Gestational Trophoblastic Disease

Pei Hui M.D, Ph.D.
Department of Pathology and Obstetrics, Gynecology and Reproductive Sciences
Yale University School of Medicine

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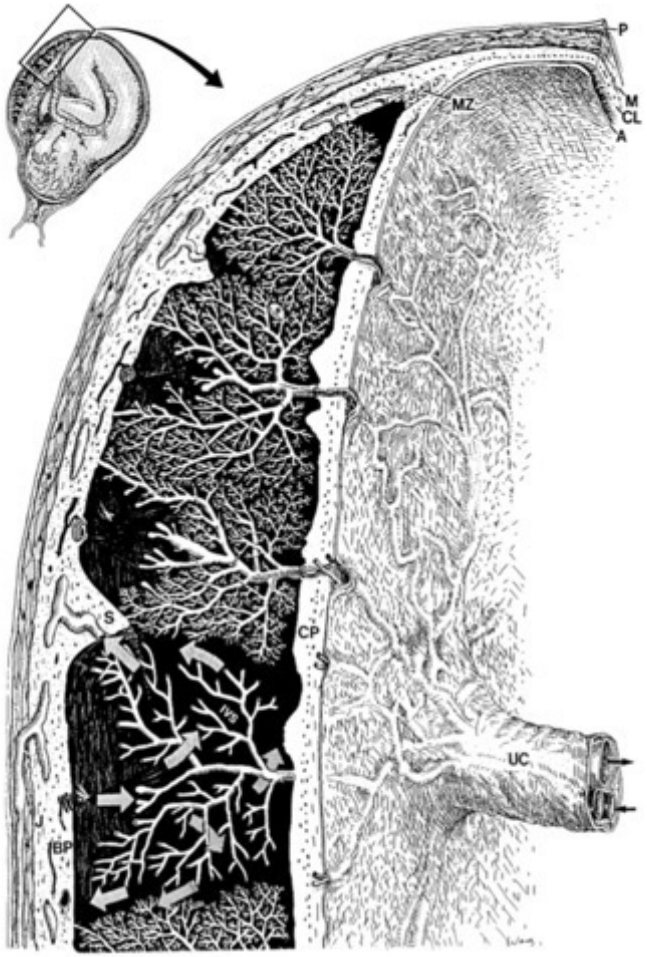
Disclosure of the Conflict of Interest

- NONE

2020 WHO Classifications of GTD



Villous Trophoblast

Hydatidiform Moles
- Complete Hydatidiform Mole (CHM)
- Partial Hydatidiform Mole (PHM)
- Invasive Hydatidiform Mole

Abnormal (nonmolar) villous lesions
Choriocarcinoma

Implantation Site Trophoblast

Exaggerated Placental Site Reaction
Placental Site Trophoblastic Tumor

Chorion Laeve Trophoblast

Placental Site Nodule/Atypical Placental Site Nodule)
Epithelioid Trophoblastic Tumor

Table 1.2 World-wide incidence of GTD (incidence per 1,000 pregnancies)

Population	Hydatidiform Mole	Choriocarcinoma or aggressive GTD
Indonesia	13 (11.7[a])	5.4 (1.7[a])
Philippine	5.0	0.7
Taiwan	8.0[a]	2.0[a]
Korea	1.6[a]–4.1[a]	0.39[a]
Hong Kong	1.8 (4.0[b])	0.7
Singapore	1.2	0.23
India	2.0[b]	
Mexico	1–6.3	0.11–1.5
Turkey	10.6[a]	2.35[a]
China	0.8–5.0	
Iran	3.2	
Japan	1.9–3.7(3.0[a])	0.12
Israel	0.42–1.1[a]	0.055[a]
USA	0.5–1.84 (3.9 for native Alaskans and 1.2[b] for Hawaii)	0.025–0.05
Europe	0.6–1.0 (1.54[a])	0.02–0.05
New Zealand	0.68	
Australia	0.9–1.4 (0.7[a])	0.07
Samoa	0.9[a]	
South America (Paraguay and Brazil)	0.23–0.9 (0.26[b])	
Africa (Nagiria and Uganda)	2.6–8.2	1.2–1.9(1.5[b])

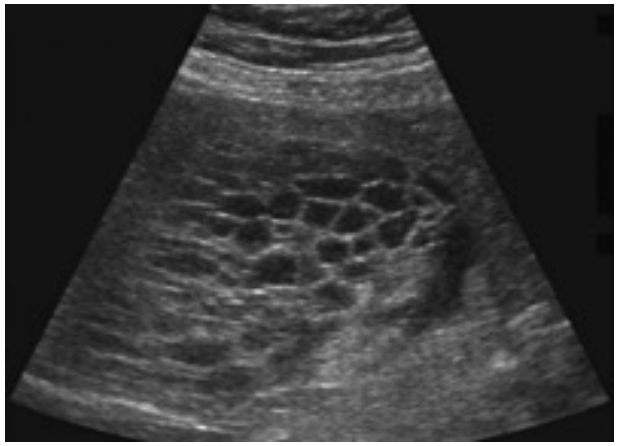
[a] Per 1,000 live birth or deliveries
[b] Complete mole only

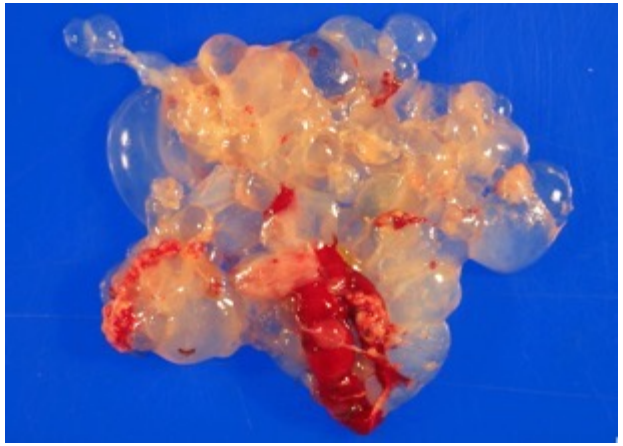
Hydatidiform Moles – Clinical Implications

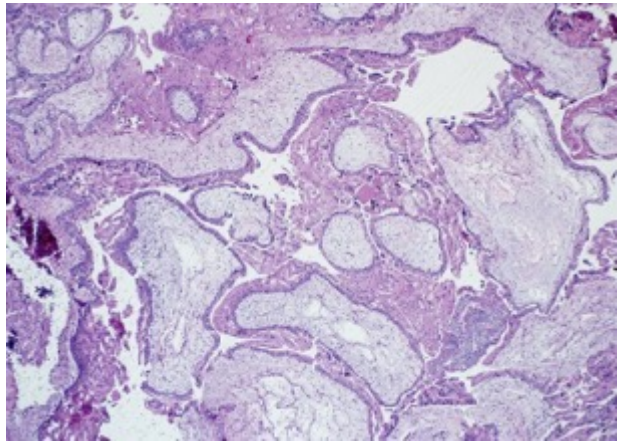
- Risk of persistent GTD (invasive or metastatic mole):
  - ~15-20% after CHM (similar for VECM and FBCHM)
  - ~0.5-5% after PHM
- Risk of choriocarcinoma:
  - ~2-3% after CHM (Heterozygous/dispermic CHM may have a higher risk)
  - 0.1% after PHM (3 well documented cases)

Hydatidiform Moles – Clinical Implications

- Follow-up with serial hCG levels
  - Weekly until non-detectable for 3 weeks
  - Then monthly until non-detectable for 6 months
- Contraception is advised during the entire interval of hCG monitoring
- Significant consequences of both under- and overdiagnosis





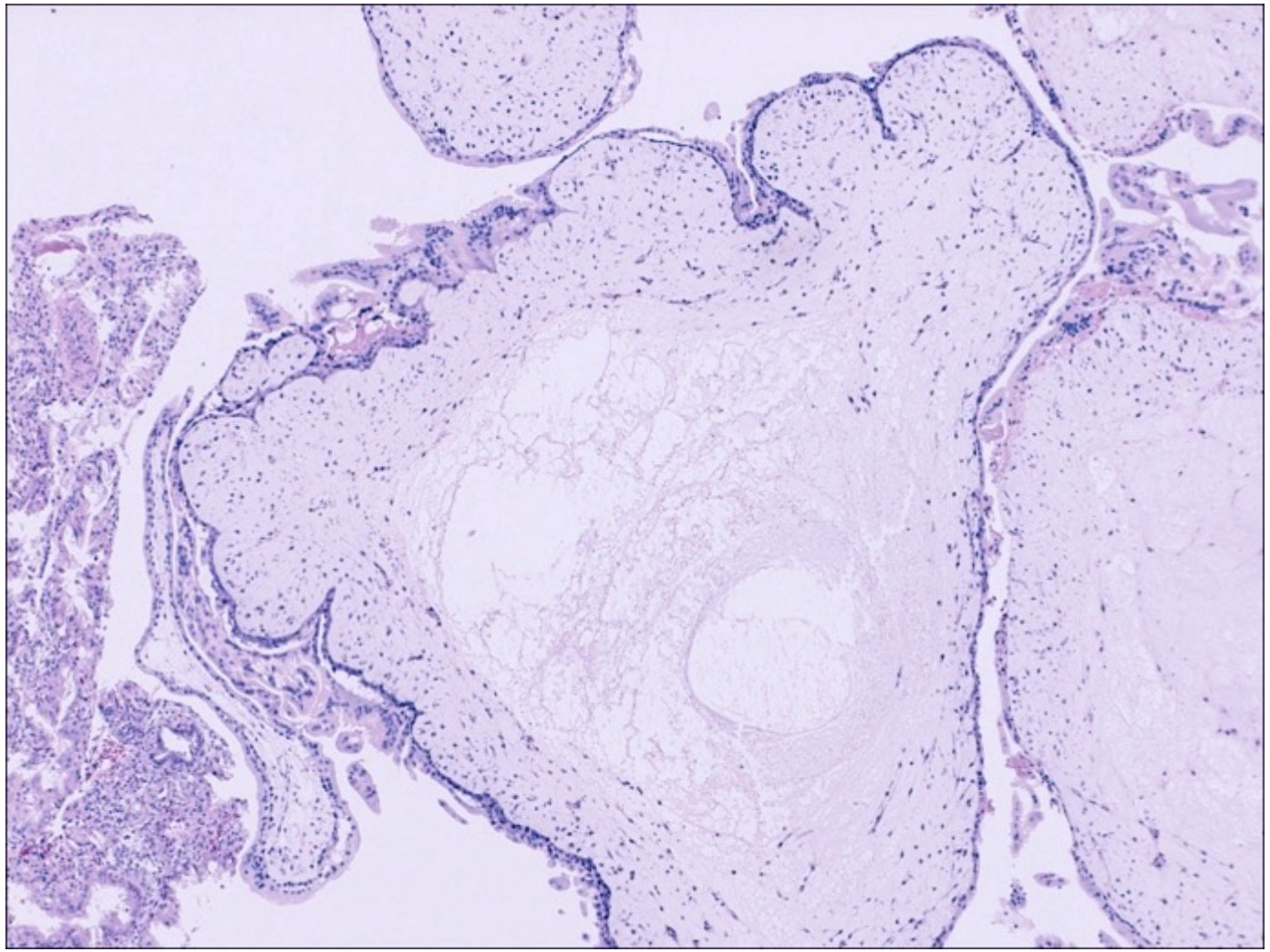


Complete Hydatidiform Mole (CHM)

- Classic:
  - Vaginal bleeding during 2nd trimester
  - Excessive uterine size
  - Markedly elevated serum hCG (hyperemesis)
  - Toxemia, hyperthyroidism
  - “Snowstorm” appearance on U/S
- Early CHM:
  - Vaginal bleeding
  - Missed abortion
  - Lack of fetal heart beat on U/S

