**Pathology of Gestational Trophoblastic Disease**

**Modified WHO classification of GTD**

- **Molar lesions**
  - Hydatidiform mole
    - CHM
    - PHM
    - Invasive mole
- **Non molar lesions**
  - Choriocarcinoma
  - Placental site trophoblastic tumor (PSTT)
  - Epithelioid trophoblastic tumor (ETT)
  - Miscellaneous trophoblastic lesions
    - Exaggerated placental site
    - Placental site nodule

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**Molar pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>Normal pregnancy</th>
<th>PHM</th>
<th>CHM</th>
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</thead>
<tbody>
<tr>
<td><strong>Ploidy</strong></td>
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<tr>
<td><strong>Chromosome</strong></td>
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<td>46XX</td>
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<td>46XY</td>
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<td>69XX (95%)</td>
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<td>69XX (27%)</td>
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<td>69XX (3%)</td>
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<td>69XYY (70%)</td>
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<td>69XX (7%)</td>
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<tr>
<td>69XYY (3%)</td>
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<td>46XX</td>
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<td>46XY (13%)</td>
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<td>46XY (13%)</td>
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<tr>
<td><strong>Parentality</strong></td>
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</tbody>
</table>

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**Pathology of CHM**

- **Macro**: Vesicles, maximal diameter 2 cm.
- **Micro**
  - Enlarged villi, cavitation (necrosis)
  - Trophoblastic proliferation around villi with minimal atypia
  - *Absence or paucity of fetal stromal BVs*
  - Atypia of ITs at decidual implantation site.
Large swollen villi
Central cistern

Concentric CT & ST hyperplasia
Atypical implantation site

Pathology of early CHM

- In the 1960s mean GA of CHM = 17 wks
- Nowadays = 9.4 wks
- Common error is diagnosis of early CHM as PHM
- Macro
  - Resemble abortus with some vesicles

Early CHM

- Micro
  - Slight enlargement with scattered cavities in villi
  - Typical villous morphology: cauliflower like (lobulated appearance)
  - Focal to diffuse trophoblastic atypia
- Villous stroma
  - Hypercellular (stellate mesenchymal cells in blue myxoid matrix) = fibroadenoma like
  - Prominent karyorrhexis in villous mesenchymal cells, stromal nuclear debris
  - Numerous vessels with nucleated RBCs

Early CHM

Typical features in early CHM

- Abnormally shaped villi (bullous or polypoid)
- Stromal mucin
- Stromal nuclear debris (resulted of increased stromal proliferation and apoptosis

Early CHM

- Moderate villous enlargement
- Not prominent cistern
- Concentric trophoblastic hyperplasia
- Hypercellular stroma
  - Blushed appearance
- Irregular villous contours
  - “knuckles or toes”
- Atypical implantation site
Partial Hydatidiform Mole

**Pathology of PHM**
- Micro
  - **Two population of villi**
    - Smaller fibrotic normal appearing villi
    - Larger irregular shaped, hydropic villi
  - **Central cisterns**
  - **Irregular scalloped border** (Norwegian fjord type, sharp angulated)
  - Invagination of trophoblast and round inclusions (solid or cystic)
- **Evidence of fetal development**: No fetal tissue does not rule out PHM.
- Late PHM,... *Angiomatoid malformation*

**Pathological mimics of PHM**
- **Early CHM**
- Hydropic spontaneous miscarriage
- Twin gestation with CHM and existing fetus
- Placental angiomatous malformation
### Genetics abnormality in PHM

- **1% of conceptus = triploidy**
- **Triploidy** 80% **diandric** PHM 20% **digyny** Non molar
- Most of PHMs are triploid
- Reported teraploid (> 1 paternal set of chromosome)

### Special investigation in Dx of molar pregnancy

**Immunohistochemistry**
- P57kip2 (maternally expressed imprinted gene): CHM VS non CHM

**Ploidy analysis**
- Triploid PHM VS non-PHM

**Interphase cytogenetics**
- Identify chromosome aberrations by in situ hybridization (ISH) using chromosome specific probes (chromosome 1, X, Y)

### P57kip2 or IPL/PHLDA2

- Located at chromosome 11p15.5
- Strongly **paternally imprinted**, being expressed predominately from maternal allele
- **Potent cell cycle inhibitor and tumor suppressor**
- Lack of its activity can lead to loss of cell cycle control and hyperproliferation
- Normal pregnancy and PHM: positive at nuclei of villous stroma, villous CT, decidual and extravillous trophoblasts
- **CHM**: negative at nuclei of villous stroma, villous CT

### Features

<table>
<thead>
<tr>
<th>Features</th>
<th>CHM</th>
<th>PHM</th>
<th>Hydropic abortus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villi</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Villous outlines</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Villous inclusion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Villous stroma</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Reference tables

