Gestational Trophoblastic Diseases

The common and the Rare

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Gestational Trophoblastic Disease

• Molar

• Non-Molar
A Common Question

• The villi in this P.O.C. seem a bit edematous and there are some (maybe?) trophoblastic proliferation. Is it a molar pregnancy?
CLASSICAL COMPLETE MOLE
EARLY COMPLETE MOLE
PARTIAL MOLE
HYDROIC ABORTUS
<table>
<thead>
<tr>
<th></th>
<th>ECM</th>
<th>CM</th>
<th>PM</th>
<th>HA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trophoblast Proliferation</strong></td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Villi</strong></td>
<td>Spectrum sizes</td>
<td>Spectrum sizes</td>
<td>2 populations</td>
<td>Balloon-like</td>
</tr>
<tr>
<td><strong>Scalloped villous contours</strong></td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>+</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Club-like projections</strong></td>
<td>+</td>
<td>-/+</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Cisterns</strong></td>
<td>Variable</td>
<td>Prominent</td>
<td>Variable</td>
<td>Absent/rare</td>
</tr>
<tr>
<td><strong>Pseudoinclusion</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Karyorrhexis</strong></td>
<td>+++</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td><strong>Fetal tissue</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Persistent GTD</strong></td>
<td>10-30%</td>
<td>10-30%</td>
<td>0.5-1 %</td>
<td>-</td>
</tr>
</tbody>
</table>
Ancillary tests

- P57 immunohistochemistry
- Ploidy analysis
  - Traditional karyotyping
  - Flow cytometry
  - FISH
- Short tandem repeat (STR) genotyping
Hydatidiform Mole

**COMPLETE MOLE**
- 80%
- All chromosomes are derived from the sperm - androgenesis

**PARTIAL MOLE**
- 90%
- Monospermy with reduplication or Tetraploid

**ANDROGENETIC (DIANDRIC DIPLOID)**
- 46XX
- 46XY

**DIANDRIC MONOGYNIC TRIPLOID**
- 69XXY
- 69XXX
- 69XYY
p57 → PATERNALLY IMPRINTED (MATERNALLY EXPRESSED)

Most likely not a complete mole

Complete mole

Negative in cytotrophoblast
Negative in stromal cells
Review
Hydatidiform Moles: Ancillary Techniques to Refine Diagnosis

Brigitte M. Ronnett, M.D., Cheryl DeScipio, Ph.D., and Kathleen M. Murphy, Ph.D.
NON MOLAR
(Biparental Diploidy)
Monospermic

Androgenetic

Diploidy
Diandric Triploid: Partial Hydatidiform Mole
Abnormal P57 results:

Discordant P57 expression in androgenetic biparental diploidy mosaic/chimmaric conception

CM with aberrant P57 expression - androgenetic diploidy with retained maternal chromosome 11
Androgenetic Diploid with Retention of Maternal Chr 11 (p57 positive CHM)
Potential Pitfalls

• Twin pregnancy
• Mosaic/chimeric conceptions
• Biparental CM
• Egg donor gestation
Morphologically suspicious for hydatidiform mole

P57 Immunohistochemistry

- P57 Negative
  - Morphology yes
    - Diandric diploidy
      - CM
  - Morphology equivocal
    - Diandric triploidy
    - Trisomy or monosomy

- P57 Positive, equivocal, aberrant, discordant
  - Molecular genotyping
    - Diandric triploidy
    - Digynic triploidy
    - Biparental diploidy
    - Non-molar
A Common Question

• There is something looks like trophoblastic, do I need to worry about it?
CASE 1

27 F

G2P2

Plateau of hCG = 27-30, several months after pregnancy

Spotting

?Mild dilation of cornua on ultrasound
CASE 2

34 F

G4P4

Spotting 12 months following last pregnancy

No hCG elevation
CASE 3

34 F

G4P3A1(aborted a complete hydatidiform mole)

Spotting 6 months following evacuation

Low level elevations of hCG: 17
CASE 4

28F

G1P1 (normal baby girl)

2 years post delivery: spotting and microscopic hematuria

hCG: 104; ultrasound normal
Case 5

- 48-year-old woman
- G2P0
- Vaginal bleeding, nausea, and increase in breast size
- Serum beta-hCG: 435,915
- D&C
History Con’t

• Rising serum beta-hCG post D&C

• Treatment:
  – Methotrexate and leucovorin
  – TAH-BSO
History Con’t

• Chemotherapy
• Patient was followed for the next 6 years
• An elevated serum beta-hCG (30.1) was noted on routine follow up
• CT: a 0.7 cm nodule in the upper lobe of the left lung
• Wedge lung resection
Epithelioid Trophoblastic Tumor

A tumor composed of chorionic-type intermediate trophoblastic cells
Epithelioid Trophoblastic Tumor