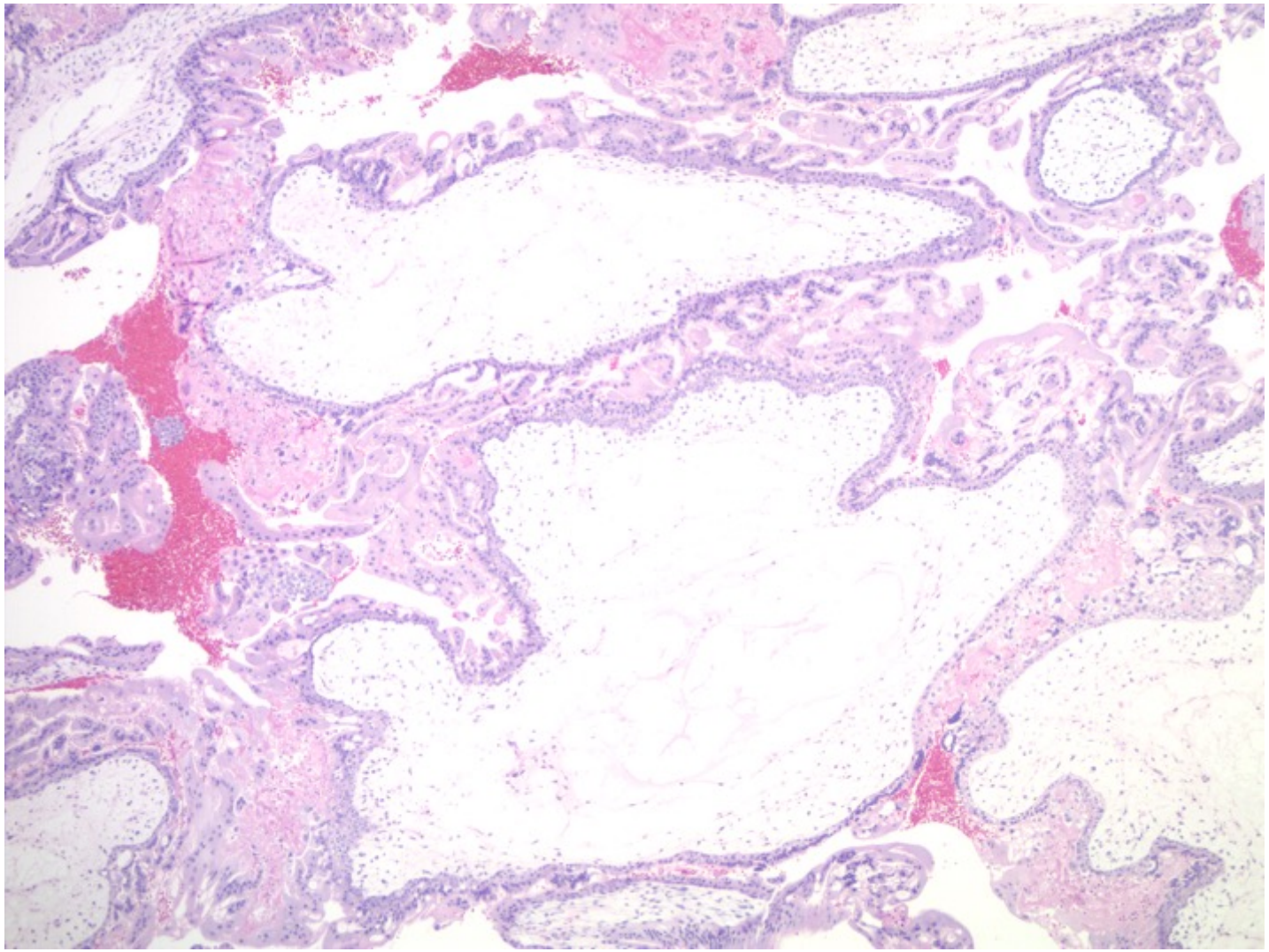
CHM – Microscopic features

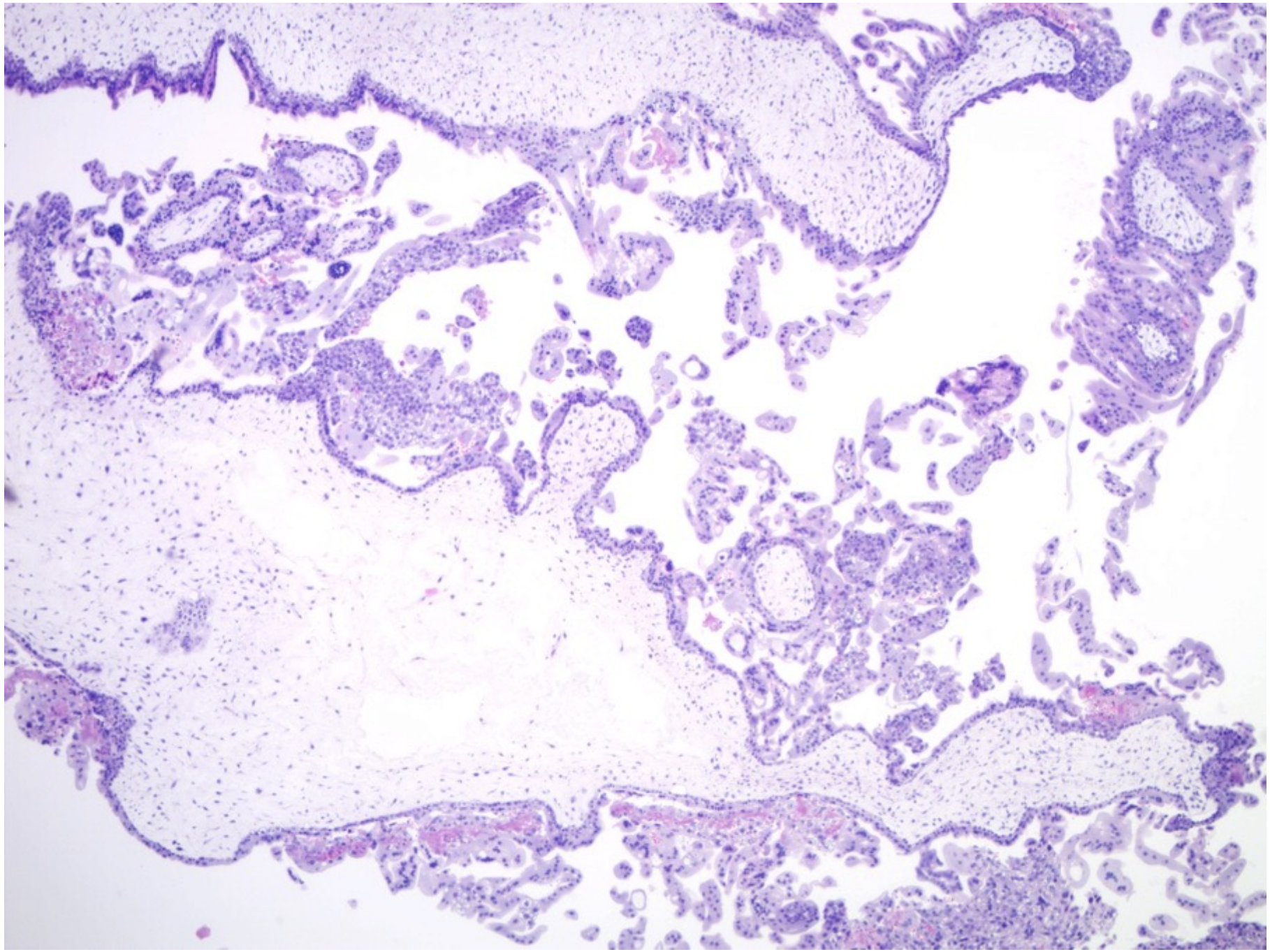
Villous Hydrops and Cisterns

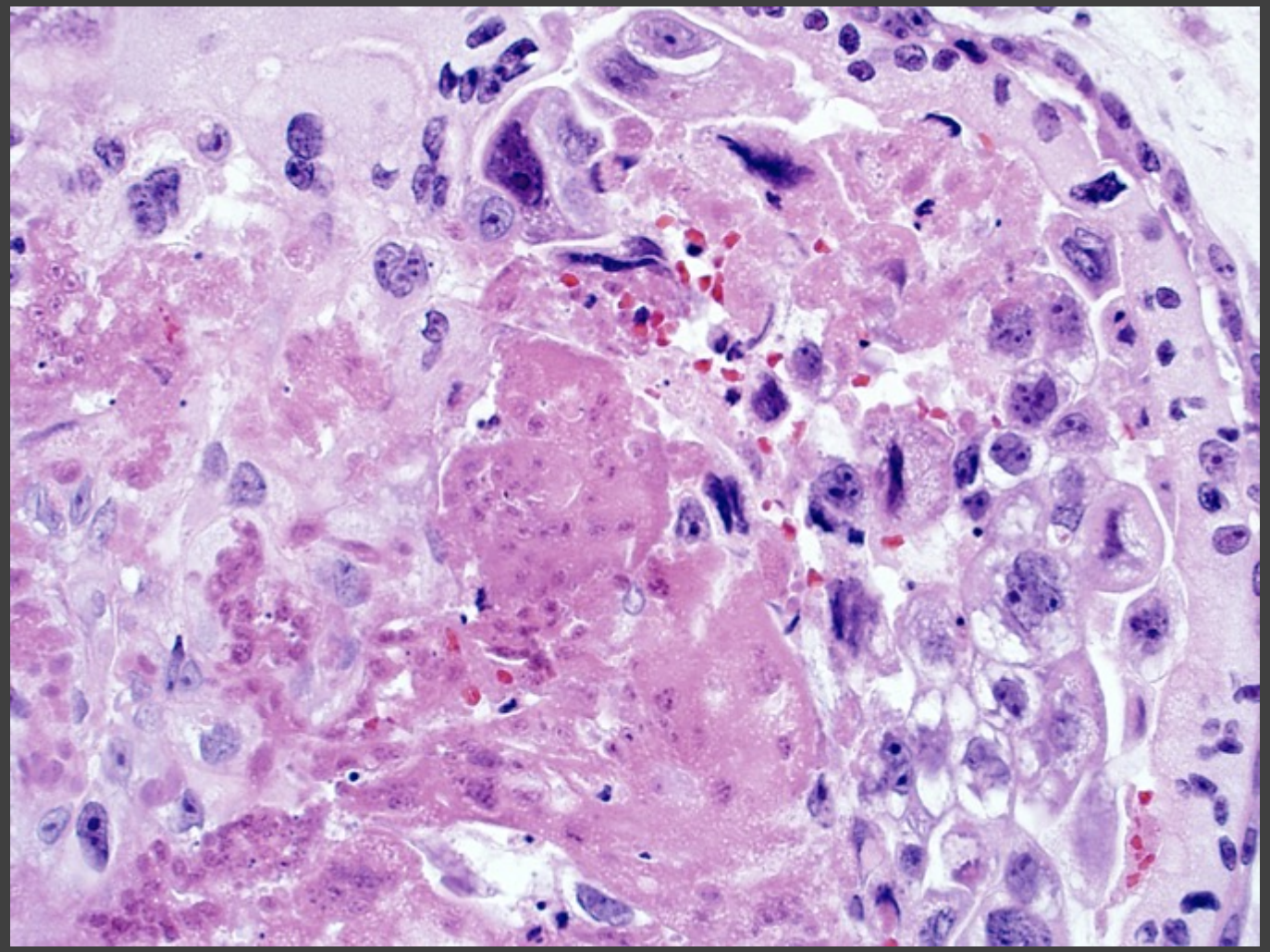


CHM –

Trophoblast hyperplasia





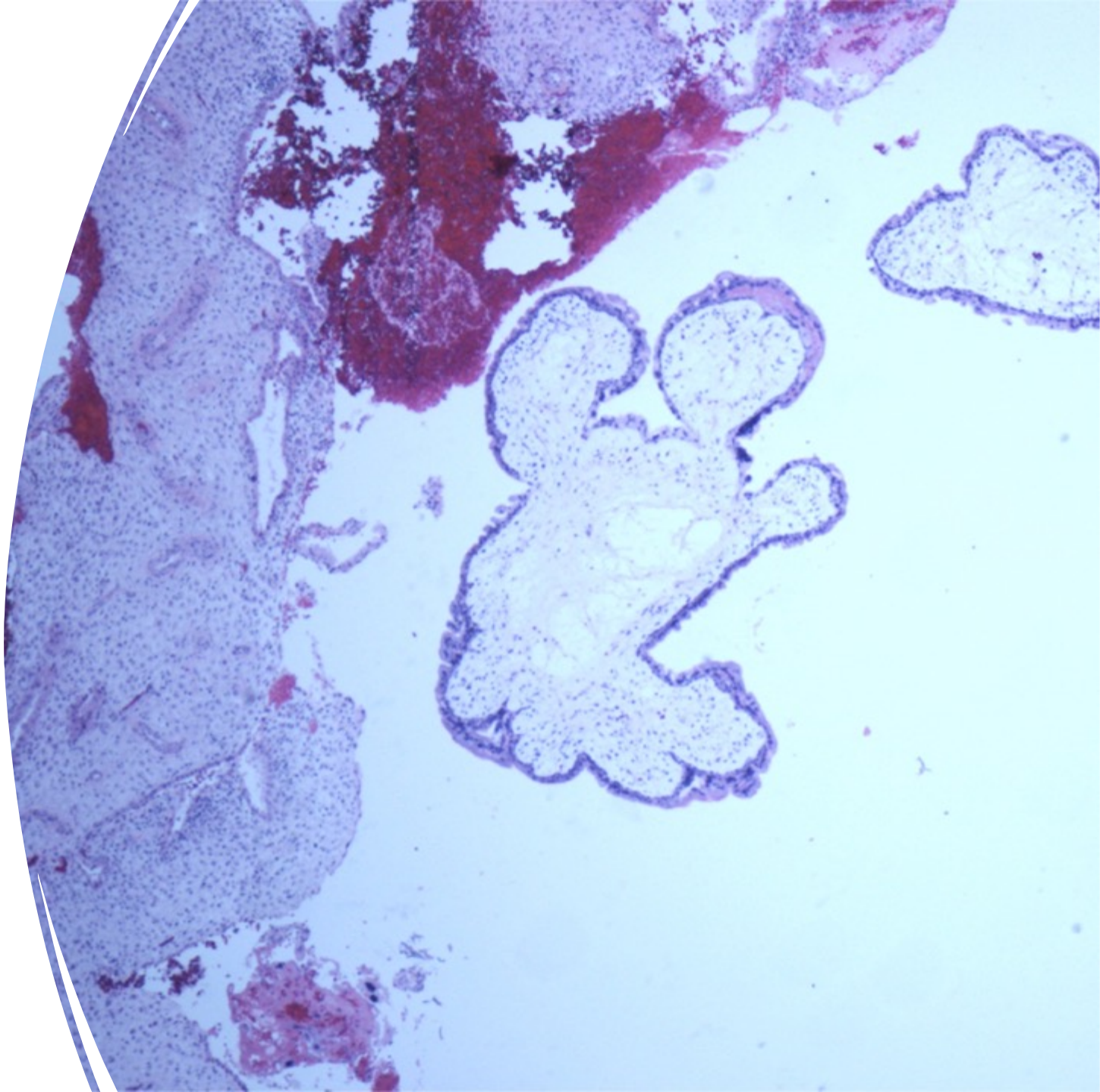


CHM –

Trophoblast atypia

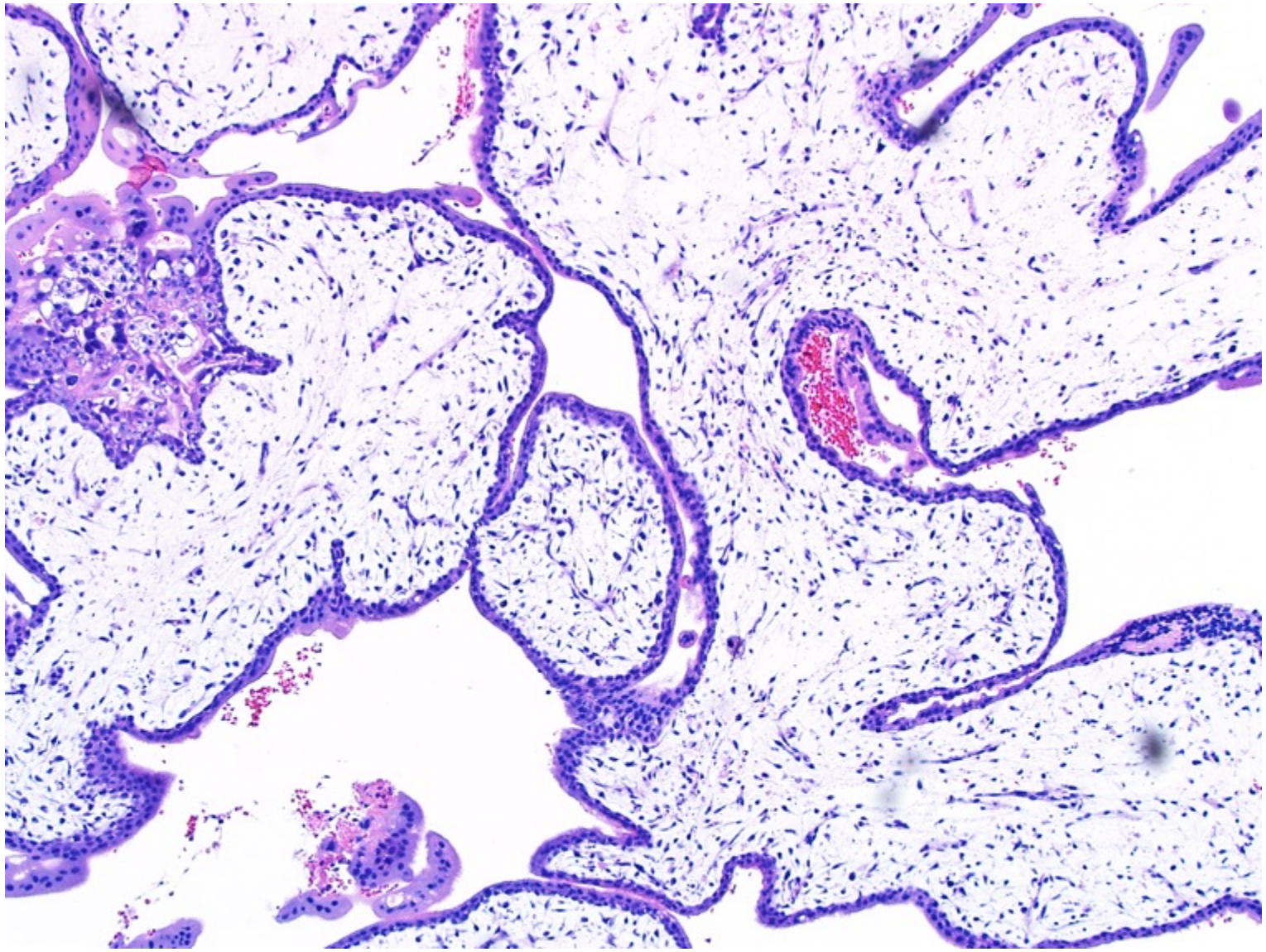
Very Early Complete Mole (VECHM)

- Polypoid chorionic villi
- Cellular myxoid villous
- Prominent karyorrhexis in the villous stroma
- No or focal trophoblastic hyperplasia