- Villous VSSs: Presence in early CHM
  - Absence in late CHM
  - Angiomatoid malformation in late PHM
- Trophoblasts: Multifocal or circumferential
  - Significance of increased atypia at implantation site
- Embryonic tissue: Absent
  - Presence, malformed fetus, IUGR
- Karyotype: 46XX, Uniparental
  - Generally triploid, biparental

### Images

- ![Normal villous](image1.png)
- ![Hydropic villous](image2.png)
- ![P57kip2](image3.png)
**Markers for molar pregnancy**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>PHM</th>
<th>CHM</th>
<th>Hydropic abortus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal placenta (all GA)</td>
<td>No loss</td>
<td>Loss</td>
<td>No loss</td>
</tr>
<tr>
<td>Hydropic degeneration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P57&lt;sup&gt;kip2&lt;/sup&gt;</td>
<td></td>
<td></td>
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</table>

**Ploidy**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Ploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHM</td>
<td>Triploid</td>
</tr>
<tr>
<td>CHM</td>
<td>Diploid</td>
</tr>
</tbody>
</table>

*Intervillous trophoblast


**Pathology of invasive mole**

- Hydatidiform in which hydropic villi invade **myometrium** or **BVs** or even the **extrauterine sites**
- Dependent on extent of invasion

**Non molar lesions**

Invasive mole
GTDs are distinct from other tumors in the human body in that they are genetically or allograft in the mother’s body.

They are fetal tumors that are arising in the mother’s body.

The remarkable curability of GTDs with chemoRx might reflect the underlying immune response of the mother to paternal antigens expressed on the surface of trophoblastic cells.

*Int J Gynecol Cancer 2006;16:1500-15*

Trophoblasts

- Trophoblastic differentiation at 7 days blastocyst
- Type:
  - Villous
  - Extravillous

**Vacuolated Trophoblast** at chorion in late pregnancy (described by Yeh, 1989)

Trophoblastic cells

<table>
<thead>
<tr>
<th>Features</th>
<th>CT</th>
<th>ST</th>
<th>IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Small polyhedral</td>
<td>Large</td>
<td>Medium polyhedral, to spindle</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Clear, distinct cell border</td>
<td>Amorphophilic or eosinophilic, fibrinous to coarsely vacuolated (irregular lacy pattern)</td>
<td>Eosinophilic</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Single, vesicular</td>
<td>Small, hyperchromatic</td>
<td>Single, bi, multi-nucleation at placental site</td>
</tr>
<tr>
<td>Mitosis</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Location</td>
<td>Inner layer of villi covering</td>
<td>Outer layer of villi covering</td>
<td>Sit in fibrin material within endometrium In walls or lumens of spiral arterioles</td>
</tr>
</tbody>
</table>

Trophoblastic tumor differentiation

- Choriocarcinoma
- PSTT
- Exaggerated placental site
- Vacuolated T
- ETT
- Placental site nodule

Int J Gynecol Cancer 2006;16:1500-15
Pathology of Choriocarcinoma

**Macro**: Well circumscribed nodular lesion with dominantly hemorrhagic structure

**Micro**
- *No choriocytic villi*
- Peripheral trophoblasts (lack intrinsic tumor vasculatures)
- **Bilaminar pattern** (recapitulates trophoblast of early implanting blastocyst)
- Extensive myometrial invasion without destruction or necrosis of myometrium
- Tumor in dilated vascular sinuses

**Special study of choriocarcinoma**
- **Immunohistochemistry**
  - Useful
  - Positive
    - *hCG (sg +ve)*, *CK, EMA, CEA, Ki67, hPL* (fewer cells), *PLAP* (rare)
- **Genetic polymorphisms**
  - DDX gestational or non gestational choriocarcinoma
  - To define prognosis and influencing therapeutic decision
  - To understand biology of trophoblastic tumor

**Pathology of Choriocarcinoma**

**Hormone production**

<table>
<thead>
<tr>
<th>Trophoblast</th>
<th>hCG</th>
<th>hPL</th>
<th>PLAP</th>
<th>Inhibin</th>
<th>Cytokeratin</th>
<th>P63</th>
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<tbody>
<tr>
<td>CT</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>IT</td>
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</tr>
<tr>
<td>Vacuolated</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>TA isoform</td>
</tr>
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</table>

**Choriocarcinoma**

- Biphasic trophoblasts
- Hemorrhagic necrosis
- Marked trophoblastic atypia
Pathology of PSTT

Macro
- Variable appearance
- Ill-defined mass
- Well circumscribed nodule
- In myometrium with or without projection into endometrial cavity
- No striking hemorrhage or necrosis

