Gestational Trophoblastic Disease

**Placental Site Nodule**

Benign. Often incidental finding in reproductive age after pregnancy (interval can be years!)

Well-circumscribed, usually <5 mm, lobulated. Intermediate trophoblasts embedded in abundant eosinophilic extensively hyalinized matrix. **Degenerated-appearing** → lobulated hyperchromatic nuclei. Absent mitoses.

IHC: (+)CK, p63, GATA-3, inhibin. Low Ki67 (< 5%).

If larger size, more cellular, and/or increased mitoses/atypia → Consider “Atypical placental site nodule” (precursor to ETT)

**Exaggerated Placental Site**

Refers to unusually striking proliferation of implantation site intermediate trophoblasts.

**Recent pregnancy**. Non-mass-forming, but infiltrative. Low Ki67 and no mitoses.

Can be cytologically very atypical!!

**Physiologic** → regress spontaneously.

If no recent pregnancy, mass-forming, destructive invasion, Ki67 >10% → consider Placental Site Trophoblastic Tumor (PSTT)

**Hydropic Abortus**

**Early spontaneous abortion** with edematous placental tissue → significant as histologically resembles Molar pregnancy!

Villi relatively the same size with variable hydropic change.

**Cisterns rare/absent.**

**Trophoblasts are often attenuated.**

Often hypovascular

Usually scant tissue (1-2 blocks).
Molar Pregnancies

Complete Hydatidiform Mole

Formed by: anuclear ovum + sperm (either 2 sperm or 1 that replicates) → diploid and diandric with two sets of paternal chromosomes (androgenetic diploidy).

Clinical findings: **Very high serum hCG (>100k)**
Large uterus, bleeding, “Snowstorm” on ultrasound.

Grossly: **hydropic “grape-like” villi**

**Diffusely hydropic villi**

- **Cistern formation** (fluid-filled cavities)
- **Irregular in size and shape** with club-like extensions.
- Avascular → no fetal RBC’s

**Circumferential trophoblastic proliferation**

- Can be variable.
- Cytotrophoblasts may have marked nuclear pleomorphism. Syncytiotrophoblasts can form lacy “medusa-head” festoons on the villous surface.

IHC: absent/sparse (<10%) p57 nuclear staining of cytotrophoblast and villous stromal cells

**Risk of Choriocarcinoma** (<5%)

Treat with medication and removal
Follow serum hCG for disease monitoring

Incomplete (“Partial”) Hydatidiform Mole

Usually Diandric triploidy (one maternal and two paternal sets of chromosomes).

In contrast to complete mole, usually small/normal uterus and normal/mildly elevated hCG.

Grossly unremarkable, gestational sac and/or fetal parts may be present.

**Two populations of villi:** 1) Enlarged, hydropic villi and 2) small/normal-sized fibrous villi.

**Irregular villi with scalloped borders** (think coast of Norway).

Occasional cistern formation and trophoblastic proliferation (but less than complete).

Stromal blood vessels with fetal RBCs present.

IHC: Retained staining with p57
Molecular: genotyping can confirm diandric triploidy

Usually good outcome. <1% risk of persistent disease or subsequent tumor.


“Persistent Moles”

Remaining molar tissue after original treatment (usually medication and curettage) → persistently elevated serum hCG.

*Common causes:*

**Invasive Hydatidiform Moles**—Mole that invades the myometrium and/or uterine vessels (usually complete moles)

**Metastatic Hydatidiform Moles**—Spread of abnormal chorionic villi to sites beyond the uterine cavity, most commonly vaginal wall/pelvis.

Usually effectively treated with chemotherapy

---

**Abnormal (non-molar) Villous Lesions**

Descriptive diagnosis: various non-molar villous lesions with features simulating a partial mole - Villous size irregularity, enlargement, mild trophoblastic proliferation. p57 expression intact.

Diverse origins: various chromosomal/genetic alterations. Likely includes some hydropic abortions.