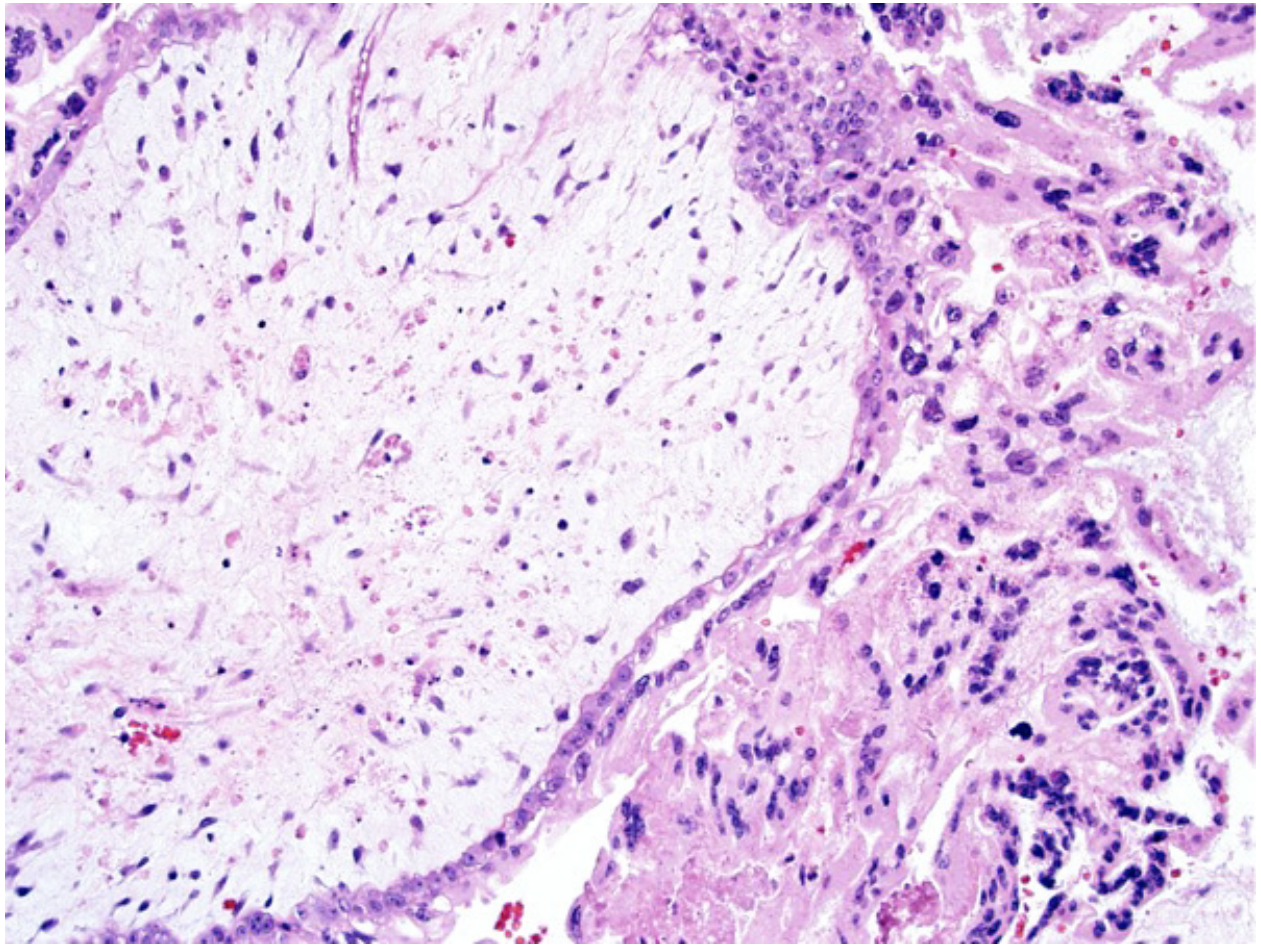
Very early CHM

Bulbous, polypoid villi

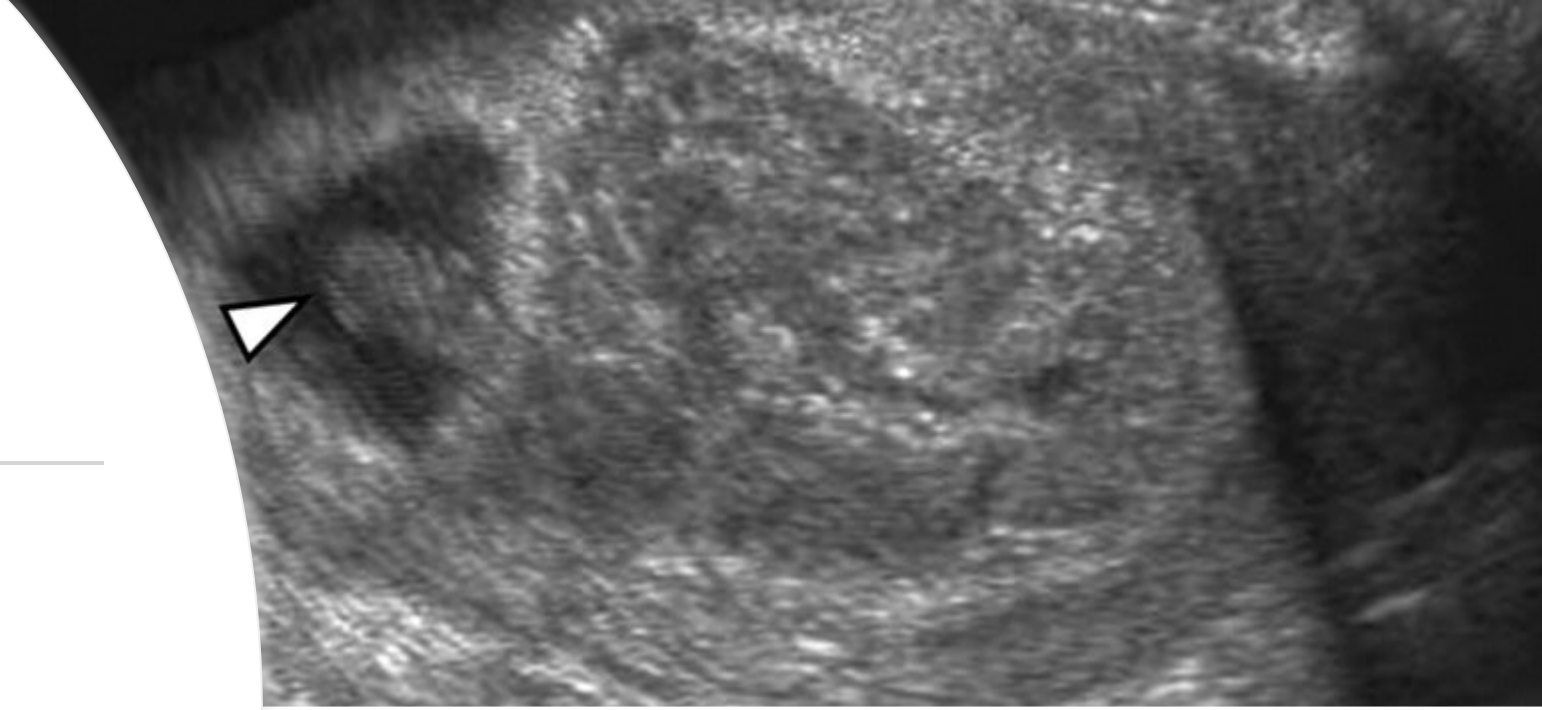


Very early CHM

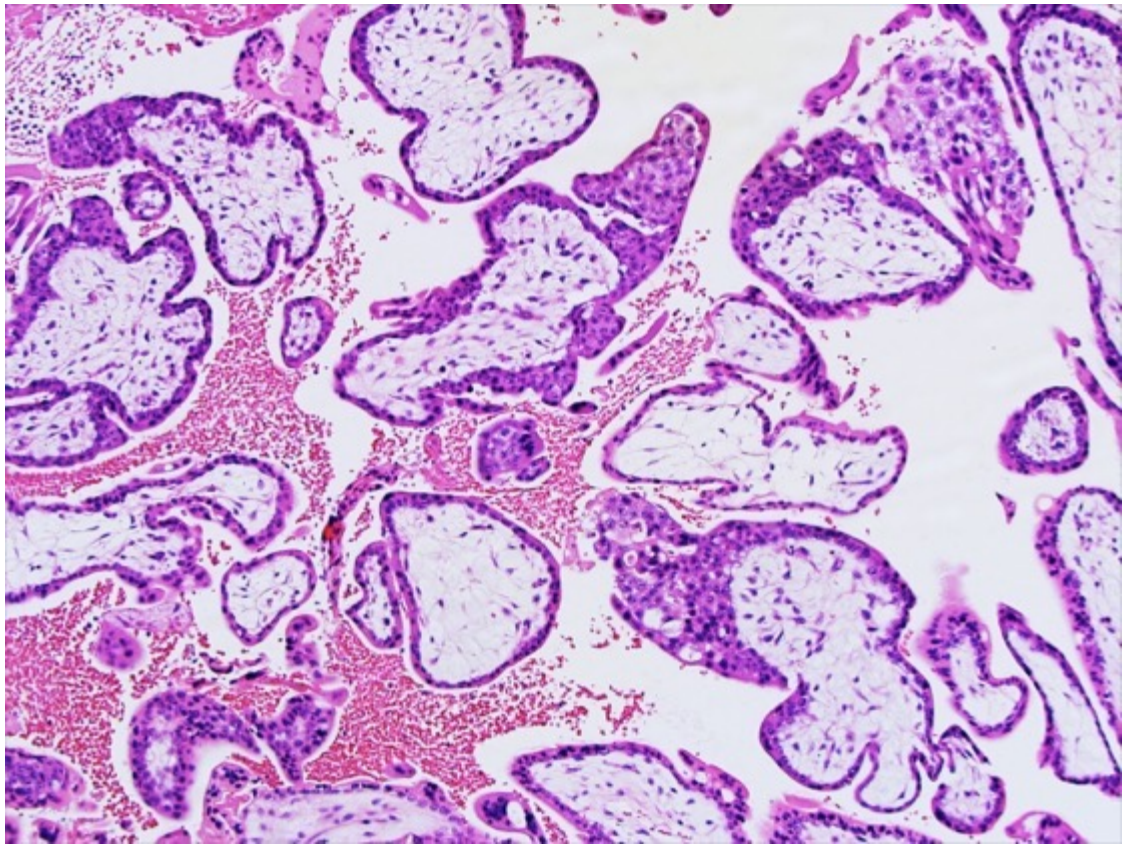
Myxoid stroma with karyorrhexis

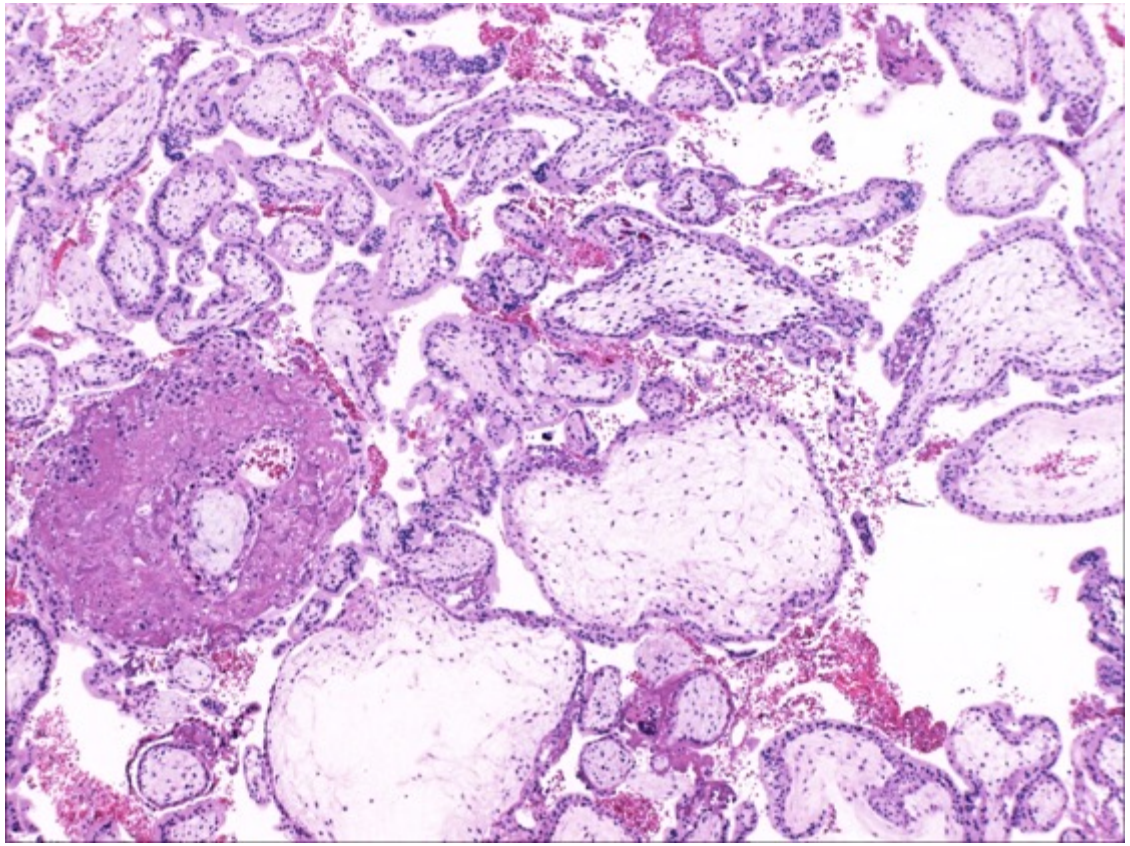


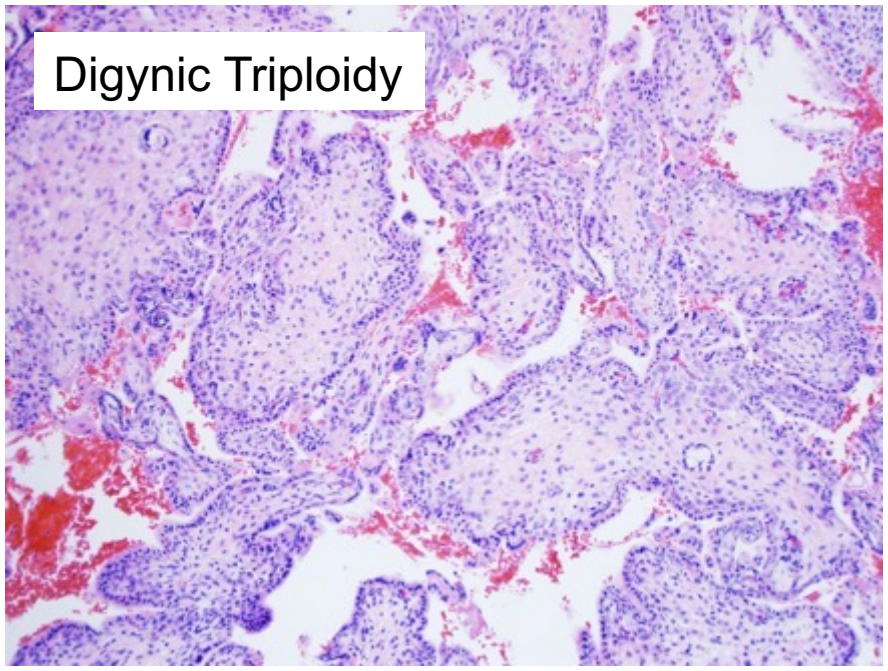
Partial Hydatidiform Mole (PHM)

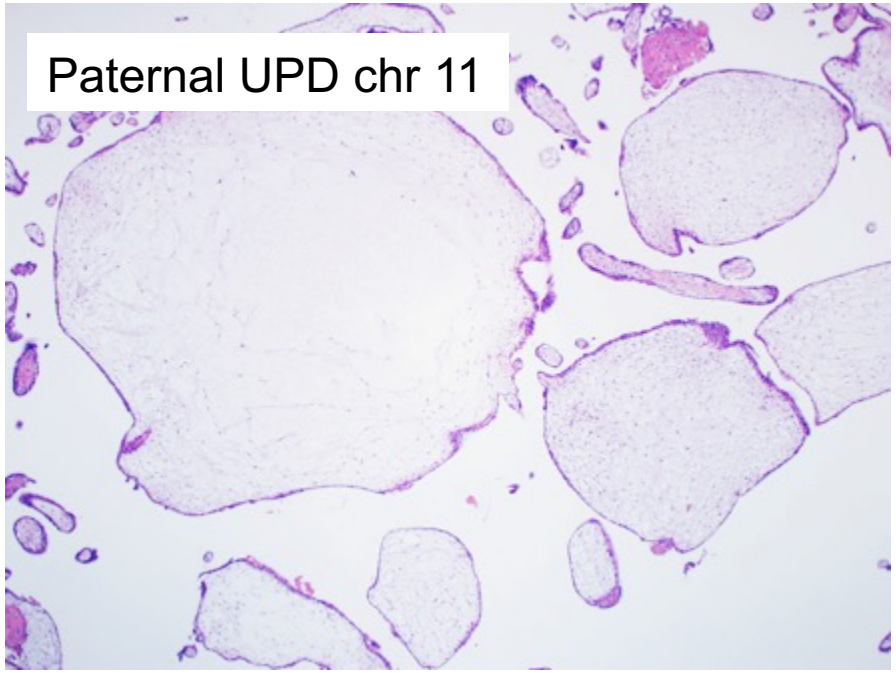


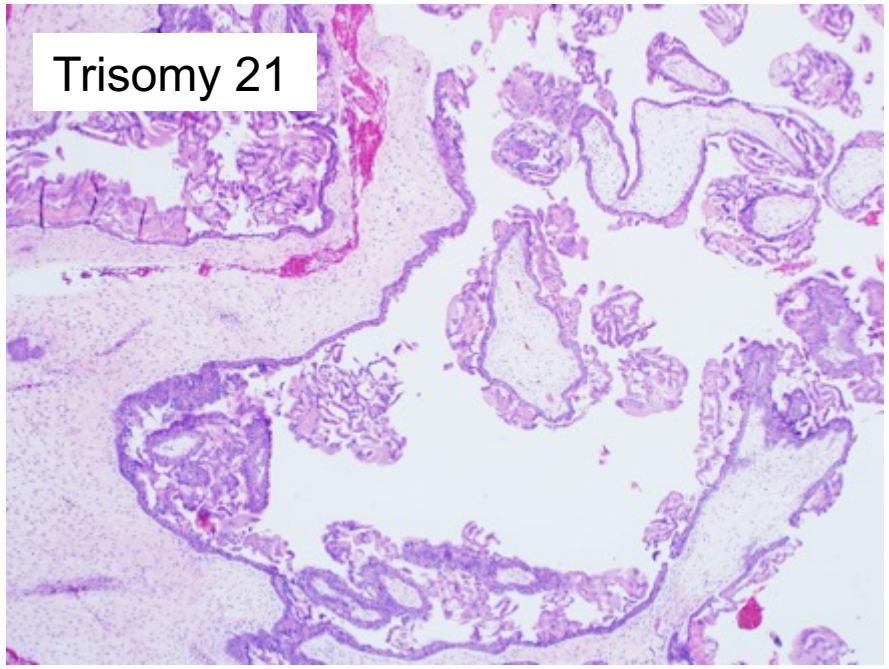
Partial Hydatidiform Mole (PHM) – Now also evacuated at first trimester

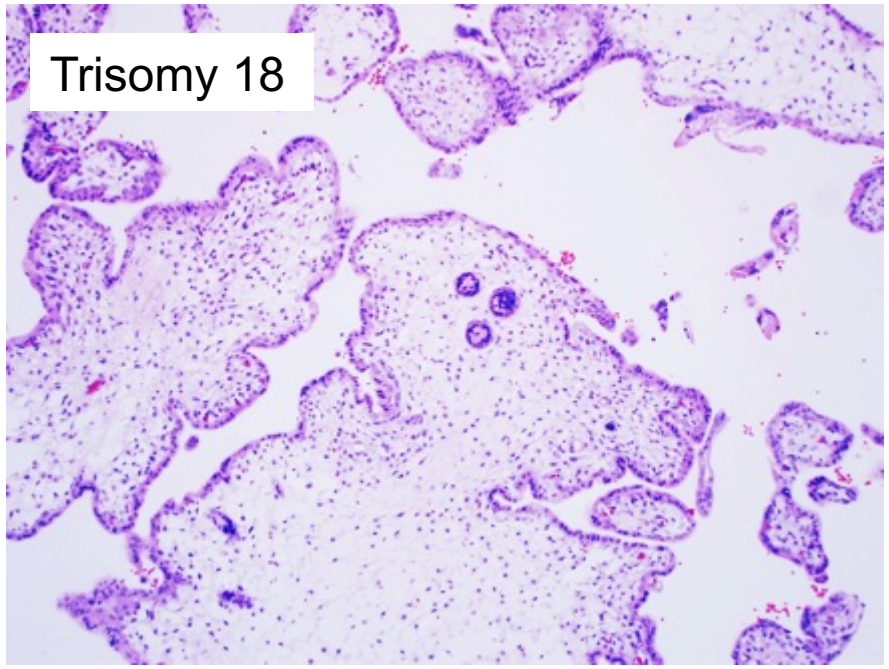





Digynic Triploidy


Paternal UPD chr 11

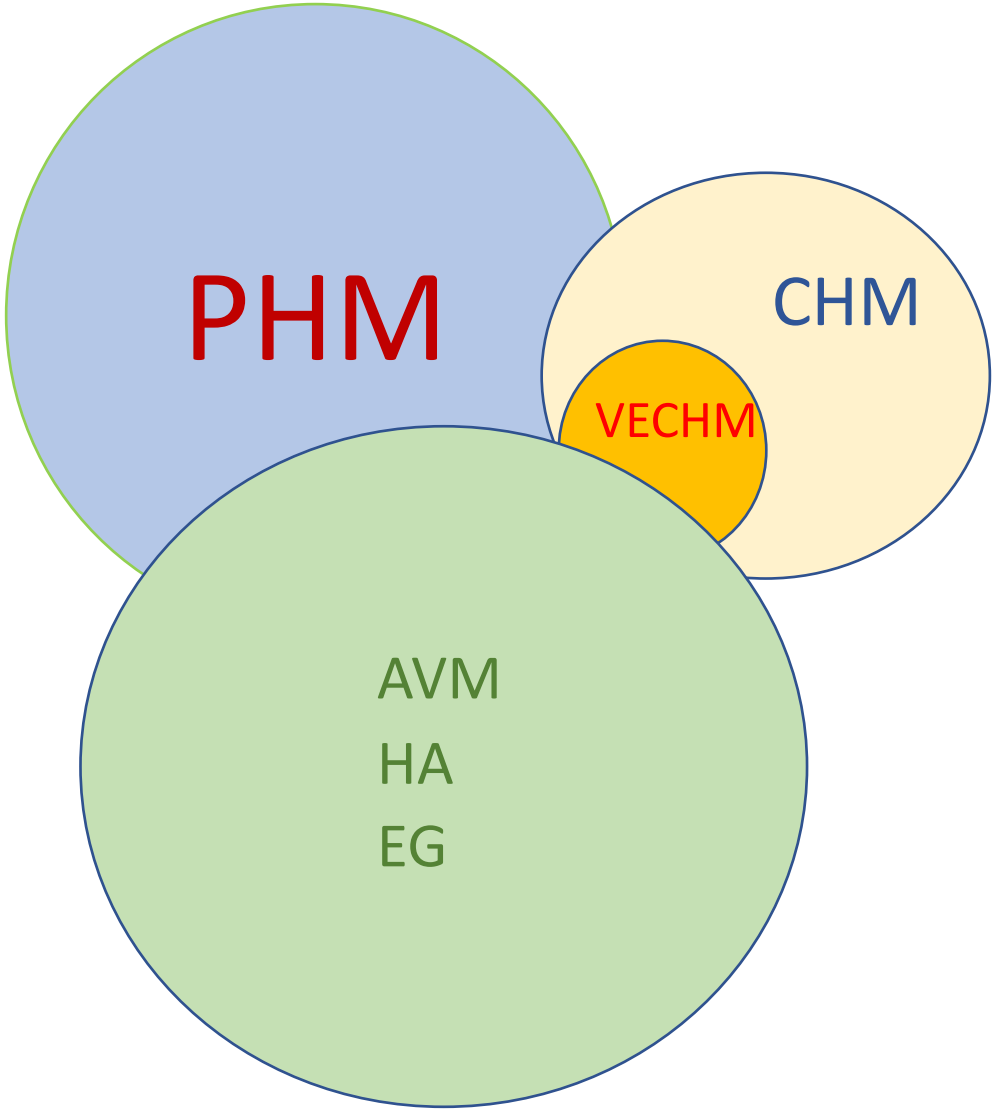

Trisomy 21


Trisomy 18

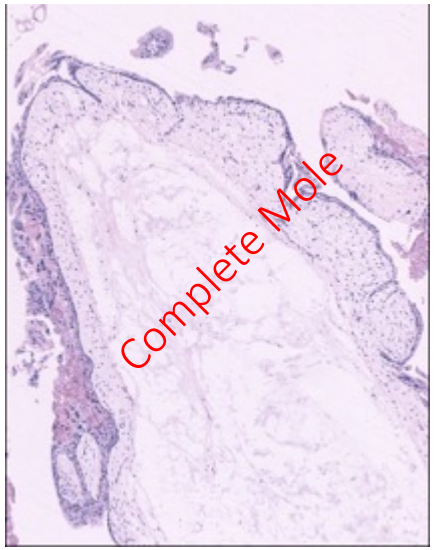
Hydatidiform moles

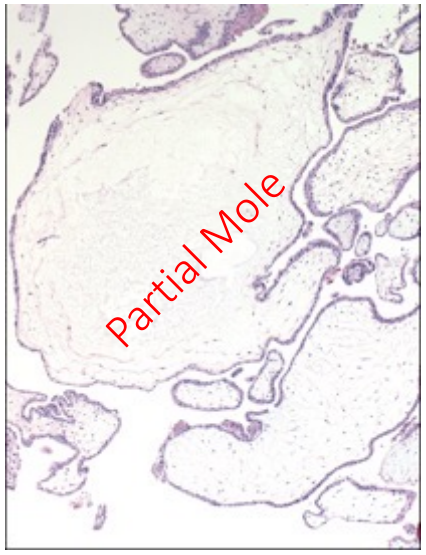
Differential diagnosis

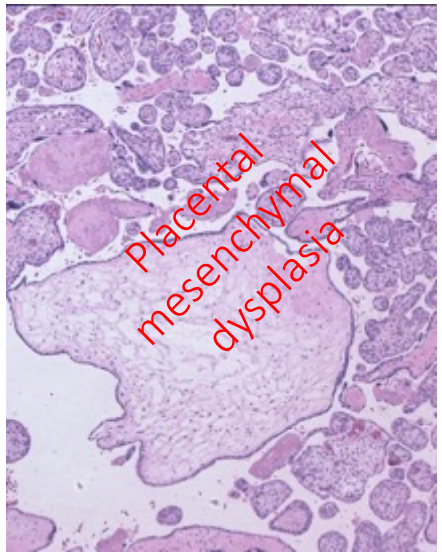
- PHM: Partial mole
- CHM: Complete mole
- VECHM: Very early complete mole
- AVM: Abnormal villous morphology
- HA: Hydropic (non-molar) abortion
- EG: Early (non-molar) gestation