Micro
- Recapitulate appearance seen at placental bed
- Diffuse infiltration of mononuclear and multinuclear IT arranged in cords, islands, sheets between myometrial bundles
- Vascular invasion recapitulates normal implantation site: cell migrate through and replace vessel walls, maintaining overall vascular architecture
- Less intravascular proliferation
- Vary mitotic activity
- Abundant extracellular eosinophilic fibrinoid material

Pathology of ETT

Proposed by Mazur in 1989

Macro
- Nodular expansile pattern
- 50% of cases arise in lower uterine segment or endocervix

Micro
- Mixture of mononuclear cells with eosinophilic or clear cytoplasm forming nests or cords
- Areas of hyalinization or eosinophilic debris simulating tumor cell necrosis at center of tumor nests (resembling keratin material in SCC)
- Characteristic geographic pattern
- Dysmorphic calcification in areas of necrosis
- Low mitotic activity
was expressed

focal

(1)

class I)

HLA

CAM = MUC18

Melanoma cell adhesion molecule (Mel)

Inhibin

hPL

hCG

Markers for trophoblasts

- hCG
- hPL
- Inhibin α
  - Shih & Kurman showed that Inhibin α was expressed by all population of trophoblasts except CT
- Melanoma cell adhesion molecule (Mel-CAM) = MUC18
  - Kurman found that Mel-CAM is specific and sensitive marker for ET in normal placental implantation site and GTD lesion
- HLA-G (non classical major histocompatibility class I)
  - Singer et al showed positivity in all GTD lesions, but negative in non trophoblastic uterine neoplasms

Clinical features of PSTT, ETT and choriocarcinoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>PSTT</th>
<th>ETT</th>
<th>Choriocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Missed abortion</td>
<td>Abnormal vaginal bleeding</td>
<td>Persistent GTD after HM</td>
</tr>
<tr>
<td>Last Pregnancy or GTD</td>
<td>Variable, can be remote</td>
<td>Variable, can be remote</td>
<td>months</td>
</tr>
<tr>
<td>History of mole</td>
<td>0-8%</td>
<td>14%</td>
<td>50%</td>
</tr>
<tr>
<td>Serum hCG</td>
<td>Low (&lt;10-2,000 IU/L)</td>
<td>Low (15 – 500 IU/mL)</td>
<td>High (&gt;10,000 IU/mL)</td>
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<tr>
<td>Behavior</td>
<td>Variable</td>
<td>Variable</td>
<td>Aggressive if untreated</td>
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<tr>
<td>Response to chemotherapy</td>
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<td>Variable</td>
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<tr>
<td>Treatment</td>
<td>Surgery hysterectomy</td>
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<td>Chemotherapy</td>
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Biomarkers for diagnosis GTDs

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<tbody>
<tr>
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<tr>
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<td>Inhibin α</td>
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<tr>
<td>PLAP</td>
<td>Occasional cells</td>
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</tr>
<tr>
<td>P63</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Ki67</td>
<td>&gt;10%</td>
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<tr>
<td>Mel-CAM</td>
<td>–</td>
<td>–</td>
<td>focal</td>
</tr>
<tr>
<td>Inhibin a</td>
<td>–</td>
<td>–</td>
<td>focal</td>
</tr>
<tr>
<td>CK</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>HLA-G</td>
<td>–</td>
<td>–</td>
<td>+</td>
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</table>
**P63**

- Nuclear transcription factor belonging to P53 family
  - **Two major isoforms**
  - CT expresses N isoform
  - **Chorionic type IT** expresses TA isoform
- Different P63 isoforms may be important in control of trophoblastic differentiation and placental development


**HLA-G**

- Presence on all types of non villous trophoblast, but not detected in villous CT and ST
- **All trophoblastic tumors and tumor like lesions express HLA-G strongly and diffusely**
- Vast majority of non-trophoblastic tumors do not express HLA-G
- Melanoma, renal cell, breast, ovarian and large cell carcinoma of lung may show focal expression

**Practical immunohistochemistry approach to diagnosis of lesions of non-villous trophoblast in biopsy specimens**

1. **To confirm trophoblastic nature of cells**
   - hPL, inhibin a, HLA-G, Mel-CAM(CD146)
   - CK (CAM 2, AE1/AE3, CK18)
     - Discriminate trophoblast from CK–ve maternal decidua
2. **To differentiate between non-neoplastic and neoplastic trophoblast**
   - IHC is of little help
   - Ki-67 >10% in neoplastic lesions

3. **To differentiate neoplastic trophoblastic cells from others**
   - SCC
   - Smooth muscle cell tumor
4. **In practical terms, distinction between PSTT and ETT is not really an important one**