

Gestational Trophoblastic Disease

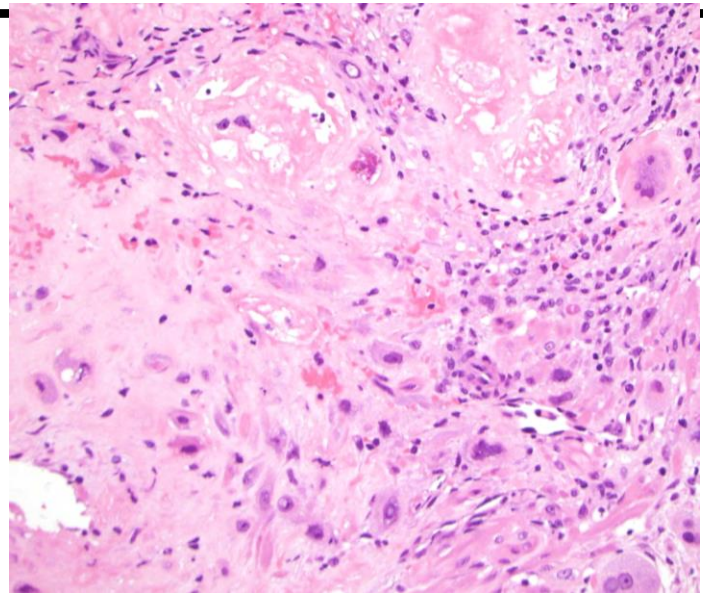
Placental Site Nodule

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

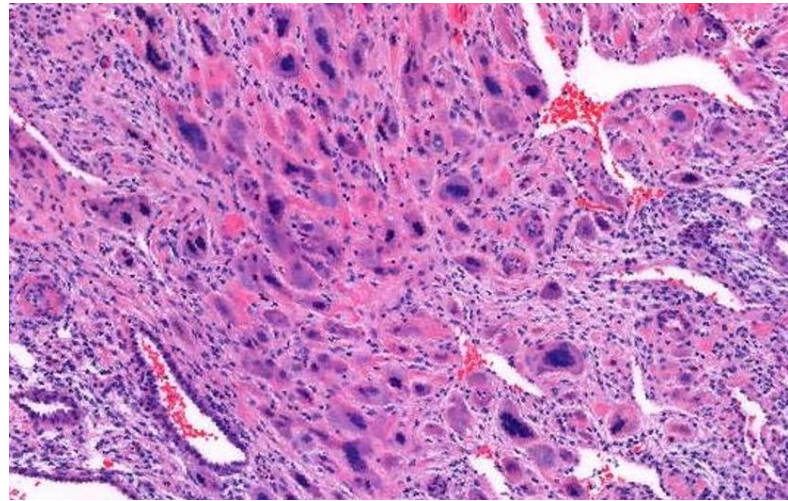
Refers to unusually striking proliferation of implantation site intermediate trophoblasts.

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!

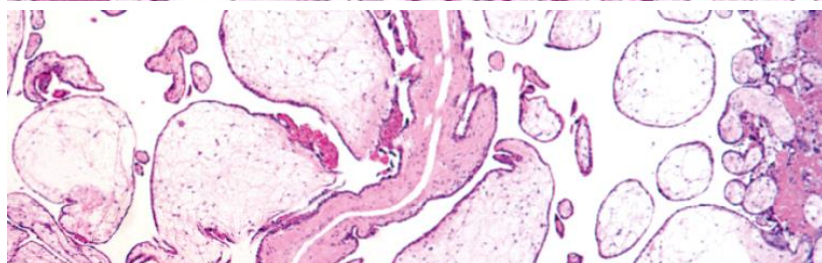
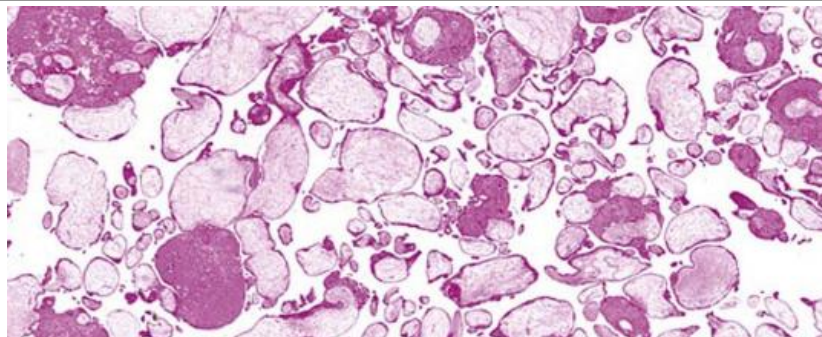
Villi relatively the same size with variable hydropic change.

