The Pathology of Gestational Trophoblastic Neoplasia

Professor Mike Wells
University of Sheffield
Histopathological classification of Gestational Trophoblastic Disease

- Hydatidiform mole - complete
  - partial
- Invasive hydatidiform mole
- Choriocarcinoma
- Placental site trophoblastic tumour
- Epithelioid trophoblastic tumour
Hydatidiform mole

gestational age at evacuation

- **1960s**: 17 weeks
- **2000s**: 9.4 weeks
Early complete mole

- abnormally shaped villi
  - branching or polypoid
- stromal mucin
- stromal vessels may be present
- STROMAL NUCLEAR DEBRIS
cases of partial mole and hydropic miscarriage exhibit no or inconspicuous karryorrhletic debris
Partial mole

- fetal parts may be present
- focal hydropic change
- cistern formation
- irregular profile of villi
- round trophoblastic pseudoinclusions
- excess trophoblast may be subtle
- abnormal (angiomatoid) vasculature in second trimester
Partial mole
Partial mole
Partial mole v non-molar triploidy – pragmatic approach to diagnosis

(4-14% of hydropic miscarriages - non-molar triploid)

• partial mole
• favour partial mole
• possible partial mole/partial mole cannot be excluded
• non-molar
Genetic Origin of Triploid Conceptions

**Partial Mole**

Two sperm fertilise a normal oocyte to form a conceptus with 69 chromosomes

- Hyperplasia of the placenta
- Poor fetal development

The extra chromosome set is paternal

69,XXX; 69,XXY or 69,XY

**Non-Molar Triploid**

One sperm fertilises a diploid oocyte to form a conceptus with 69 chromosomes

- No placental hyperplasia
- Abnormal fetal growth, often with large head

The extra chromosome set is maternal

69,XXX or 69,XXY
Diploid complete mole
Triploid partial mole
- paternally imprinted gene
- maternally expressed
- villous cytotrophoblast p57kip2 -ve in CM
- villous cytotrophoblast p57kip2 +ve in PM
- syncytiotrophoblast always p57kip2 –ve
P57kip2 in hydatidiform mole

**Complete mole**
- Cytotrophoblast –ve
- Syncytiotrophoblast -ve

**Partial mole**
- Cytotrophoblast +ve
- Syncytiotrophoblast -ve

Non-villous trophoblast is p57 +ve even in complete mole (courtesy of Neil Sebire)
# Refining the diagnosis of hydatidiform mole: image ploidy analysis and \( p57^{kip2} \) immunohistochemistry

H Crisp, J L Burton, R Stewart & M Wells

*Academic Unit of Pathology, Division of Genomic Medicine, University of Sheffield Medical School, Sheffield, UK*

Date of submission 13 February 2003
Accepted for publication 28 May 2003

<table>
<thead>
<tr>
<th>Suspected diagnosis</th>
<th>Image cytometry</th>
<th>( p57^{kip2} ) status</th>
<th>Revised diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial mole</td>
<td>Triploid</td>
<td>+ve</td>
<td>Partial mole</td>
</tr>
<tr>
<td>Complete mole</td>
<td>Triploid</td>
<td>+ve</td>
<td>Partial mole</td>
</tr>
<tr>
<td>Partial mole</td>
<td>Diploid</td>
<td>-ve</td>
<td>Complete mole</td>
</tr>
<tr>
<td>Partial mole</td>
<td>Diploid</td>
<td>+ve</td>
<td>Hydropic miscarriage</td>
</tr>
</tbody>
</table>
Complete mole in twin pregnancy
Sections stained with $P57^{\text{KIP2}}$ showing negative staining for the complete mole (above) and positive staining for normal placental tissue (right)
Severe atypia of placental site trophoblast in complete mole
Persistent trophoblastic disease = gestational trophoblastic neoplasia (WHO) 
not a histopathological diagnosis