---

<table>
<thead>
<tr>
<th></th>
<th>Complete Mole</th>
<th>Partial Mole</th>
<th>Hydropic Abortus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amount of placental tissue (compared to normal)</strong></td>
<td>Voluminous 5-10x increase</td>
<td>Moderately increased to normal</td>
<td>Scant</td>
</tr>
<tr>
<td><strong>Villous size</strong></td>
<td>Spectrum: Large and small</td>
<td>Two populations</td>
<td>Mostly similar</td>
</tr>
<tr>
<td><strong>Villous shape</strong></td>
<td>Round to Bulbous</td>
<td>Irregular (like coast of Norway)</td>
<td>Round/smooth</td>
</tr>
<tr>
<td><strong>Trophoblastic hyperplasia</strong></td>
<td>Moderate to marked; often circumferential</td>
<td>Mild, rarely circumferential</td>
<td>Absent, polar</td>
</tr>
<tr>
<td><strong>Cisterns</strong></td>
<td>Common</td>
<td>Focal</td>
<td>Absent/inconspicuous</td>
</tr>
<tr>
<td><strong>Villous stroma</strong></td>
<td>Mucoid, hydropic, no fibrosis</td>
<td>Some fibrotic Some hydropic</td>
<td>Mostly hydropic, some fibrous</td>
</tr>
<tr>
<td><strong>Fetal tissue</strong></td>
<td>Usually none</td>
<td>Usually present</td>
<td>Usually none</td>
</tr>
<tr>
<td><strong>Fetal membranes</strong></td>
<td>Rare</td>
<td>Common</td>
<td>Maybe</td>
</tr>
<tr>
<td><strong>p57 nuclear staining of cytotrophoblast and villous stromal cells</strong></td>
<td>Absent or sparse (&lt;10% of cells)</td>
<td>Prominent</td>
<td>Prominent</td>
</tr>
<tr>
<td><strong>Ki67 of cytotrophoblast</strong></td>
<td>High (&gt;70%)</td>
<td>High (&gt;70%)</td>
<td>Low (&lt;25%)</td>
</tr>
<tr>
<td><strong>DNA Content</strong></td>
<td>Diploid (diantric)</td>
<td>Triploid (diantric, monogynic)</td>
<td>Diploid (biparental)</td>
</tr>
<tr>
<td><strong>Chromosome number</strong></td>
<td>46</td>
<td>69</td>
<td>46 ±</td>
</tr>
</tbody>
</table>

Differential Diagnoses

**Villous Enlargement**

*Mesenchymal Dysplasia:*
- Stem villous size irregularity and enlargement (dysmorphic), Vascular proliferation

*Aneuploid Gestation:*
- Moderate villous enlargement, Absence of cisterns, Nucleated RBC’s

**Incomplete (Partial) Mole:**
- Two villous populations, Irregular contours, Cisterns, Nucleated RBC’s

**Complete Mole:**
- Myxoid stroma, Trophoblast hyperplasia, No or rare nucleated RBC’s, Villous stromal karyorrhexis,

**Trophoblast Hyperplasia**

**Early Gestation:**
- Polarized (eccentric)

**Incomplete (Partial) Mole:**
- Minimal, syncytial, Triploid

**Complete Mole:**
- Variable hyperplasia, Concentric, festooning, p57-

**Implantation Site Atypia**

**Early Gestation:**
- Mild nuclear hyperchromasia

**Implantation Site Nodule:**
- Lobulated, Uniform nuclear spacing, Low Ki67 (<5%)

**Complete Mole:**
- Conspicuous atypia, Minimal necrosis,

**Choriocarcinoma:**
- Marked atypia, Necrosis and hemorrhage, Biphasic

**Placental Site/Epithelioid Trophoblastic Tumor:**
- Irregular/diffuse, Scattered polyhedral cells, Atypia, High Ki67 (>10%)

Modified from: Diagnostic Gynecologic and Obstetric Pathology, Second edition. Christopher P. Crum, MD et al. 2011
**Trophoblastic Neoplasms**

**Placental Site Trophoblastic Tumor**

**Malignant.** Derived from implantation site intermediate trophoblasts. Mass-forming.

**Infiltrative** aggregates of *large, polyhedral* to round, predominantly mononucleated cells.
Scattered multinucleated cells.