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.

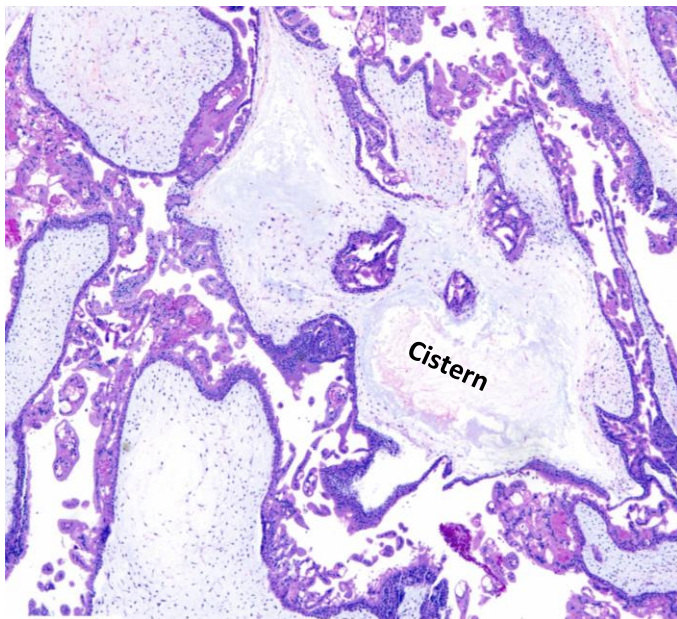
Cytotrophoblasts may have marked nuclear pleomorphism. Syncytiotrophoblasts can form lacy "medusa-head" festoons on the villous surface.

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).

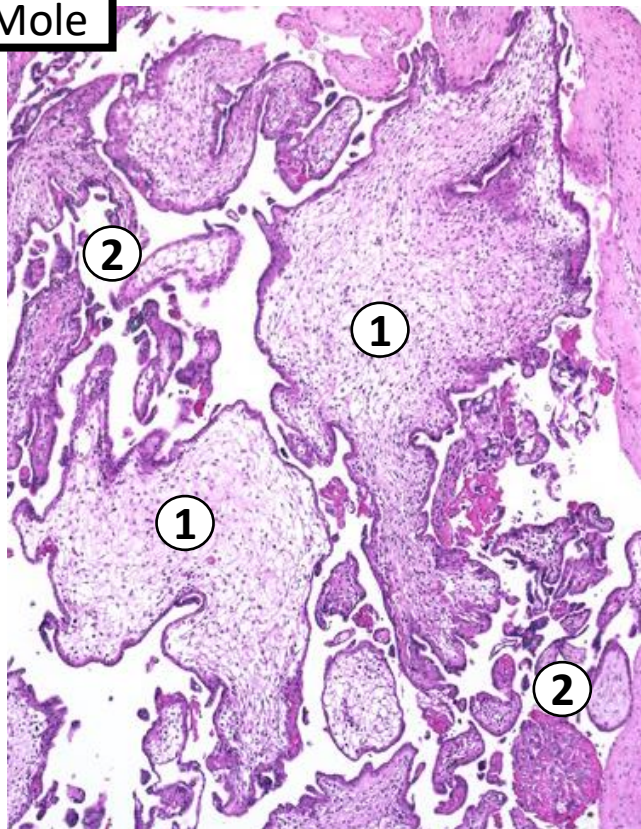
Occasional cistern formation and trophoblastic proliferation (but less than complete).

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.