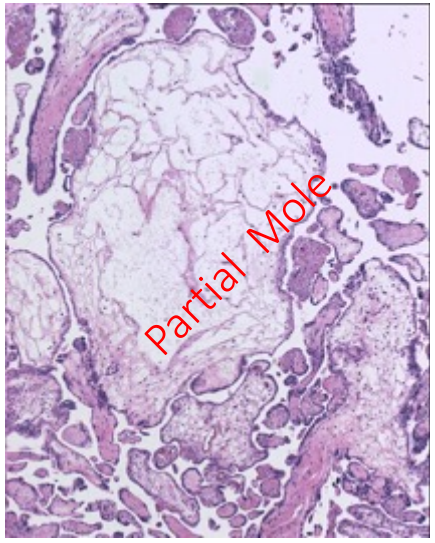


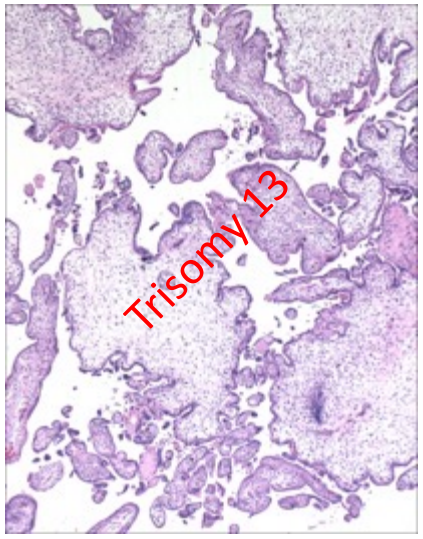
Differential Diagnosis

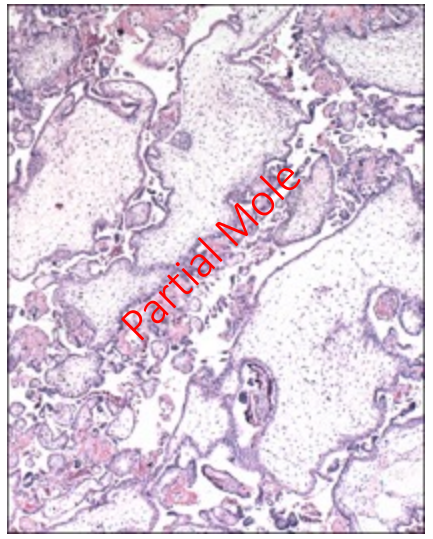


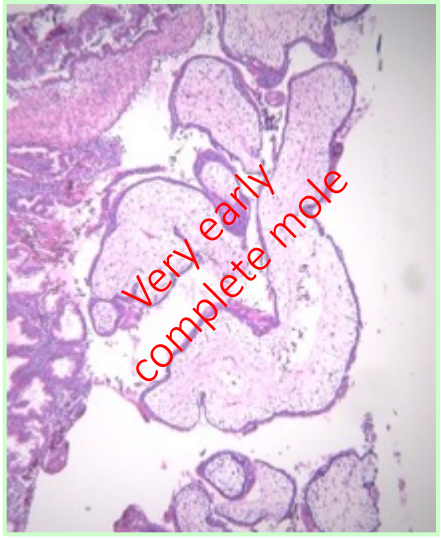




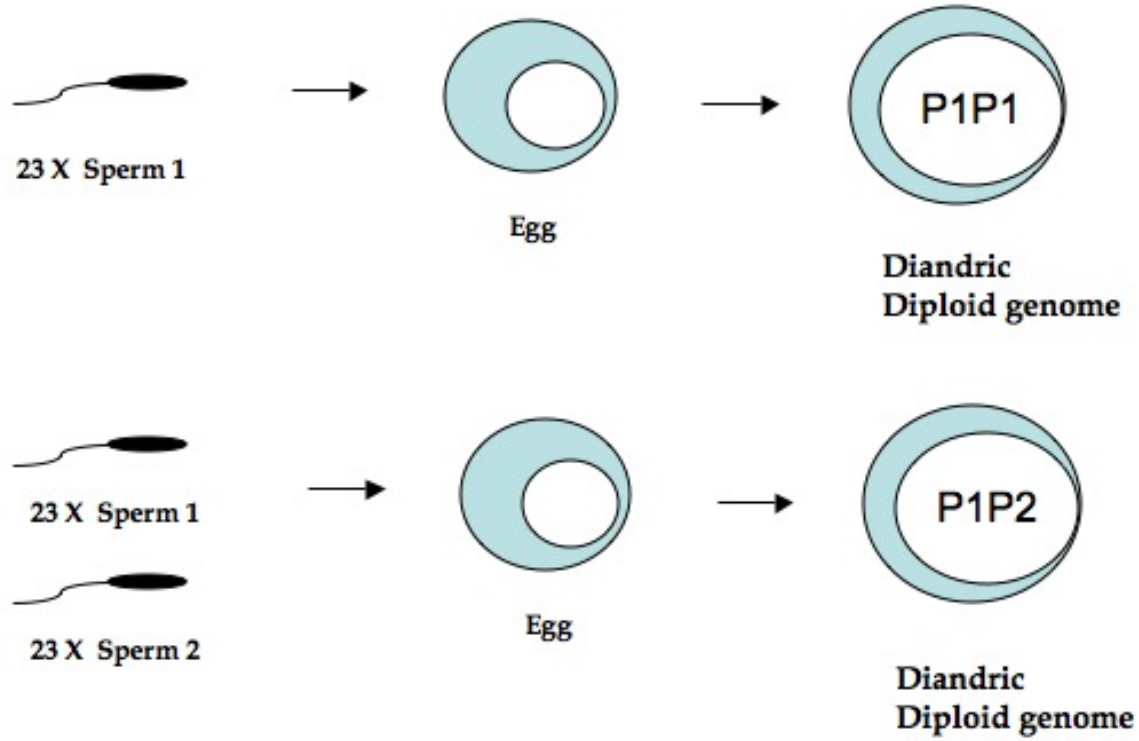








CHM – Pathogenesis

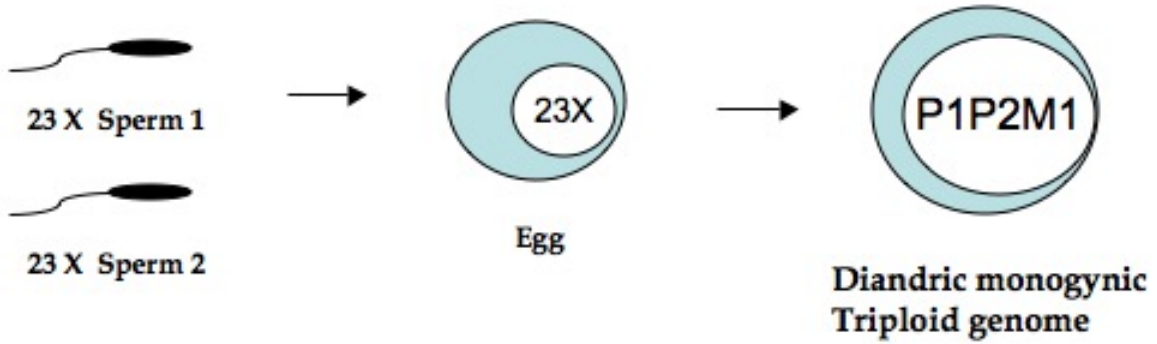


Monospermic
(Homozygous) – 90%

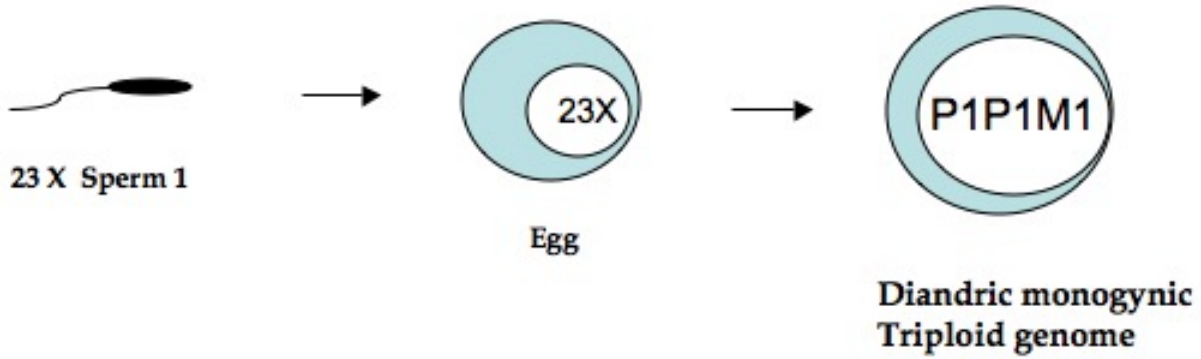
Dispermic
(Heterozygous) – 10%

*Rare exception: Familial Biparental CHM

PHM - Pathogenesis

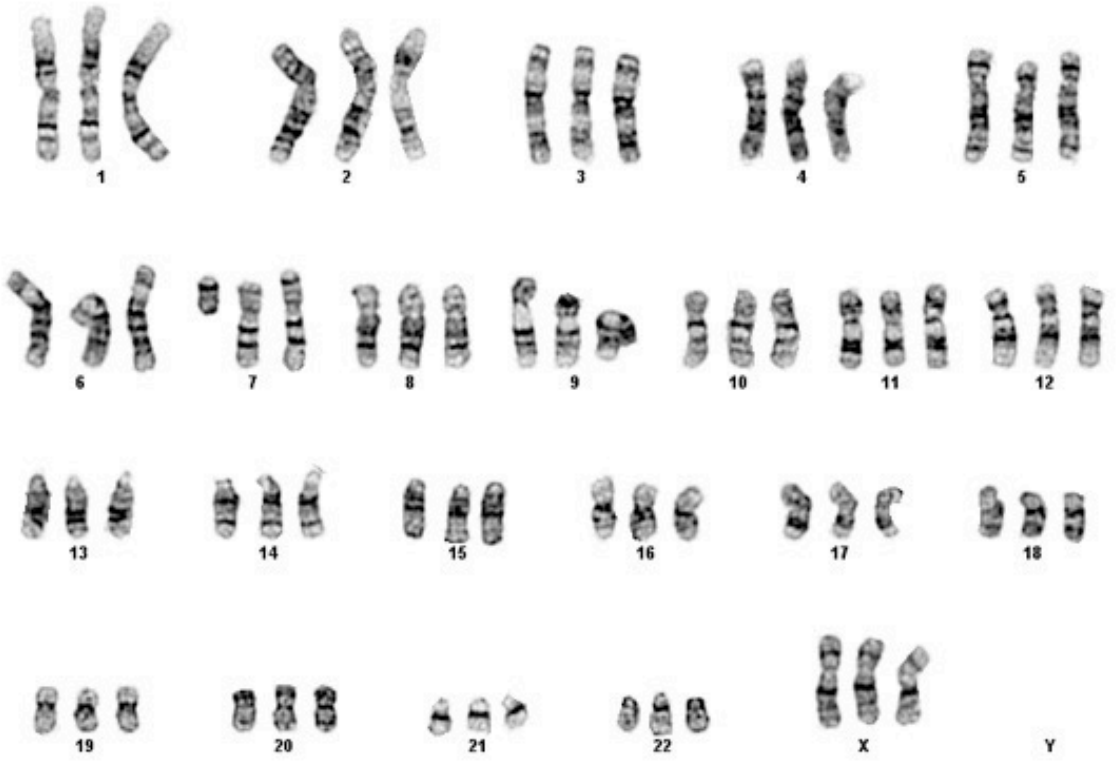


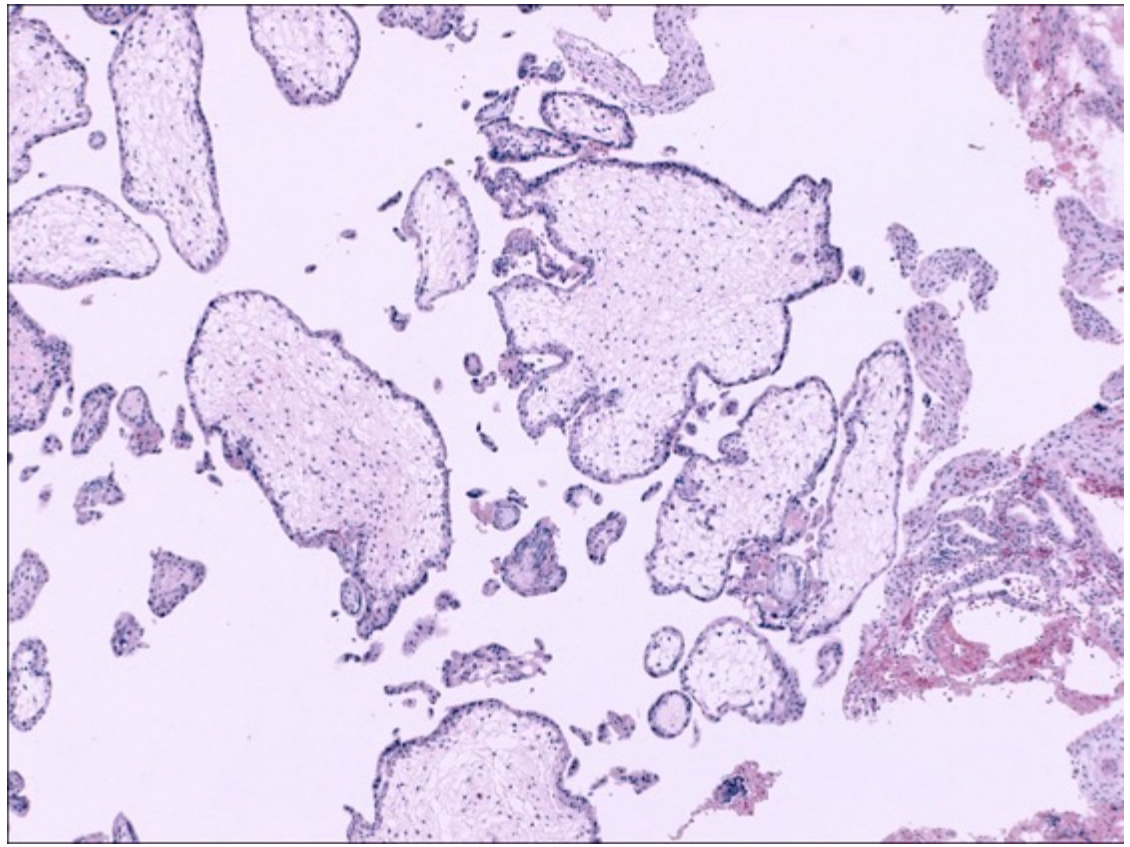
Dispermic
(Heterozygous) – 95%



Monospermic
(Homozygous) – 5%

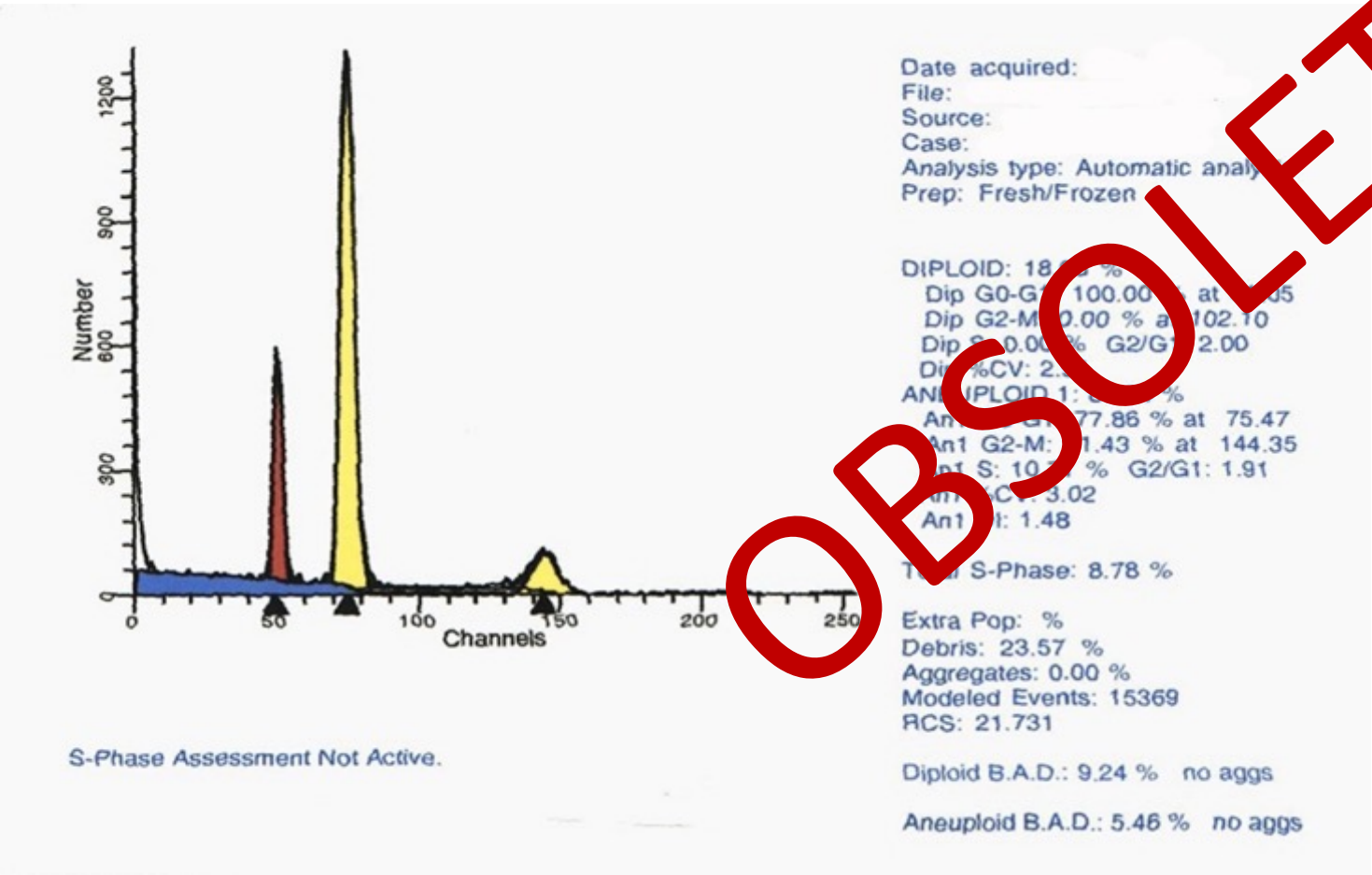
Triploidy ≠ Partial Mole





All ancillary Studies are based on molar genetics

Ploidy Analysis by Flow Cytometry



OBSOLETE

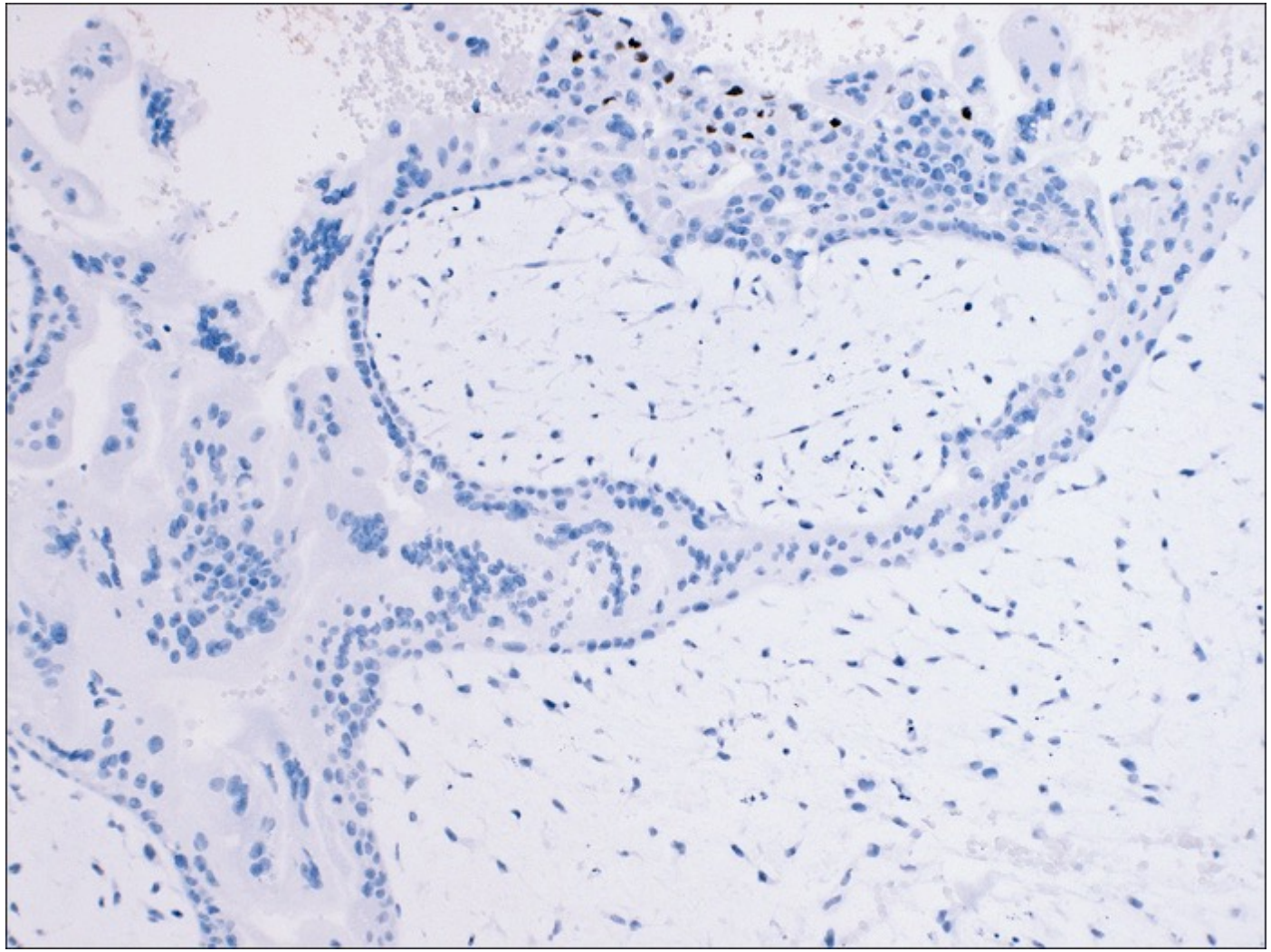
Ancillary Studies – p57 IHC

- Cyclin-dependent kinase inhibitor protein
- Encoded on 11p15.5
- Paternally imprinted – expressed only from the maternal allele
  - Normal expression (nuclear) in gestations containing maternal genetic material:
    - PHM (Diandric triploidy)
    - Digynic triploidy
    - Non-molar hydropic abortions
    - Chromosomal trisomies