• Majority are uterine or cervical primaries
• Pregnancy or GTD history
  – Variable, can be remote
• History of mole
  – 14%
• Serum hCG: low (<2,000 mIU/ml)
• Behavior: Self-limited, persistent, or aggressive
• Response to Chemo: variable
Epithelioid Trophoblastic Tumor

- Reported pulmonary primaries - rare

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Serum β-hCG (mIU/mL)</th>
<th>Likely Antecedent Pregnancy (Interval)</th>
<th>Primary Treatment</th>
<th>Follow-up (Overall Survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>400</td>
<td>Unknown</td>
<td>Wedge resection, lobectomy</td>
<td>NED (90 mo)</td>
</tr>
<tr>
<td>49</td>
<td>400</td>
<td>Miscarriage (12 mo)</td>
<td>EMA/EP, lobectomy, LAVH, BSO</td>
<td>NED (45 mo)</td>
</tr>
<tr>
<td>34</td>
<td>426</td>
<td>Full-term delivery (24 mo)</td>
<td>Segmentectomy, EMA/EP, hysterectomy</td>
<td>NED (22 mo)</td>
</tr>
</tbody>
</table>

BSO indicates bilateral salpingo-oophorectomy; EMA/EP, multi-agent chemotherapy regimen consisting of etoposide, methotrexate, dactinomycin alternating with cisplatin, etoposide; hCG, human chorionic gonadotrophin; LAVH, laparoscopic-assisted vaginal hysterectomy; NED, no evidence of disease.
Differential Diagnosis

• Squamous cell carcinoma of the cervix

• Primary lung carcinoma
  – Squamous cell carcinoma
  – Pleomorphic carcinoma
  – Other carcinomas with trophoblasts

• Primary or metastatic germ cell tumor with trophoblastic differentiation

• Other gestational trophoblastic tumors
Squamous Cell Carcinoma

Resemble ETT

- Location
  - Cervical/lower uterine segment
  - Lung
- Morphology
  - Epithelioid with pink cytoplasm
  - Necrosis
- P63 positive

Different from ETT

- Clinical features
- Pathologic features
- Immunohistochemistry
## Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>ETT</th>
<th>Squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>P63</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CK5/6</td>
<td>- or focal</td>
<td>+</td>
</tr>
<tr>
<td>P16</td>
<td>-</td>
<td>+ (in HPV associated cervical SCC)</td>
</tr>
<tr>
<td>Inhibin</td>
<td>+</td>
<td>20%</td>
</tr>
<tr>
<td>CD10</td>
<td>+</td>
<td>20%</td>
</tr>
<tr>
<td>HSD3B1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>hPL</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Mel-CAM</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>
Pleomorphic Carcinoma

Resemble ETT

• Polygonal cells with eosinophilic cytoplasm
• Large multinucleated cells

Different from ETT

• Neutrophilic infiltrate, sometime within the cytoplasm
• Association with other type of carcinoma
• Often TTF-1 positive
Non-Molar Gestational Trophoblastic Disease

• Choriocarcinoma

• Placental site trophoblastic tumor (PSTT)

• Epithelioid trophoblastic tumor
## Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>ETT</th>
<th>PSTT</th>
<th>Choriocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>Vaginal bleeding</td>
<td>Missed abortion</td>
<td>Persistent GTD after hydatidiform mole</td>
</tr>
<tr>
<td><strong>Last known pregnancy or GTD</strong></td>
<td>Variable</td>
<td>Variable</td>
<td>Months</td>
</tr>
<tr>
<td><strong>History of mole</strong></td>
<td>14%</td>
<td>5-8%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Serum hCG</strong></td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Hysterectomy</td>
<td>Hysterectomy</td>
<td>Chemotherapy</td>
</tr>
</tbody>
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Intermediate Trophoblastic Lesion

**Implantation Site Intermediate Trophoblast**
- P63 - hPL+++
- Ki-67 <1%
  - EIS
- Ki-67 >10%
  - PSTT

**Chorionic type Intermediate Trophoblast**
- P63 + hPL-/+
- Ki-67 <5%
  - Ki-67 >15%
    - Cyclin E -
    - Cyclin E ++
      - PSN
      - ETT

Inhibin +
LMWCK +
Low hCG
## Immunohistochemistry

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<tr>
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<tbody>
<tr>
<td>P63</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>CK18</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inhibin</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>hPL</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Mel-CAM</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>hCG</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Ki-67</td>
<td>10-25%</td>
<td>&gt;50%</td>
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Choriocarcinoma

• Treated choriocarcinoma
• Choriocarcinoma with areas predominantly composed of intermediate trophoblasts
Ki-67
CASE 7

37F

G1P1 (2 year old baby girl)

Vaginal bleeding and bulky uterus on ultrasound

Hysterectomy for “fibroids”

Pre-op hCG = 27 000
What is your diagnosis?
What is your diagnosis?

How do you explain a beta-hCG of 27 000?
Immunohistochemistry

Clinical history and clinical presentation are important in distinguishing ETT from Choriocarcinoma.

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Reference