- 15% of patients with complete mole
- 0.5% of patients with partial mole
- majority are invasive moles
- choriocarcinoma
<table>
<thead>
<tr>
<th>FIGO RISK SCORING</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 40</td>
<td>≥ 40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td>-</td>
</tr>
<tr>
<td>Interval months from index pregnancy</td>
<td>&lt; 4</td>
<td>4 - &lt; 7</td>
<td>7 - &lt; 13</td>
<td>≥ 13</td>
</tr>
<tr>
<td>Pre-treatment serum hCG (IU/L)</td>
<td>&lt; $10^3$</td>
<td>$10^3$ - $10^4$</td>
<td>$10^4$ - $10^5$</td>
<td>≥ $10^5$</td>
</tr>
<tr>
<td>Largest tumour size (including uterus) cm</td>
<td>&lt; 3</td>
<td>3 - &lt; 5</td>
<td>≥ 5</td>
<td>-</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastro-intestinal</td>
<td>Liver, brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>-</td>
<td>1-4</td>
<td>5-8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>-</td>
<td>-</td>
<td>Single drug</td>
<td>2 or more drugs</td>
</tr>
</tbody>
</table>
hCG monitoring of GTD
Criteria for chemotherapy

- static or rising hCG after 2nd/3rd uterine evacuation
- hCG >20,000iu after 2nd/3rd uterine evacuation
- persistent uterine haemorrhage with raised hCG
- persistent elevation of hCG 6 months post-uterine evacuation
- pulmonary metastases with static or rising hCG
Hydatidiform mole - predictive factors for PTD (GTN)

- ↑ telomerase activity
- ↓ apoptotic indices (TUNEL & M30 CytoDeath antibody)
- ↑ *Mcl-1* (anti-apoptotic gene)
- ↓ ferritin light polypeptide & IGFBP-1

Cheung *et al*
Placental site trophoblastic tumour

- weeks to years after pregnancy
- average interval 18-30 months
- invasive uterine mass (mean - 5cms diameter)
- paternal allele present
- absence of Y chromosome
Placental site trophoblastic tumour mirrors properties of normal non-villous trophoblast (extravillous or intermediate trophoblast)

- occasional binucleate/multinucleate cells
- myometrial infiltration
- intravascular tumour
- fibrinoid necrosis in vessel wall
Placental site trophoblastic tumour

- cords, islands, sheets of polygonal, round or spindle cells
- scattered mitoses
- Ki67 > 5%
- hPL, PLAP, inhibin +ve
- focal hCG +ve
- p63 - ve
Compared to Choriocarcinoma

- Slow growing
- Late metastases
- Lymph node involvement more common
- Less chemosensitive
- Less hCG
Placental site trophoblastic tumour factors associated with poor prognosis

(Baergen et al Gynecol Oncol 2006; 100: 511-520)

- deep invasion
- clear cells
- extensive necrosis
- mitoses+
PSTT Methods

• Retrospective study:
  – 62 patients with PSTT
  – Evaluated and/or treated between 1975 and 2006 in the UK GTD service (35,550 women registered)
  – Pathology centrally reviewed

### PSST Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>34.6</td>
<td>(13%)</td>
</tr>
<tr>
<td>Range</td>
<td>20-54</td>
<td>(60%)</td>
</tr>
<tr>
<td><strong>Antecedent Pregnancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Mole</td>
<td>8</td>
<td>(13%)</td>
</tr>
<tr>
<td>Partial Mole</td>
<td>1</td>
<td>(2%)</td>
</tr>
<tr>
<td>Termination</td>
<td>6</td>
<td>(10%)</td>
</tr>
<tr>
<td>Miscarriage/Stillbirth</td>
<td>10</td>
<td>(16%)</td>
</tr>
<tr>
<td>Term</td>
<td>37</td>
<td>(60%)</td>
</tr>
</tbody>
</table>
PSST Presenting Symptoms

- Vaginal Bleeding: 66.1%
- Abdominal Pain: 27.4%
- Amenorrhea: 25.8%
- Nephrotic Syndrome: 4.8%
- Respiratory Symptoms: 4.8%
- Uterine Rupture: 3.2%
- Neurological Symptoms: 3.2%
### PSST Patient Characteristics