**Abundant amphophilic to eosinophilic cytoplasm.**

**Pronounced nuclear atypia.**

**Infiltrate myometrium and vessels.**

IHC: (+) hPL, MUC4. Ki67 >10%

**Epithelioid Trophoblastic Tumor**

**Malignant.** Derived from chorionic-type intermediate trophoblasts. Mass-forming.

Well-circumscribed but destructive nodular proliferation of medium-sized trophoblastic cells.

**Uniform cells with moderate amounts of granular to clear eosinophilic cytoplasm and round nuclei.**

Distinct cell membranes. Hyaline-like material
Frequently extensive necrosis.

IHC: (+) p63, inhibin, GATA-3. Ki67 >10%

**Gestational Choriocarcinoma**

**Malignant cytотrophoblasts, trophoblasts, (mononuclear) and syncytiotrophoblasts (multinucleated)**

Abundant Hemorrhage, necrosis, and LVI.

**Marked Pleomorphism/atypia**

**Numerous mitotic figures.**

Infiltrative, destructive, solid growth.

**Very elevated Serum hCG**

Can get after molar pregnancy (most common), normal pregnancy (intraplacental), or abortion

Most common gestational trophoblastic neoplasm.
Can be mixed with other tumors.

IHC: (+) hCG, hPL, inhibin, SALL4, MUC4, p63. Ki67 >90%

**Excellent response to chemotherapy**
<table>
<thead>
<tr>
<th>Diagnostic Features</th>
<th>Gestational Choriocarcinoma</th>
<th>Non-gestational Choriocarcinoma</th>
<th>Carcinoma with trophoblastic differentiation</th>
<th>PSTT</th>
<th>ETT</th>
<th>Complete mole</th>
<th>Placental Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Reproductive Age (~30 yrs)</td>
<td>Children/young adults</td>
<td>Often post-menopausal</td>
<td>Usually reproductive (~30 yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antecedent Pregnancy</strong></td>
<td>Mole or term (months to years after)</td>
<td>Unrelated</td>
<td>Unrelated</td>
<td>Term pregnancy. Months to years after</td>
<td>Term. Months to years after</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>hCG (mIU/mL)</strong></td>
<td>Elevated &gt; 1 x 10³</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Often Elevated &lt; 1 x 10³</td>
<td>Often Elevated &lt; 3 x 10³</td>
<td>Markedly Elevated</td>
<td>Not increased</td>
</tr>
<tr>
<td><strong>Gross appearance</strong></td>
<td>Hemorrhagic mass</td>
<td>Solid mass</td>
<td>Absence of a mass lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Corpus</td>
<td>Ovary usually</td>
<td>Corpus</td>
<td>Endometrium usually</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Infiltrative tumor.</td>
<td>Bilaminar proliferation of mononuclear trophoblasts rimmed by multinucleated syncytiotrophoblasts. Extensive hemorrhage, necrosis, and atypia.</td>
<td>Carcinoma of discernable differentiation, marked atypia often present</td>
<td>Infiltrative sheets, invading myometrium, atypia.</td>
<td>Pushing tumor, Necrosis, hyaline-like material</td>
<td>Absence of atypia</td>
<td>Well-circumscribed. No overt malignancy</td>
</tr>
<tr>
<td><strong>Tumor Cells</strong></td>
<td>Villous intermediate trophoblasts, syncytiotrophoblasts, and cytotrophoblast</td>
<td>Poorly differentiated carcinoma with scattered hCG-producing multinucleated giant cells</td>
<td>Chorionic-type intermediate trophoblast</td>
<td>Chorionic-type intermediate trophoblast</td>
<td>Chorionic-type trophoblast</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IHC</strong></td>
<td>hCG, SALL4, p63, Ki67 &gt;90%</td>
<td>hCG in multinucleate cells</td>
<td>hPL. Ki67 5-10%, Negative for SALL4</td>
<td>P63. Ki67 &gt;10%, Negative for SALL4</td>
<td>hPL. Ki67 &lt;5%, Negative for SALL4</td>
<td>P63. Ki67 &lt;5%</td>
<td></td>
</tr>
</tbody>
</table>

*Modified from: WHO Classification of Tumors, 5th Edition. Female Genital Tumors. 2020.*