>3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABC</td>
<td>0</td>
<td>9 (45%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>CONTROLS</td>
<td>1 (7%)</td>
<td>11 (73%)</td>
<td>3 (20%)</td>
</tr>
</tbody>
</table>

- Similar amounts of CD4+ lymphocytes
- PABC more abundant CD8+ lymphocytes

PD-L1 is highly expressed in tumor infiltrating lymphocytes in PABC

<table>
<thead>
<tr>
<th>TIL</th>
<th>PABC</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>5.86</td>
<td>3.07</td>
<td>0.03</td>
</tr>
<tr>
<td>Strong PD-L1</td>
<td>42.9%</td>
<td>0%</td>
<td>0.01</td>
</tr>
<tr>
<td>PD-1</td>
<td>8.81</td>
<td>5.36</td>
<td>0.28</td>
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</table>

PD-L1 is highly expressed in tumor infiltrating lymphocytes in PABC.

Summary

- PABC is BC diagnosed during or after a recent pregnancy or lactation.
- PABC affects 25-30% of premenopausal women with breast cancer.
- Pregnancy results in a transient increase risk in breast cancer followed by a decrease risk (protection) over time.
- Multiple hypothesis for pregnancy’s promoting and protective effects exist.
- Tissue remodeling during mammary gland involution are similar to wound healing and inflammation and may facilitate tumor progression and metastasis.
- PABC tends to present at a more advanced stage, with larger, high grade, triple negative or HER2-positive tumors.
- PABC has worse prognosis compared with age and stage matched controls.
- Better understanding of the molecular pathways of tumor initiation and progression and prompt diagnosis and treatment in PABC may lead to better OS.