#### Interval to Antecedent Pregnancy

<table>
<thead>
<tr>
<th>Interval to Antecedent Pregnancy</th>
<th>Median</th>
<th>Range</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 12 months</td>
<td>15</td>
<td>2-264</td>
<td>(24%)</td>
</tr>
<tr>
<td>13-47 months</td>
<td>34</td>
<td></td>
<td>(55%)</td>
</tr>
<tr>
<td>≥ 48 months</td>
<td>13</td>
<td></td>
<td>(21%)</td>
</tr>
</tbody>
</table>

#### Disease manifestation

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>36</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No extra-uterine disease</td>
<td></td>
<td>(58%)</td>
</tr>
<tr>
<td>Uterine and extra-uterine, pelvic disease</td>
<td>5</td>
<td>(8%)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>21</td>
<td>(34%)</td>
</tr>
</tbody>
</table>
• Diagnosis established following
  – uterine evacuation (n=38, 61%),
  – hysterectomy (n=19, 31%)
  – or tumour biopsy (n=5, 8%).
48 months from causative pregnancy is critical

For Interval from antecedent preg

48 month cut-off

Specificity 100%
Sensitivity 93%

<table>
<thead>
<tr>
<th>Time</th>
<th>Dead</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48</td>
<td>1/49</td>
<td>98%</td>
</tr>
<tr>
<td>≥ 48</td>
<td>13/13</td>
<td>0%</td>
</tr>
</tbody>
</table>
Stage predicts survival

- Follow-up (years)
- Percentage Survival
- Stage (FIGO): 1, 2, 3, 4
- 1-censored, 2-censored, 3-censored, 4-censored
- P = 0.0003
Mitosis no clear cut-point

For Mitosis

ROC Curve

Sensitivity

1 - Specificity

Diagonal segments are produced by ties.
hCG no clear cut-point
### Univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval ≥ 48 months*</td>
<td>$p &lt; 0.00001$</td>
</tr>
<tr>
<td>Age ≥ 36 yrs</td>
<td>$p &lt; 0.00001$</td>
</tr>
<tr>
<td>hCG (continuous)</td>
<td>$p = 0.014$</td>
</tr>
<tr>
<td>FIGO Stage</td>
<td>$p = 0.0003$</td>
</tr>
<tr>
<td>No of mets</td>
<td>$p = 0.0002$</td>
</tr>
<tr>
<td>Mitosis (continuous)</td>
<td>$p = 0.008$</td>
</tr>
</tbody>
</table>

*remained significant on multivariate analysis*
PSTT

- FIGO risk score – not applicable
- Stage I disease – surgery is sufficient unless there are other risk factors
- Stage II, III & IV – combined surgery and chemotherapy
- Chemotherapy not as effective compared with other forms of GTD
- Why 48 months since antecedent pregnancy is the optimum discriminator for survival is unclear
Epithelioid trophoblastic tumour

- Cells resemble chorion laeve
- Nodular islands of trophoblast surrounded by extensive necrosis
- Hyaline-like matrix
- Cells smaller & less pleomorphic than PSTT
- p63 positive
INHIBIN
Placental site nodule

- usually incidental

- months / years post pregnancy

- small, well circumscribed

- hyalinised
Placental site nodule

- single cells, clusters or cords of bland, uniform cells
- no infiltration
- no mitoses
- Ki67 < 5%
Placental site nodule transformed into a malignant epithelioid trophoblastic tumour with pelvic lymph node and lung metastasis

Tsai et al Histopathology 2008: 53: 601-604
Placental site nodule $\nu$ atypical placental site nodule $\nu$ epithelioid trophoblastic tumour

- significant areas of necrosis
- increased Ki-67
- foci of calcification
- increased Cyclin E expression
Placental site nodule v Epithelioid trophoblastic tumour

Ki-67

p63