CHM

p57

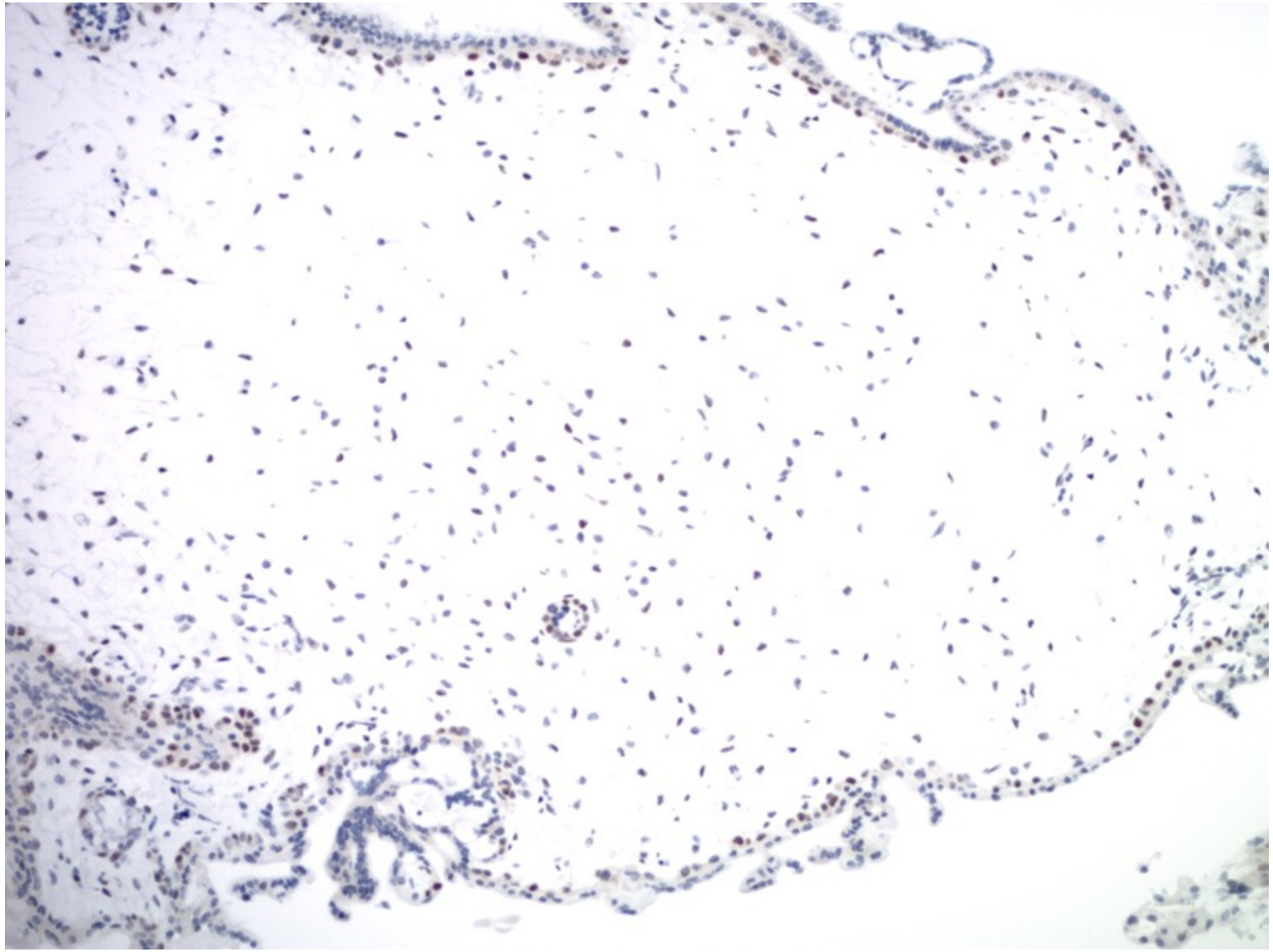
Absent in villous stroma and cytotrophoblast



PHM

p57

Retained nuclear expression

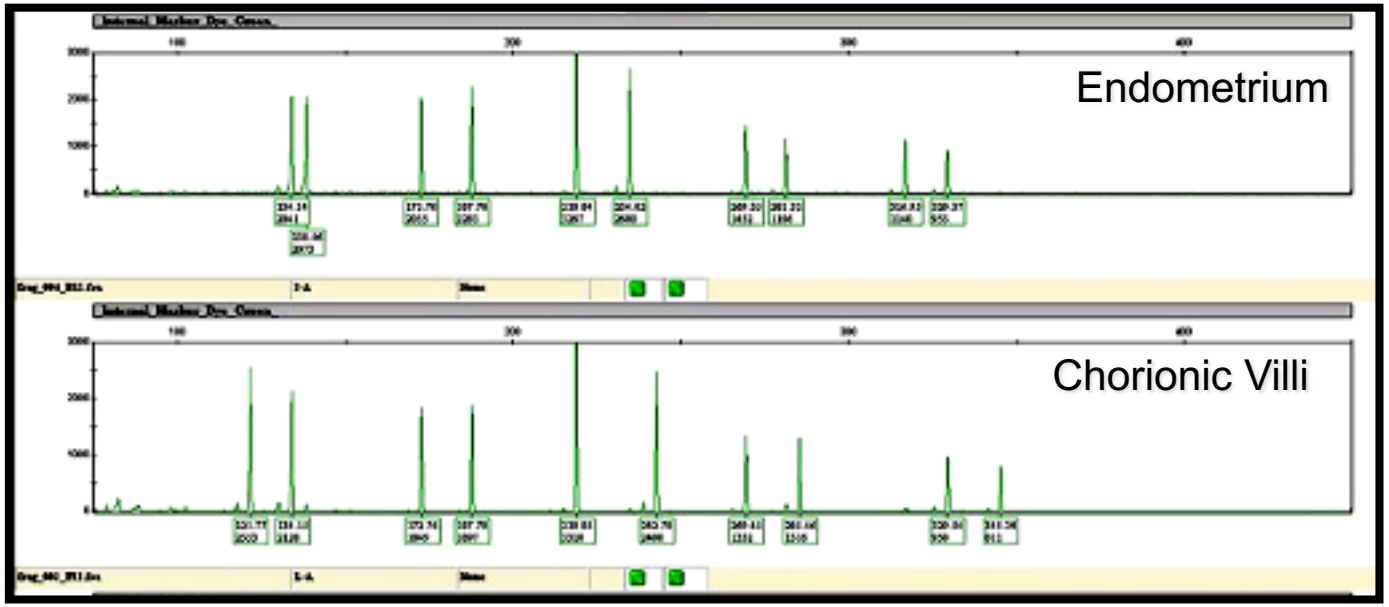


Ancillary Studies – Genotyping

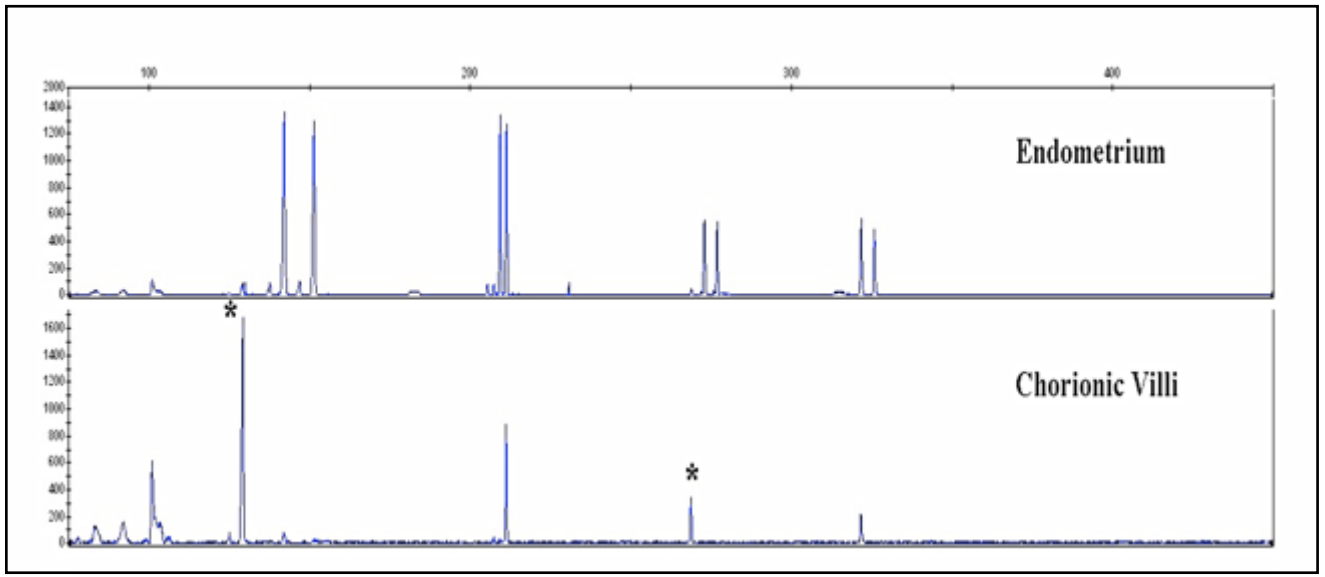
- PCR amplification of multiple short tandem repeat (STR) loci
- Comparison of allelic patterns between maternal decidua and villous tissue
- Provides information about the exact parental genetic contribution

Normal gestation

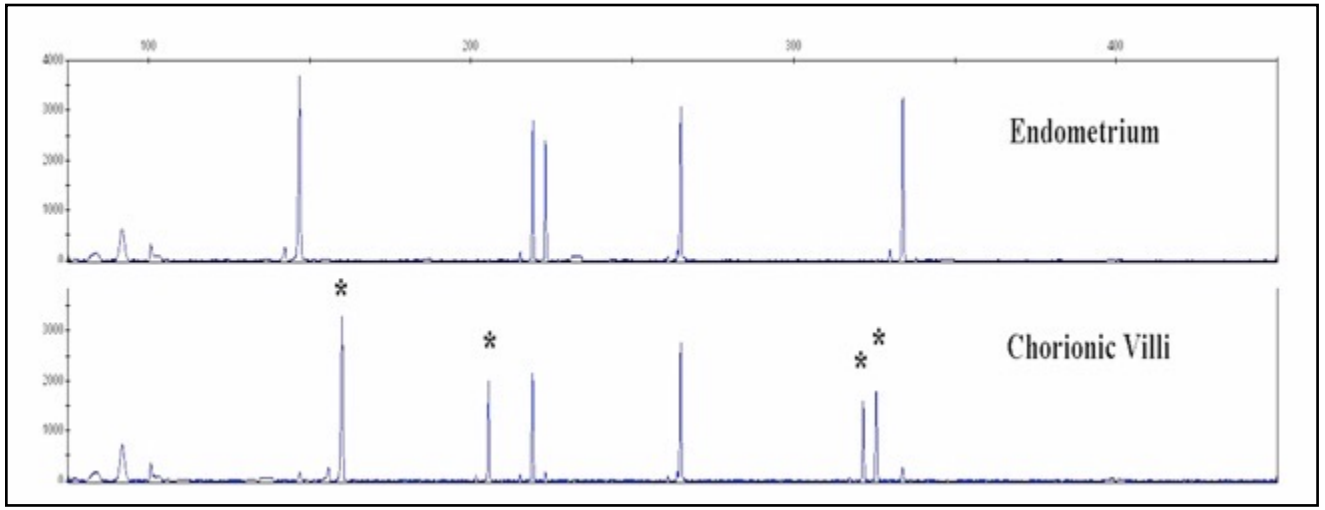
Genotyping



CHM Genotyping



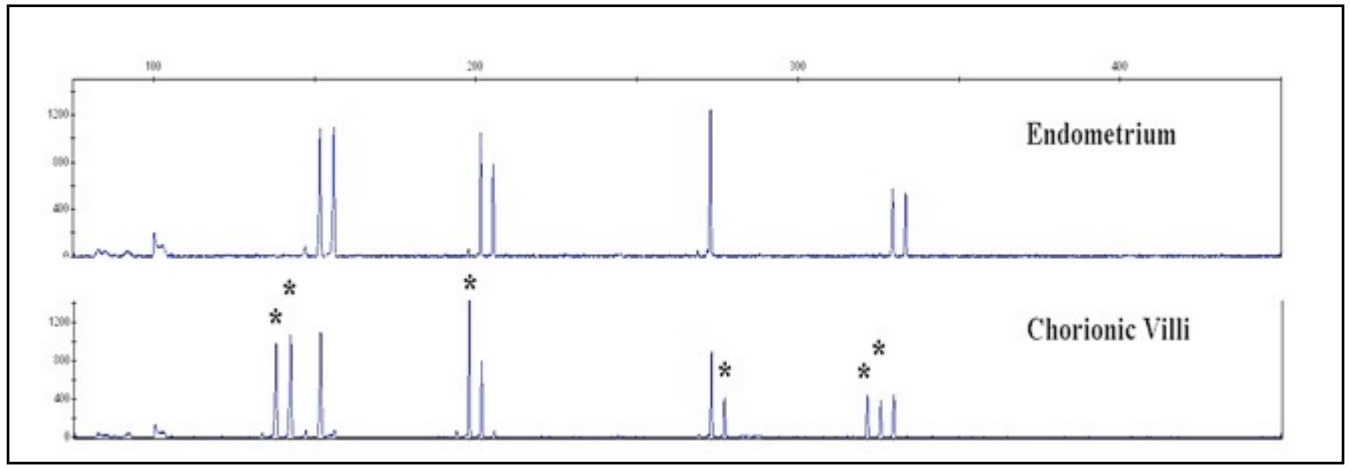
Monospermic (Homozygous) CHM



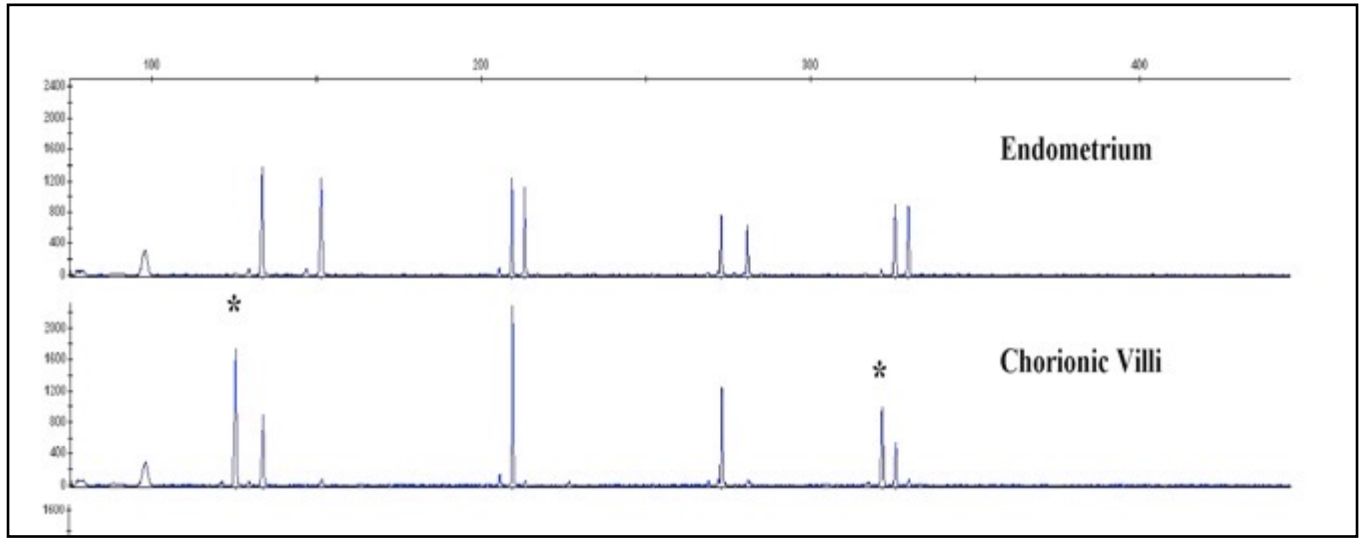
Dispermic (Heterozygous) CHM

PHM

Genotyping



Dispermic PHM



Monospermic PHM

CHM

Genotyping for Prognostic stratification

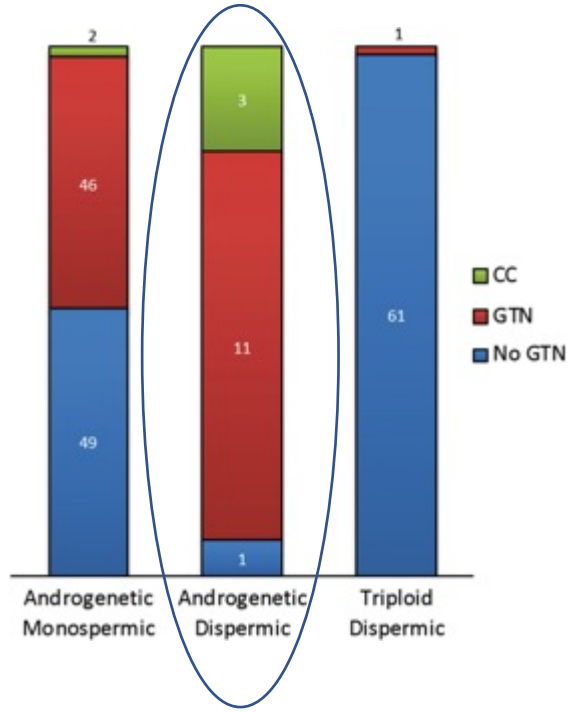
- Heterozygous CHM has a significantly higher risk for persistent GTD/ GTN than homozygous CHM