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

Differential Diagnoses

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

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%)

Trophoblastic Neoplasms

Placental Site Trophoblastic Tumor

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

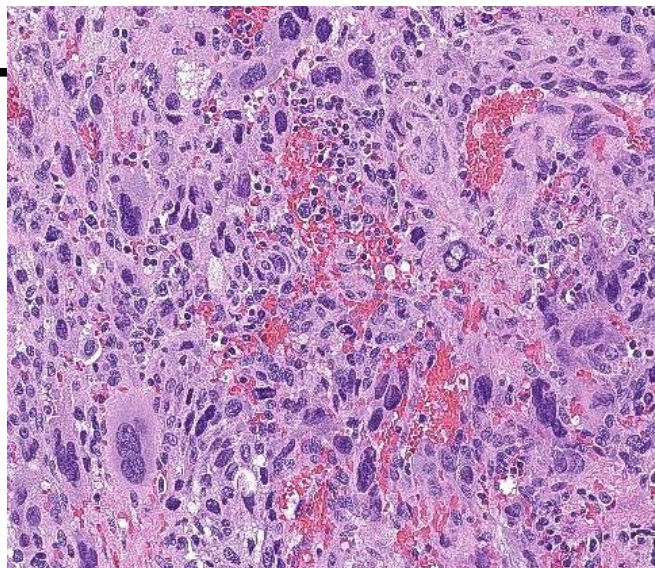
Infiltrative aggregates of **large, polyhedral** to round, predominantly mononucleated cells. Scattered multinucleated cells.

Abundant amphophilic to eosinophilic cytoplasm.

Pronounced nuclear atypia.

Infiltrate myometrium and vessels.

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



Epithelioid Trophoblastic Tumor

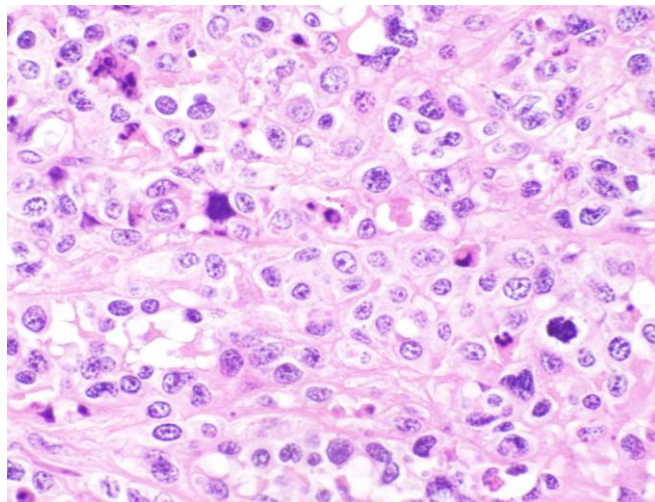
Malignant. Derived from chorionic-type intermediate trophoblasts. Mass-forming.

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 cytotrophoblasts, trophoblasts, (mononuclear) and syncytiotrophoblasts (multinucleated)

Abundant **Hemorrhage**, necrosis, and LVI.

Marked Pleomorphism/atypia

Numerous mitotic figures.

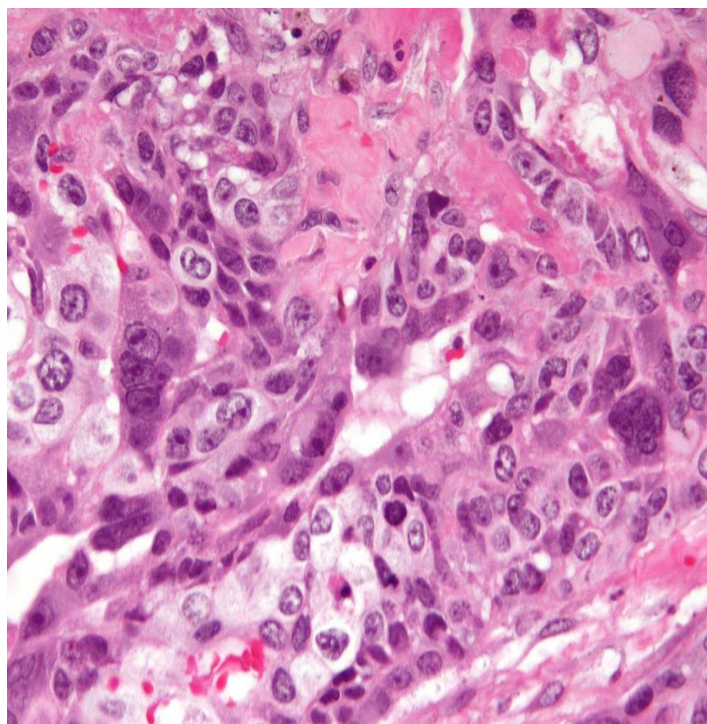
Infiltrative, destructive, solid growth.

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



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

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