Table 3. Post-molar Gestational Trophoblastic Disease

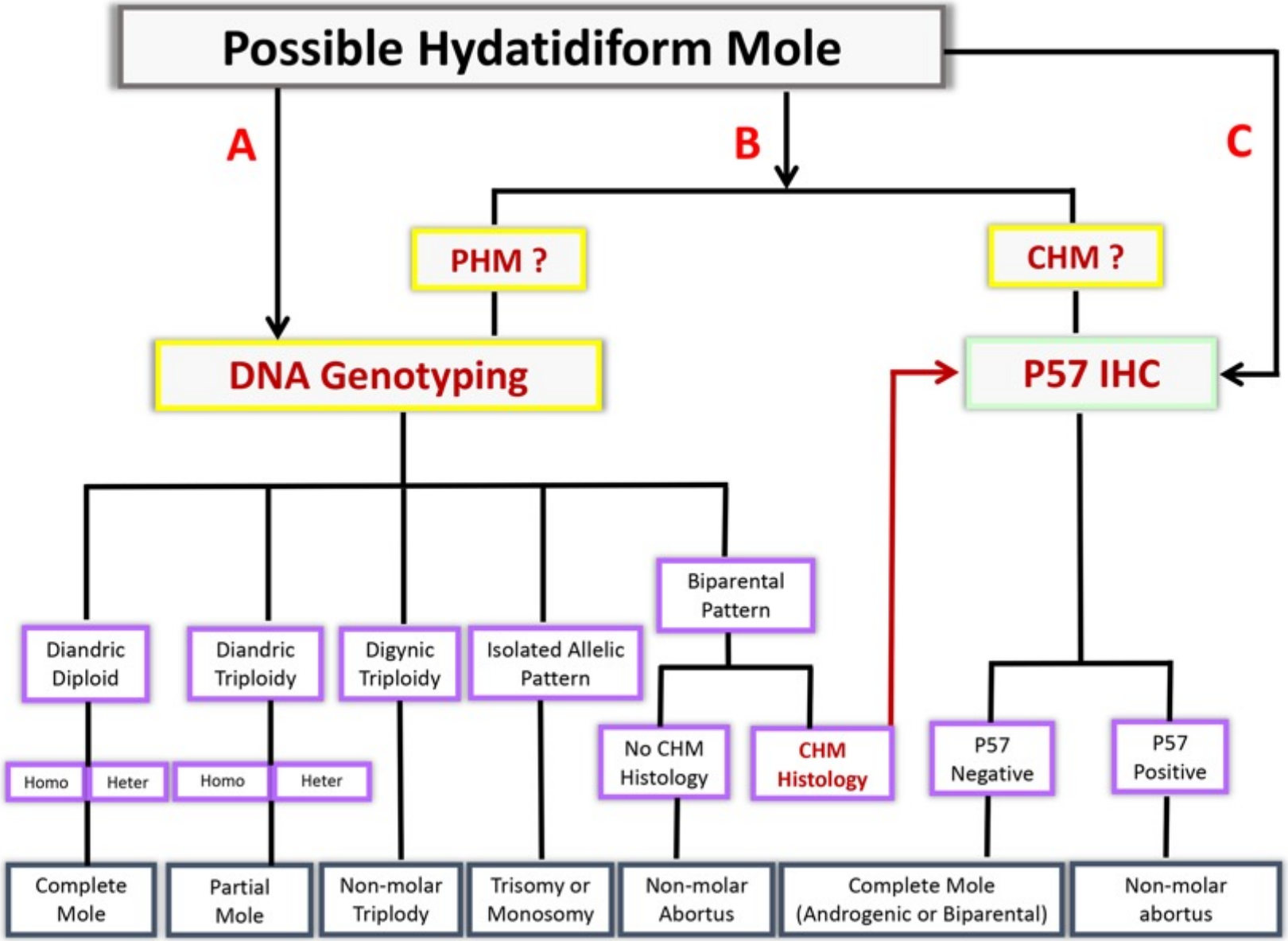
Gestational Type	Informative Follow-up	Post-molar GTD	% Post-molar GTD
Homozygous CHM	138	16	11.6##
Heterozygous CHM@@	27	10	37.0##
Triploid Homozygous PHM	2	0	0
Triploid Heterozygous PHM**	214	0	0
Tetraploid Heterozygous PHM	2	0	0
Non-molar Gestation	367	0	0
Total	750	26	3.5%

CHM: complete hydatidiform mole; PHM: partial hydatidiform mole; GTD: post-molar gestational trophoblastic disease

@@: including 2 cases of diploid heterozygous CHM with trisomy 3 or trisomy 8.
**: including 2 cases of triploid heterozygous PHM with tetrasomy 8.
##: Statistically significant difference between the two groups (p = 0.0009)



Baasanjav et al., Hum Reprod, 2010
Zheng et al., Mod Pathol, 2020
Khawajkie et al., Mod Pathol, 2020



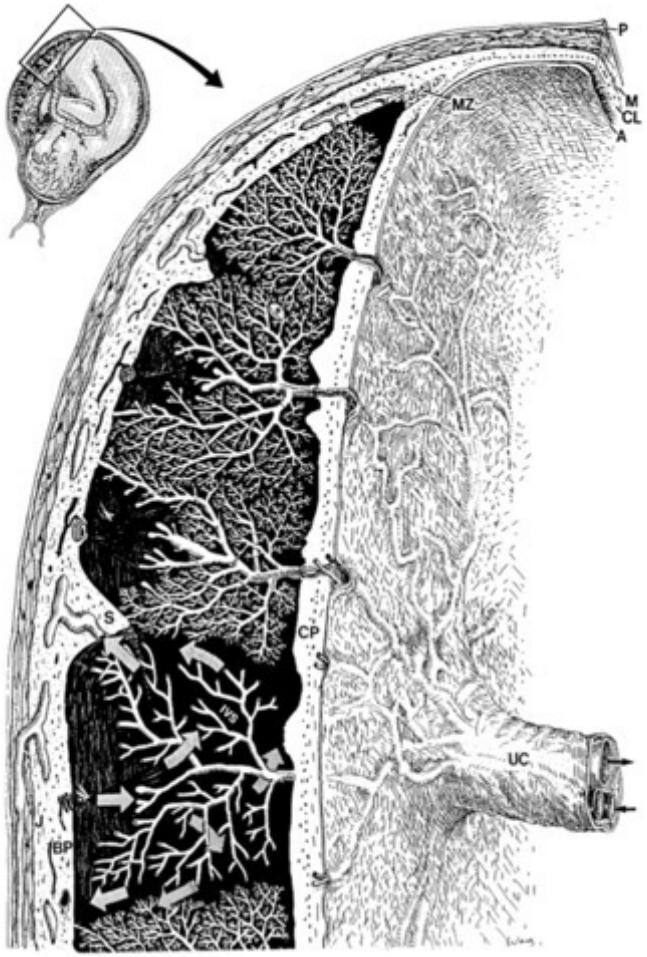
Buza and Hui, Mod Pathology, 2021,34:1658-1672

PHM – Microscopic features

- Presence of at least one of the following 3 features:
  - cistern formation
  - two villous populations
  - pseudo-inclusions
- And villous size ≥ 2.5 mm
- 61% sensitivity and 84% specificity

Buza and Hui, Int J Gynecol Pathol 2013

2020 WHO Classifications of GTD



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Abnormal (nonmolar) villous lesions
Choriocarcinoma

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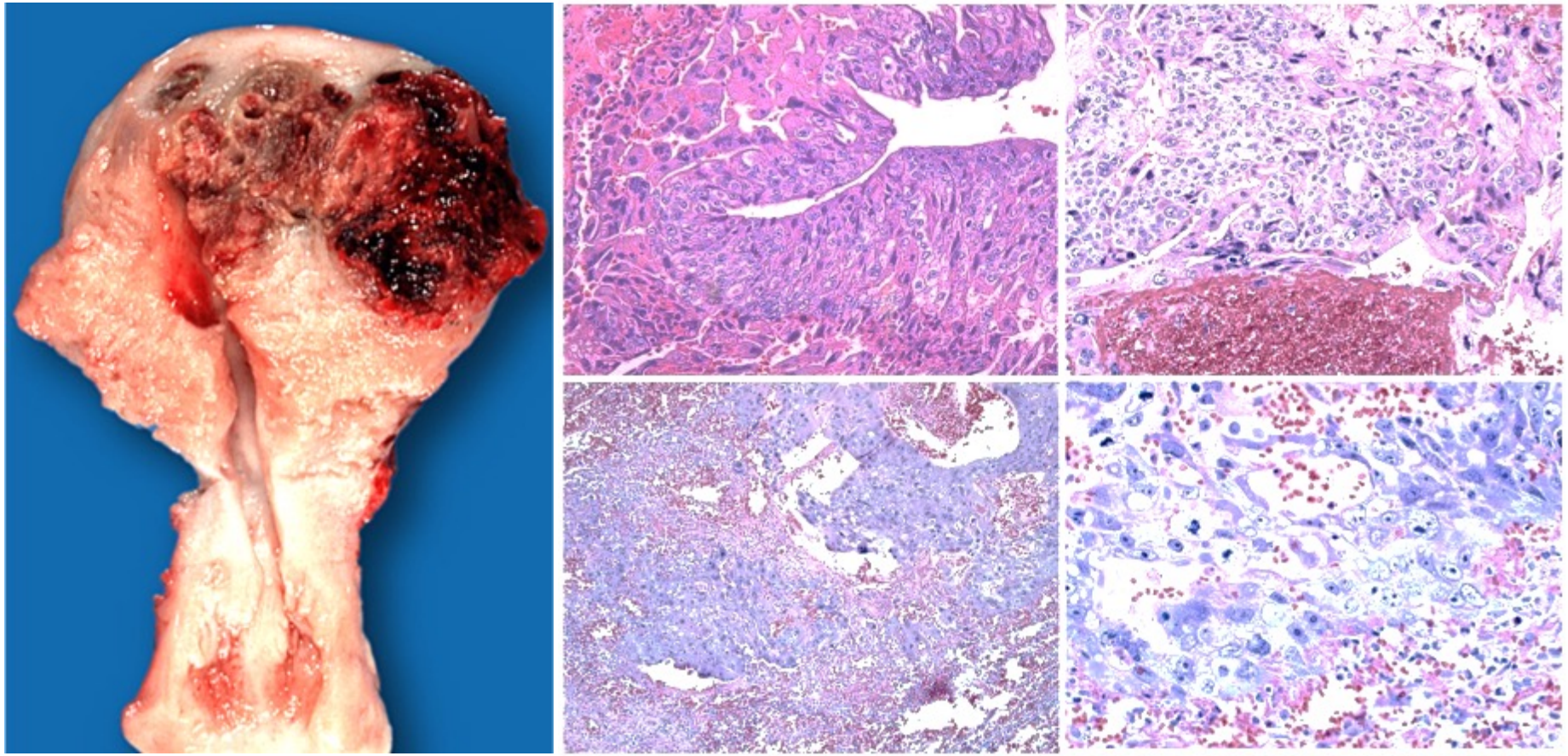
Gestational Choriocarcinoma



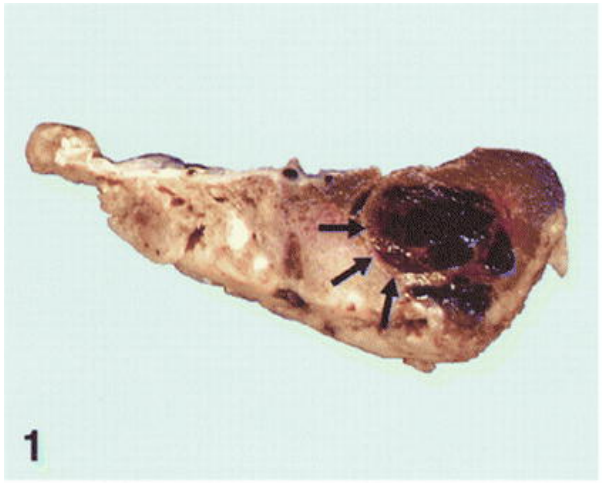
Dr. Robert Kurman

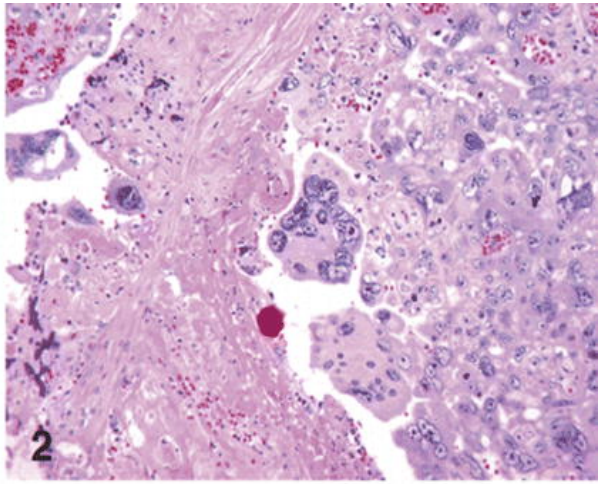
Pathogenesis of Gestational Choriocarcinomas

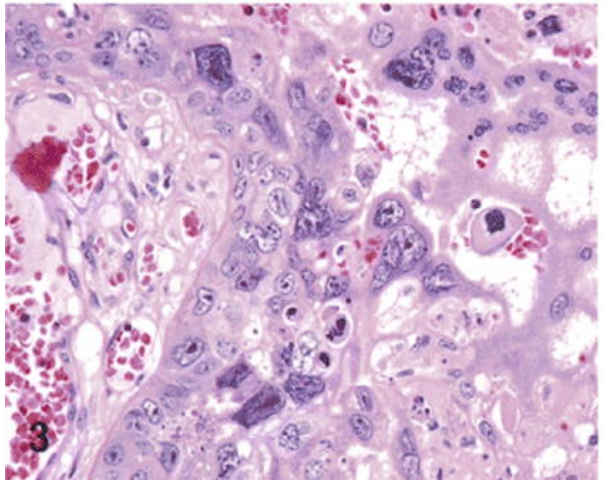
Choriocarcinoma from CHM: average 13 months after CHM-progression/transformation

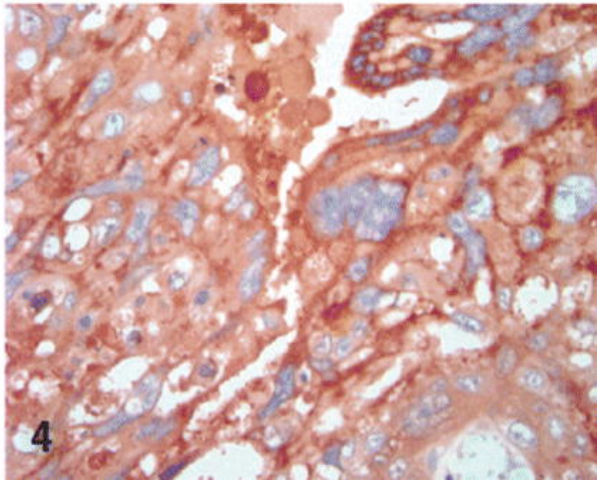
Choriocarcinoma from Term Placenta: usually 1-3 months after delivery - existing in-situ tumor

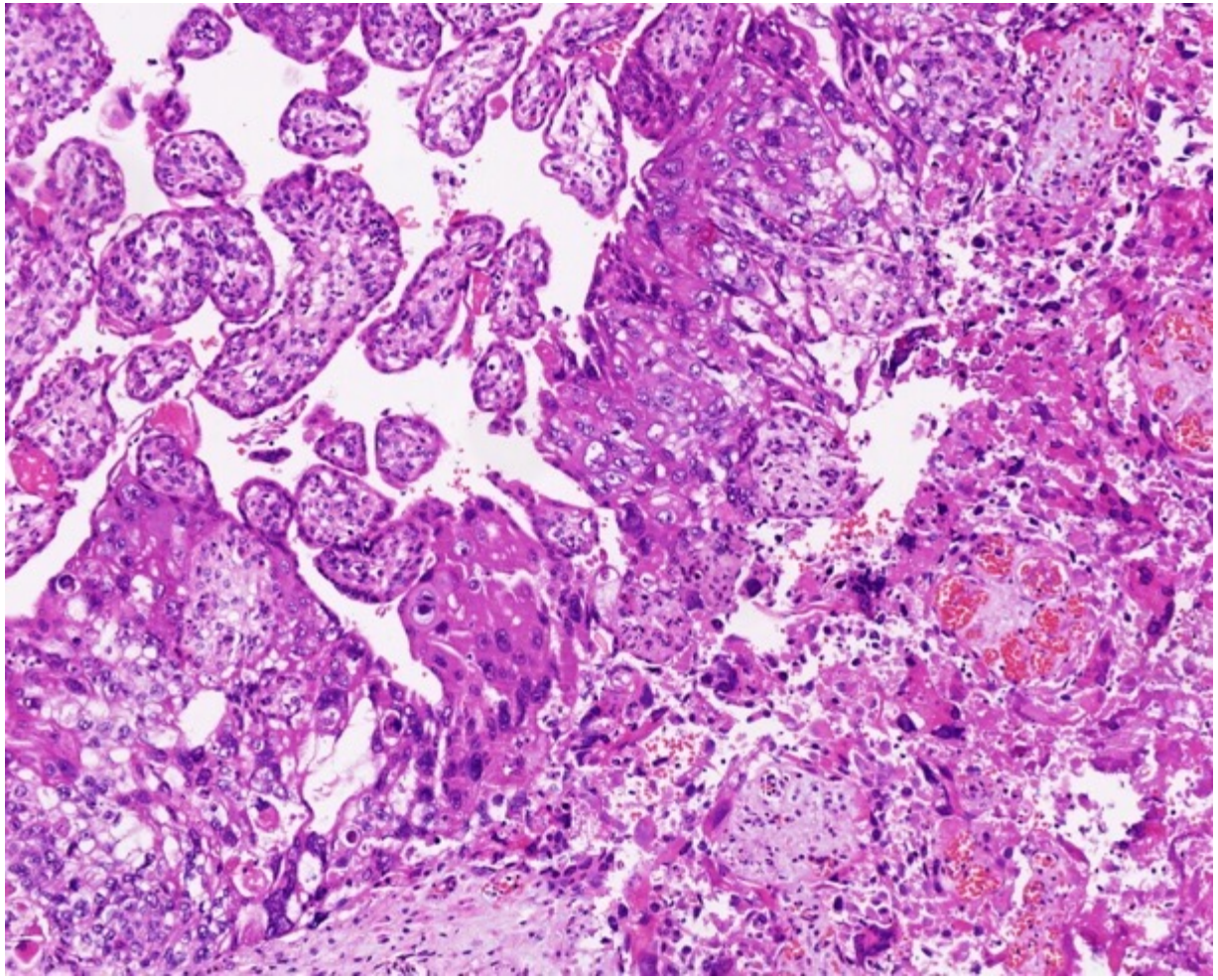
Intraplacental/in-situ choriocarcinoma in placenta







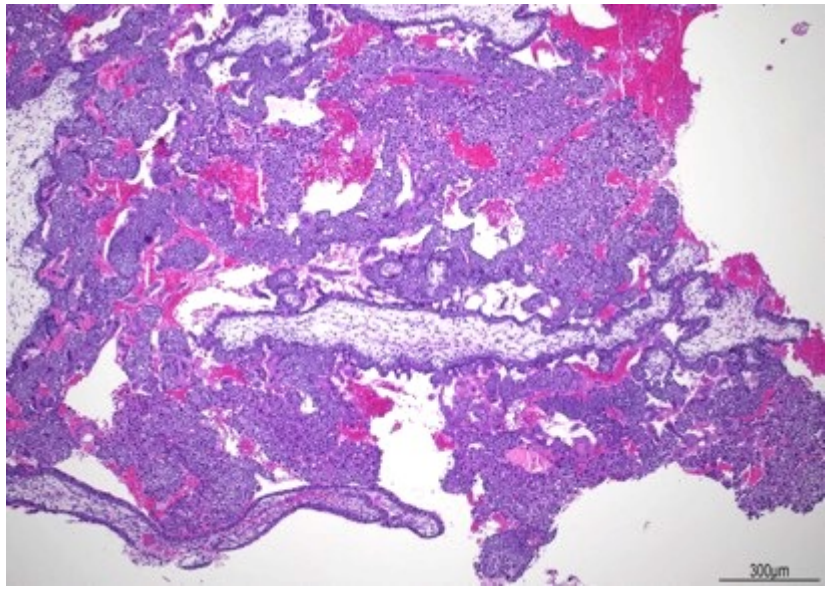


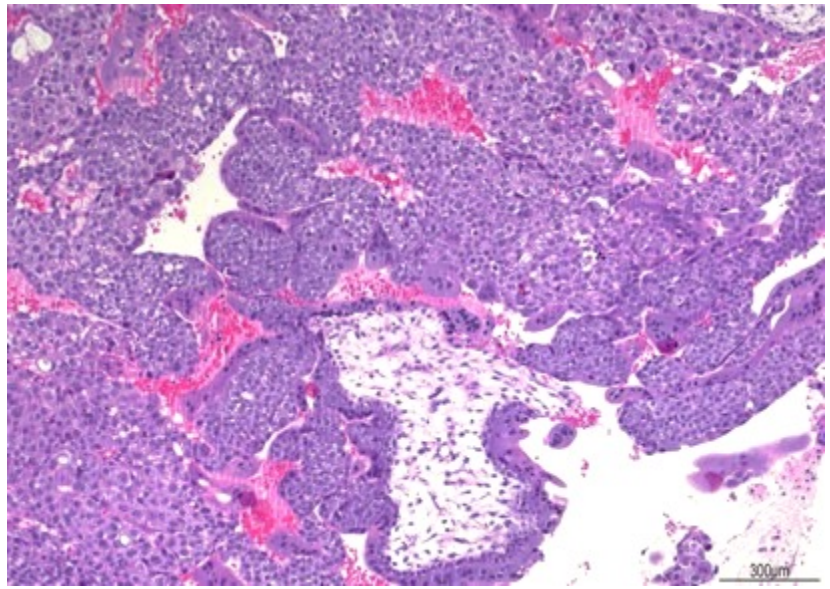


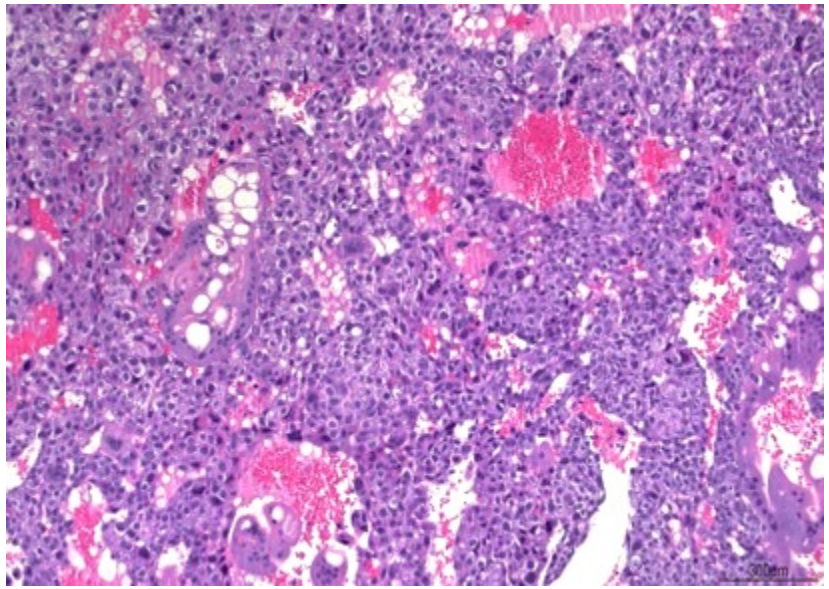
*Black et al: Archives of Pathology and Laboratory Medicine 2003;*127:e340.

Dr. Shen DH. 5th Edition WHO 2020

Intramolar Choriocarcinoma in Complete Mole



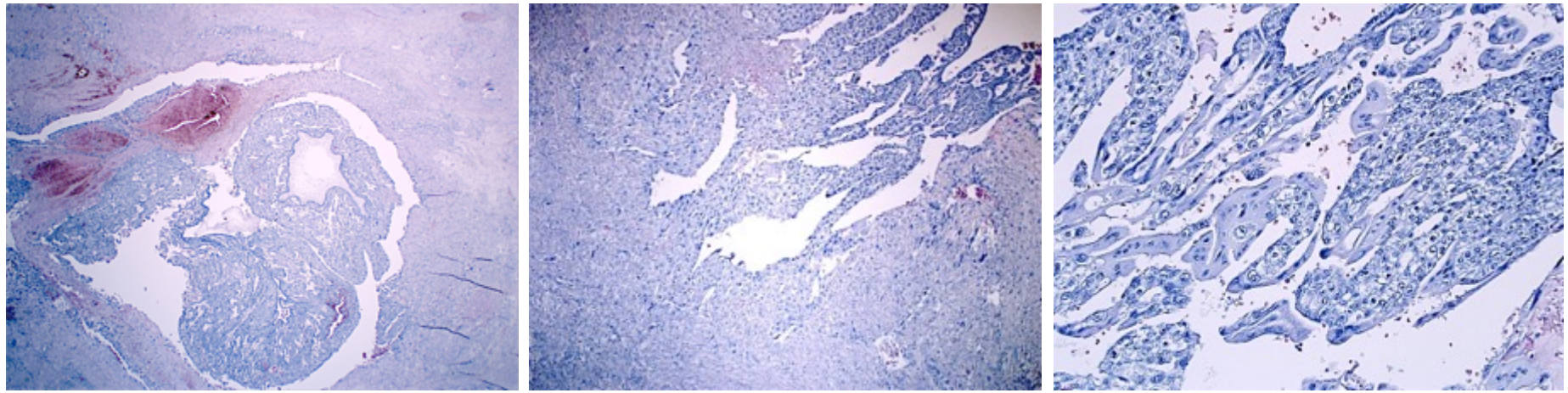




Dr. Maria Orsaria, 2021

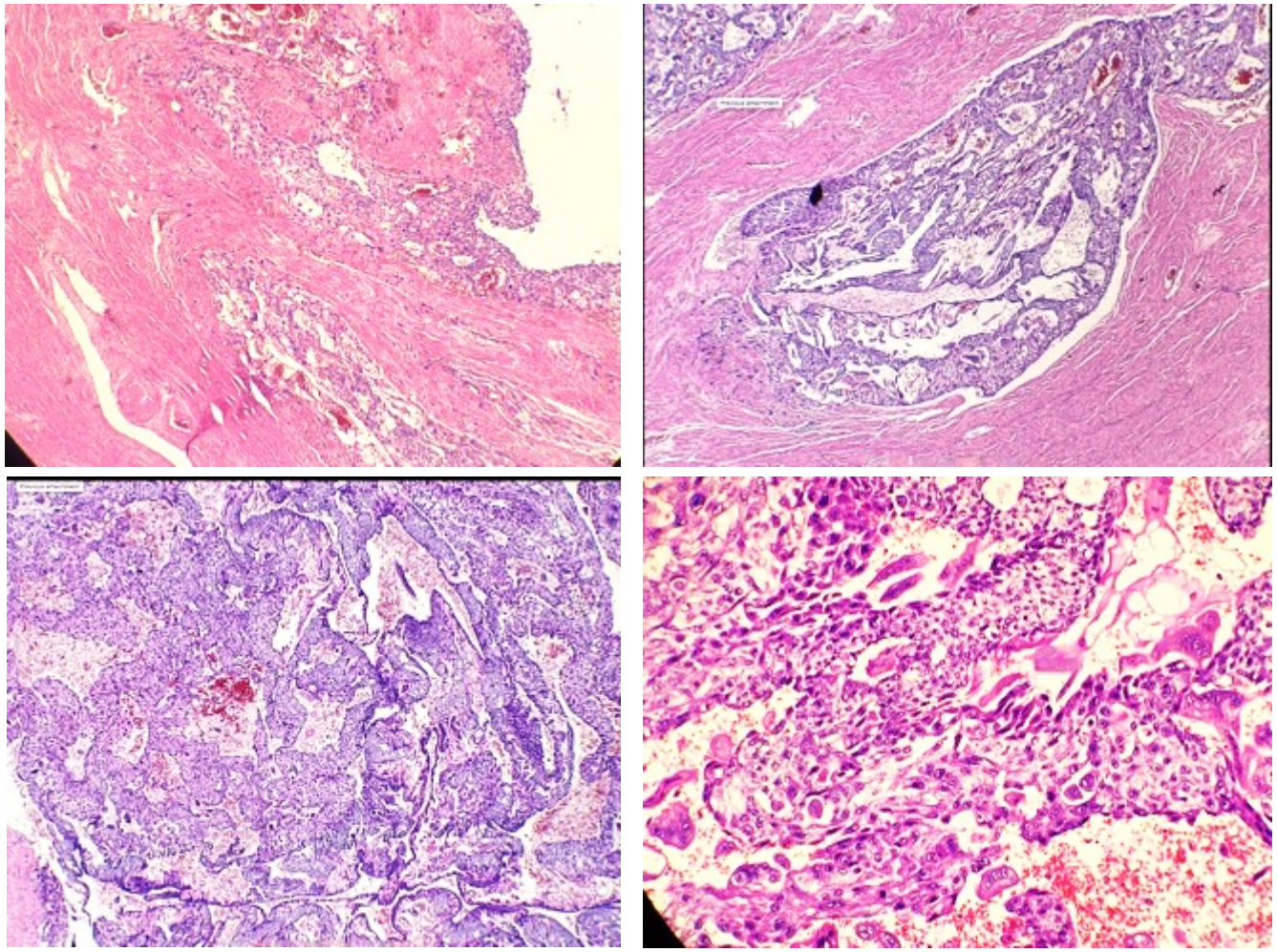
Early Choriocarcinoma Arising in Invasive Complete Mole

Malignant transformation of trophoblast with histological features of conventional choriocarcinoma in association with villi of hydatidiform mole, complete or partial



Hui P. Arch Pathol Lab Med. 2019 Jan;143(1):65-74

Early Choriocarcinoma Arising in Invasive Complete Mole



Dr. Rubina Razack, 2020

WHO Tumor Classification (2020)

Intraplacental choriocarcinoma: aggregates of cytologically malignant trophoblast morphologically resembling choriocarcinoma extending from the chorionic villi into the intervillous space.

Intramolar choriocarcinoma: molar villi surrounded by a markedly atypical trophoblastic proliferation with a focally biphasic pattern resembling that of choriocarcinoma.

Gestational Trophoblastic Neoplasia (GTN)

Invasive/metastatic/persistent mole

Gestational choriocarcinoma

Placental site trophoblastic tumor (PSTT)

Epithelioid trophoblastic tumor (ETT)

- Many primary gestational choriocarcinomas
  successfully treated without tissue diagnosis

Post-Molar Gestational Trophoblastic Neoplasia (GTN)

Four or more plateaued hCG over 3 weeks

Rise (>10%) in hCG for 3 consecutive tests in 2 weeks or more

Elevated but falling hCG 6 or more months after molar evacuation

Histological diagnosis of choriocarcinoma

Presence of metastatic disease

FIGO Oncology Committee 2002

Gestational choriocarcinomas more often now present as extrauterine metastatic tumors

Metastatic Gestational choriocarcinoma from Hydatidiform Mole

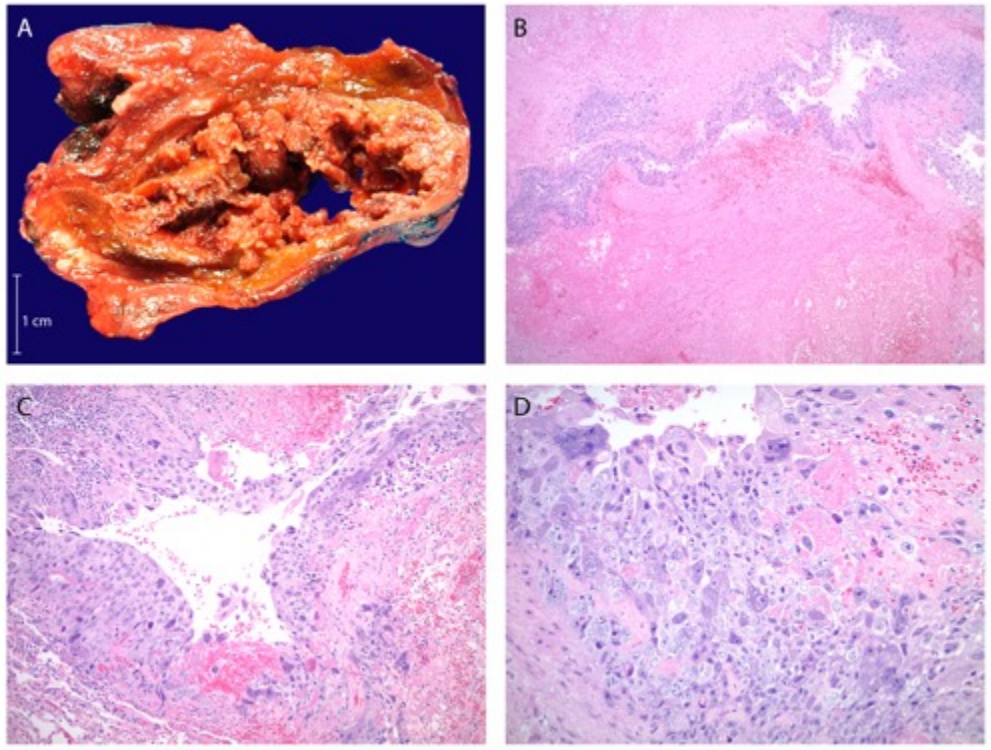
48-year-old G3P2: chest pain at emergency room

CT: right hemothorax and lung tumor

Term delivery 6 years ago with retained placenta.

Beta-hCG measurement was NOT considered preoperatively.

Lung wedge resection: 7 cm cystic hemorrhagic mass

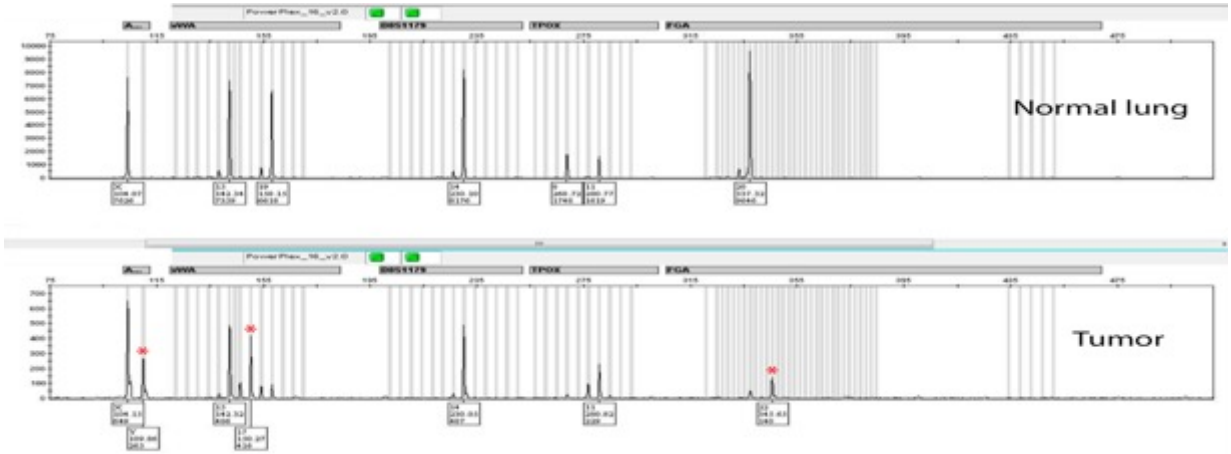


Initial pathology diagnosis: large cell carcinoma of lung (Positive for CK7, GATA3, and PAX8 but negative for p40, TTF-1, Napsin A, CK5-6, OCT4, ER and CDX2)

- Targeted next generation sequencing: no mutations
- ALK and ROS1 FISH: negative

GYN pathology consultation: rule out choriocarcinoma

Beta-hCG of 315 mIU/mL



AJCC: pT1 M1a, Stage III and FIGO risk score of 8

EMA-CO chemotherapy

Serum beta-hCG normalized after 2 cycles

Well without evidence of disease 4 months after

Buza et al: Mod Pathol. 2019;32:1271-1280.

Large cell carcinoma of lung with trophoblastic differentiation

41 year old G5P2: Heavy smoker with vaginal bleeding for 4 months

Positive urine pregnancy test but negative D/C

Last pregnancy: 6 years ago

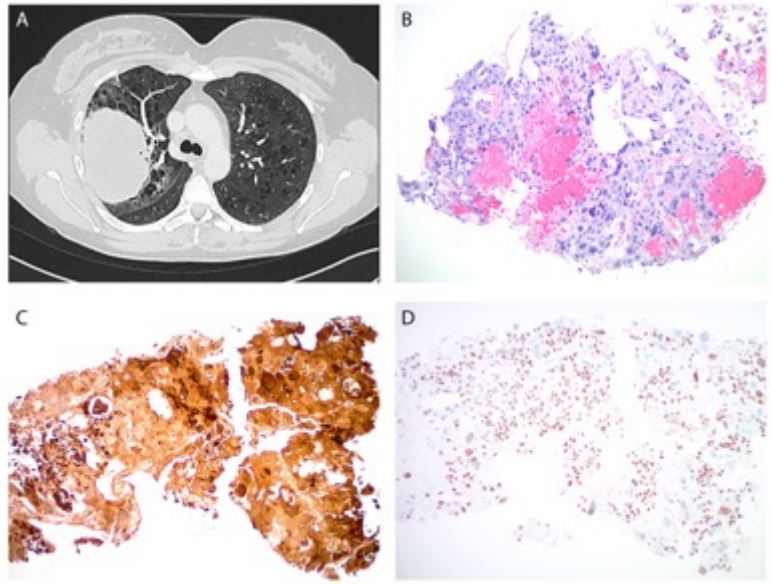
Clinical impression: ectopic pregnancy

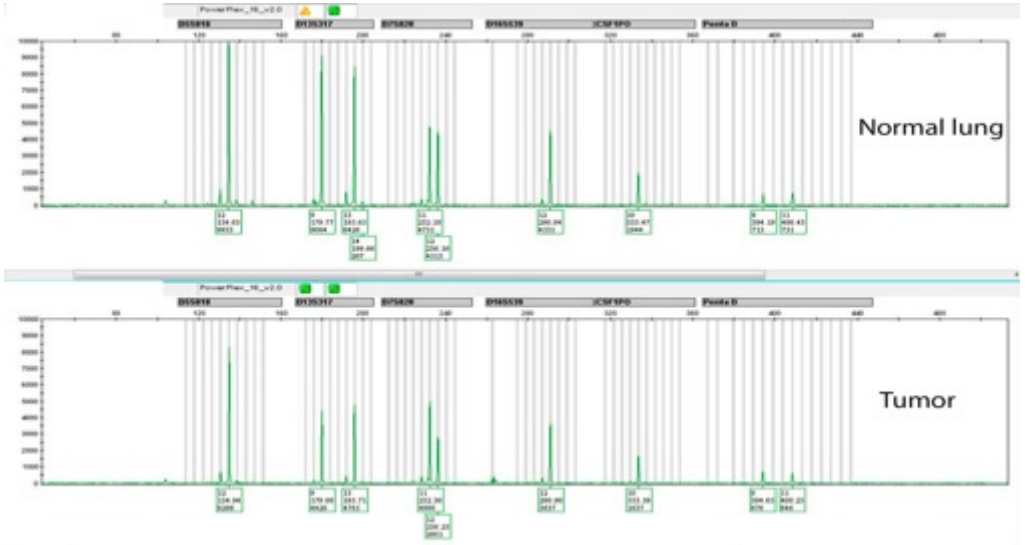
Treated with MTX but continued rising hCG

U/S: no adnexal mass or uterine lesion

CT scan: 9.7 cm lung mass

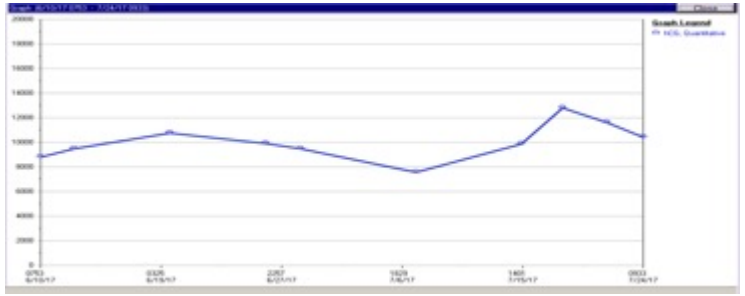
Rule out metastatic gestation choriocarcinoma





6 cycles of carboplatin, paclitaxel, followed by pembrolizumab

Patient died of the disease 15 months later



Buza et al: Mod Pathol. 2019;32:1271-1280.

Germ Cell choriocarcinoma

22-year old G1P1: "right adnexal mass" at emergency room.

Term pregnancy with C-section one year ago

Last menstrual period (LMP) was 10 weeks prior

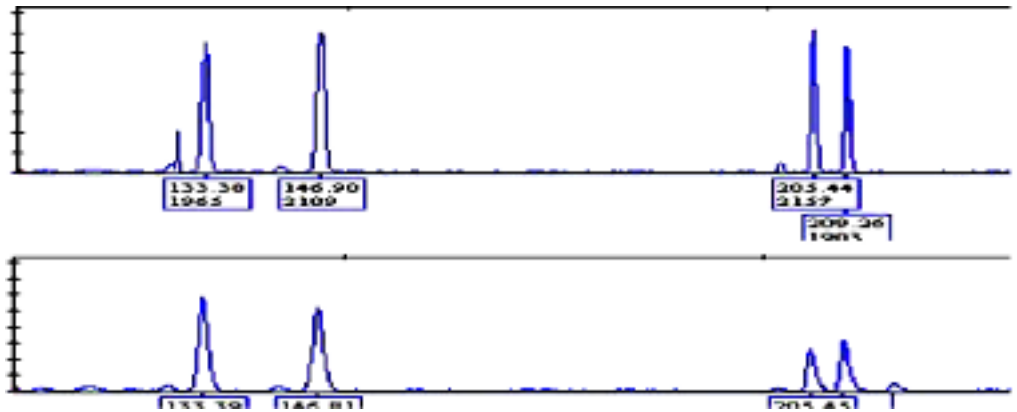
Serum β-hCG > 200,000 mIU/mL and normal AFP

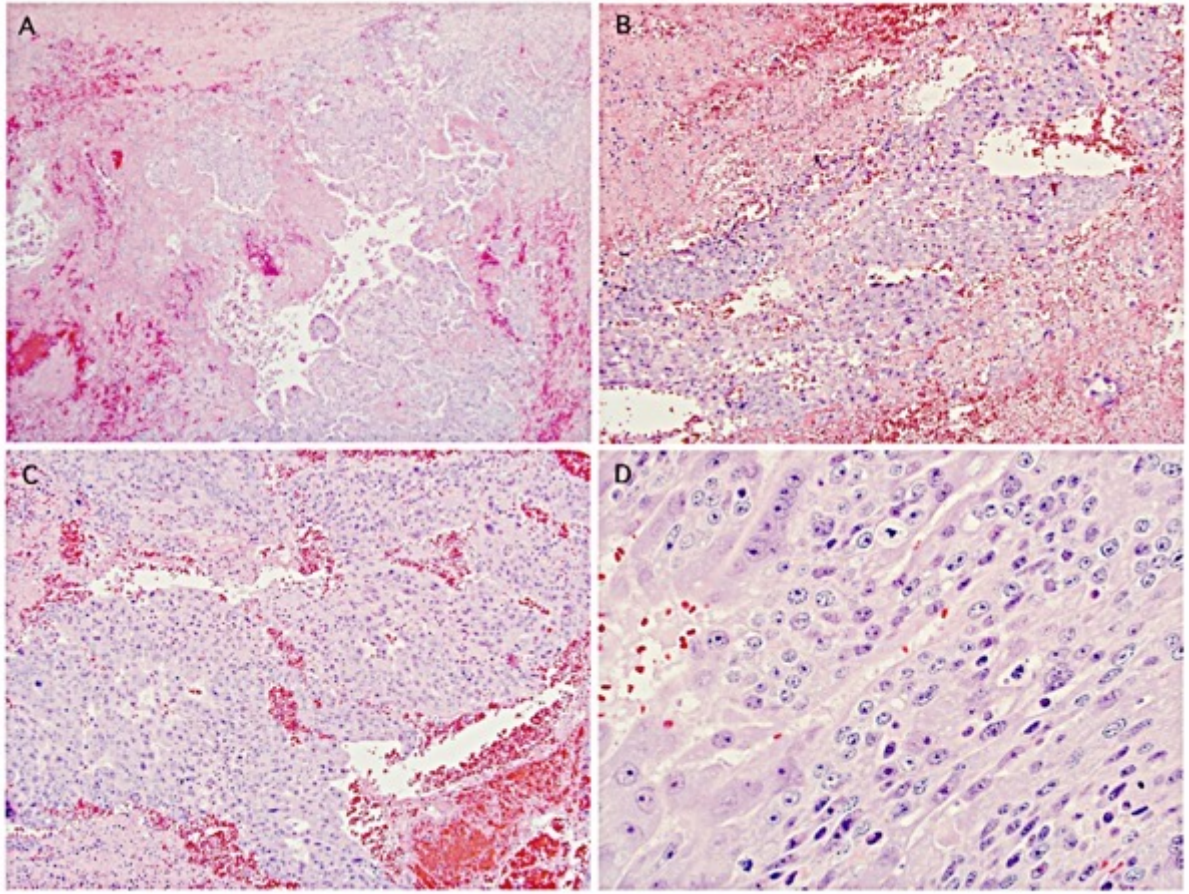
Pelvic examination: no intrauterine gestation

CT: 9.3 cm mass involving right ovary and broad ligament

Clinical diagnosis: "ruptured ectopic pregnancy"

Right salpingectomy with excision of the right broad ligament.





Buza, Hui: Int J Gyn Path 2014;33:507-10

Choriocarcinoma at Extrauterine Sites

Gestational choriocarcinoma: Trophoblast

- - From term placenta (50%)
- - From complete and partial mole (25%)
- - From missed abortion (25%)

Germ cell choriocarcinoma: Germ cell origin

- - Pure germ cell choriocarcinoma
- - Mixed germ cell tumor component

Somatic choriocarcinoma: Epithelial origin

- - Carcinoma with trophoblastic differentiation

Case number	Informative Microsatellite	Patient	Choriocarcinoma	Partner	Genetic origin of choriocarcinoma	Antecedent pregnancy	First location
1	D8S1110	272, 276	260	260	Gestational choriocarcinoma,	Induced abortion	Uterus
	D10S89	140	142	142	Secondary from androgenesis		
	D20S481	231	239	239			
2	D8S136	68, 75	68, 75		Non-gestational choriocarcinoma	/	Ovary
	D11S875	102, 117	102, 117				
	D14S306	193, 201	193, 201				
	D17S807	126, 138	126, 138				
	D22S685	184	184				
3	D8S136	75, 84	80	68, 80	Gestational choriocarcinoma,	Term delivery	Ovary
	D8S1110	280, 288	284	276, 284	Secondary from androgenesis		
	D10S89	150, 151	142, 154	142, 154			
	D11S875	110, 114	106	106, 118			
	D20S481	236, 244	231	231, 239			
4	D11S875	101, 105	103, 111		Gestational choriocarcinoma,	Term delivery	Ovary
	D17S807	116, 126	132, 134		Secondary from androgenesis		
	D20S481	243	235, 239				
5	D8S136	68, 80	68, 80	75, 82	Non-gestational choriocarcinoma	Ectopic pregnancy	Ovary
6	D8S1110	260, 276	260, 276	284	Non-gestational choriocarcinoma	Ectopic pregnancy	Ovary
	D10S189	182, 186	182, 186	188			
	D14S306	197, 209	197, 209	201, 205			
	D22S685	188	188	184, 196			
7	D22S685	192, 196	184	184, 192	Gestational choriocarcinoma,	Term delivery	Uterus
					Secondary from androgenesis		
8	D8S136	68, 80	68, 80		Non-gestational choriocarcinoma	/	Genitical gland
	D8S1110	272, 280	272, 280				
	D10S89	142	142				
	D11S875	110	110				
	D14S306	193, 197	193, 197				
	D17S807	114	114				
	D20S481	235, 239	235, 239				
	D22S685	180	180				
9	D9S43	95	76, 95	76, 91	Gestational choriocarcinoma,	Molar pregnancy	Uterus
	D20S481	239	239, 243	243	Secondary from normal fertilisation		
10	D8S136	68, 72	68, 80	80	Gestational choriocarcinoma,	Induced abortion	Uterus
	D10S89	142	142, 152	152	Secondary from normal fertilisation		
11	D3S1262	114, 120	112	112	Gestational choriocarcinoma,	Induced abortion	Uterus
					Secondary from androgenesis		
12	D2S165	96, 100	88	88, 96	Gestational choriocarcinoma,	Term delivery	Ovary
	D3S1262	119	111	111, 119	Secondary from androgenesis		
	D8S1110	260, 276	284	276, 284			
	D10S189	181	182	182			
	D20S481	232, 248	240	236, 240			

NOTE: Case 2 is a sixteen-years-old unmarried girl. The social sex of case 8 is female, but her karyotype is 46, XY. These two ladies haven't partner. "First location" = the first location of the choriocarcinoma observed. "Antecedent pregnancy" = last pregnancy clinical observed before the choriocarcinoma occurrence.

Molecular Genetic Analyses of Choriocarcinoma

TABLE 2. Genotyping Data

Case	Specimen	Diagnosis	Genotyping	Zygosity
1	Placenta	Intraplacental choriocarcinoma	Gestational, biparental (tumor matches villous tissue)	XX
2	Left fallopian tube	Choriocarcinoma (tubal ectopic)	Gestational, androgenetic	XX, homozygous
3	Uterine curetting	Choriocarcinoma with associated CHM	Gestational, androgenetic (tumor matches hydatidiform mole)	XX, homozygous
4	Right ovary	Choriocarcinoma	Nongestational (tumor matches maternal tissue and has allelic imbalances)	XX
5	Placenta	Intraplacental choriocarcinoma	Gestational, biparental (tumor matches villous tissue)	XX
6	Uterus	Choriocarcinoma in cornu; separate 21 wk placenta (dispermic "twin" gestation)	Tumor: gestational, androgenetic; villous tissue: biparental	Tumor: XX, homozygous; villous tissue XY (different sperm in tumor and villi
7	Uterine curetting	Choriocarcinoma (no villi in entirely submitted specimen)	Gestational, androgenetic	XX, homozygous
8	Uterine curetting	Choriocarcinoma with associated CHM	Gestational, androgenetic (tumor matches hydatidiform mole)	XX, homozygous
9	Placenta	Intraplacental choriocarcinoma (incidental, 1 slide)	Gestational, biparental (tumor matches villous tissue)	XY
10	Rectal mesenteric mass	Choriocarcinoma (negative endometrial specimen)	Nongestational (tumor matches maternal tissue and has allelic imbalances)	XX
11	Uterine curetting	Choriocarcinoma (no villi in entirely submitted specimen)	Gestational, biparental (no villous tissue or prior placenta available for comparative analysis)	XX
12	Right uterine cornu	Choriocarcinoma (no villi in entirely submitted specimen)	Gestational, androgenetic	XX, homozygous
13	Left fallopian tube	Choriocarcinoma (tubal ectopic; no villi in entirely submitted specimen)	Gestational, androgenetic	XX, homozygous
14	Left ovary	Choriocarcinoma (ovarian ectopic); concurrent intrauterine term placenta (dispermic "twin" gestation)	Tumor: gestational, androgenetic; villous tissue: biparental	Tumor: XX, homozygous; villous tissue: XX (different X sperm in tumor and villi)
15	Uterus	Choriocarcinoma	Gestational, biparental with allelic imbalances (no villous tissue or prior placenta available for comparative analysis)	XYY
16	Uterine curetting	Choriocarcinoma (no villi in entirely submitted uterine specimen; negative fallopian tube)	Gestational, androgenetic	XX, homozygous
17	Left uterine cornu	Choriocarcinoma (no villi in entirely submitted specimen)	Gestational, androgenetic	XX, homozygous
18	Uterine curetting, vaginal mass	Choriocarcinoma with associated CHM	Gestational, androgenetic (tumor matches hydatidiform mole)	XX, homozygous
19	Uterine curetting	Choriocarcinoma with associated CHM	Gestational, androgenetic (tumor matches hydatidiform mole)	XX, homozygous
20	Uterine curetting	Choriocarcinoma with associated very early CHM	Gestational, androgenetic (tumor matches hydatidiform mole)	XX, homozygous
21	Right ovary	Choriocarcinoma	Nongestational (tumor matches maternal tissue and has allelic imbalances)	XX
22	Right uterine cornu	Choriocarcinoma	Gestational, androgenetic (tumor matches prior hydatidiform mole)	XX, homozygous

Choriocarcinoma in Women: Analysis of a Case Series With Genotyping

Savage, Johanna MD*; Adams, Emily BS*; Veras, Emanuela MD*; Murphy, Kathleen M. PhD†; Ronnett, Brigitte M. MD*,‡

The American Journal of Surgical Pathology: December 2017 - Volume 41 - Issue 12 - p 1593–1606

Non-gestational choriocarcinoma

- Higher potential for local invasion
- Higher capacity to metastasize via lymphatics
- Resistant to conventional GTD chemotherapy

Non-gestational choriocarcinoma: According FIGO, patients are treated with cisplatin based multi-agent chemotherapy regardless of the stage and risk factor scores.

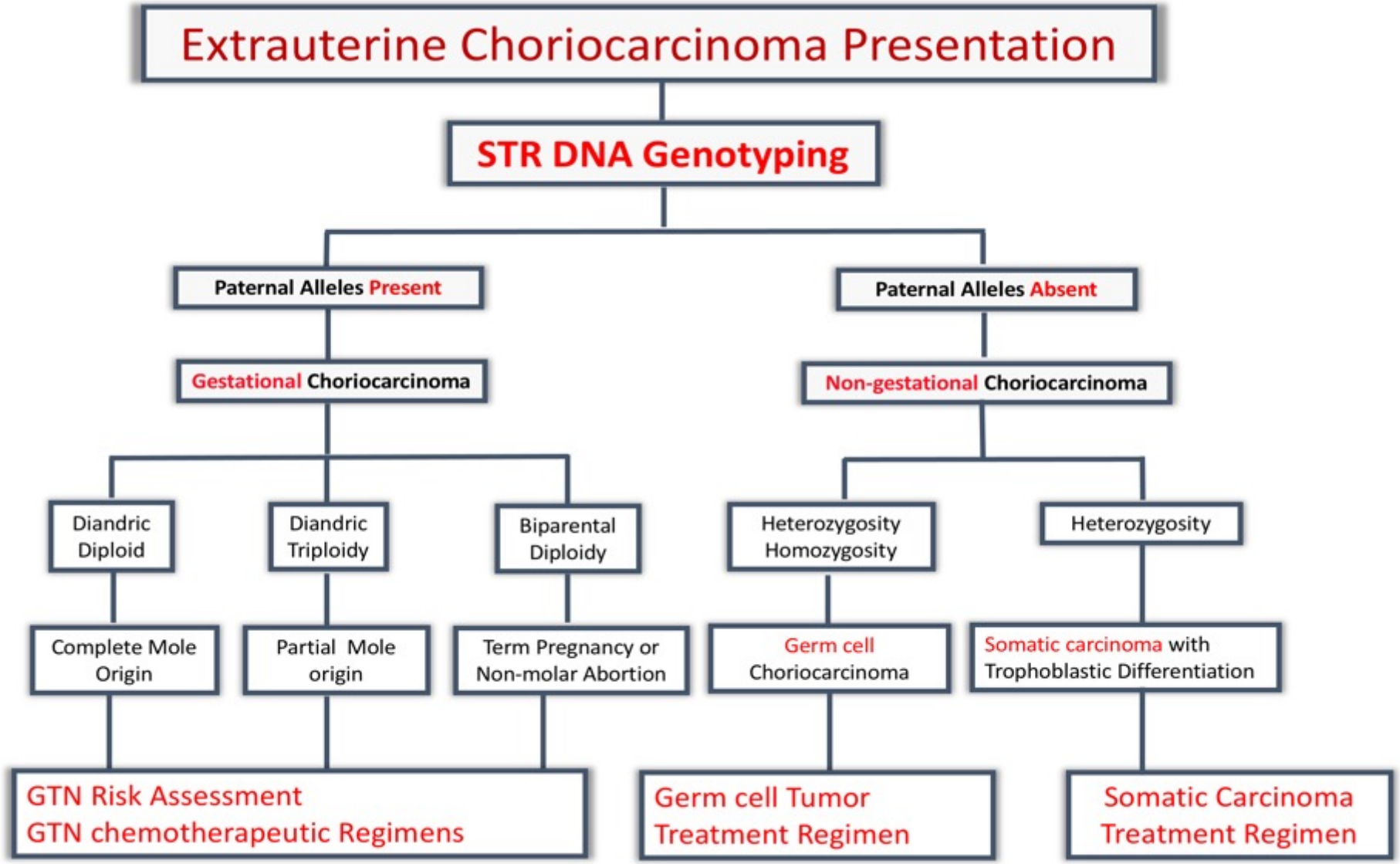
Gestational choriocarcinoma: rigorously evaluated by FIGO/WHO risk scoring scheme into low or high-risk groups for either single or multi-agent chemotherapy

FIGO/WHO Risk Factor	0	1	2	4
Age	< 40	> 40	-	-
Index pregnancy	**Mole**	**Abortion**	**Term**	
Interval from index pregnancy, months	**< 4**	**4-6**	**7-12**	**> 12**
Pretreatment hCG mIU/mL	$< 10^3$	$> 10^3$-10^4	$> 10^4$-10^5	$> 10^5$
Largest tumor size including uterus, cm	-	3-4	≥ 5	-
Site of metastases including uterus	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	-	1-4	5-8	> 8
Previous failed chemotherapy	-	-	Single drug	Two or more drugs

Post-molar Surveillance Program - No Tissue Diagnosis of Primary GTN

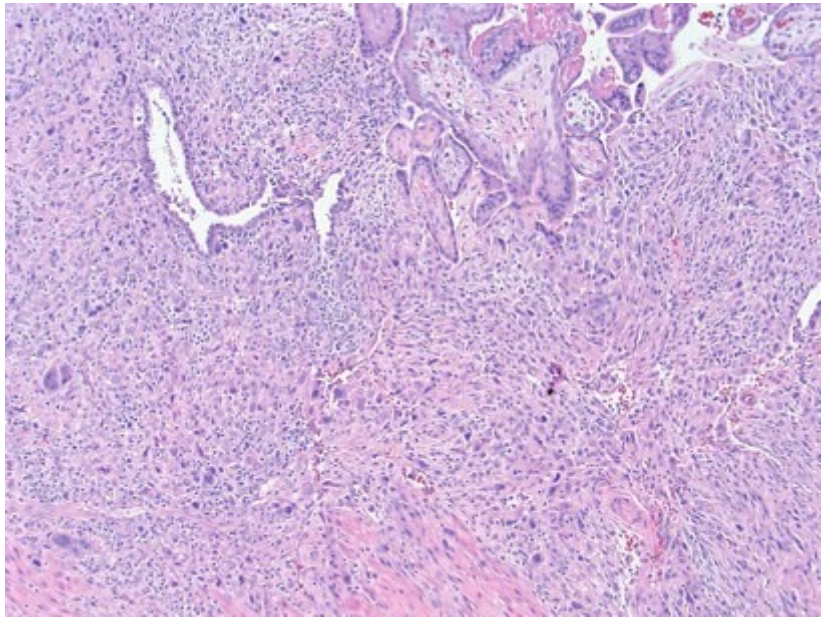
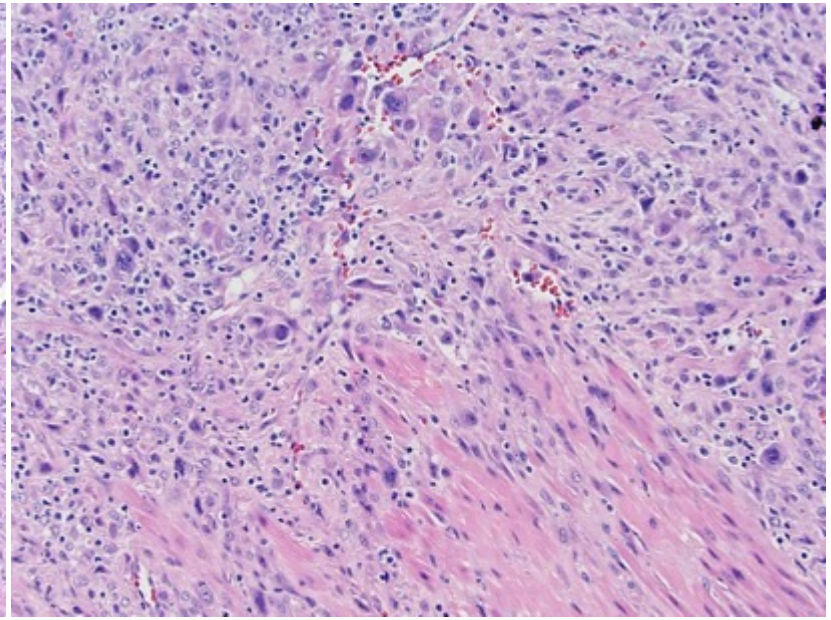
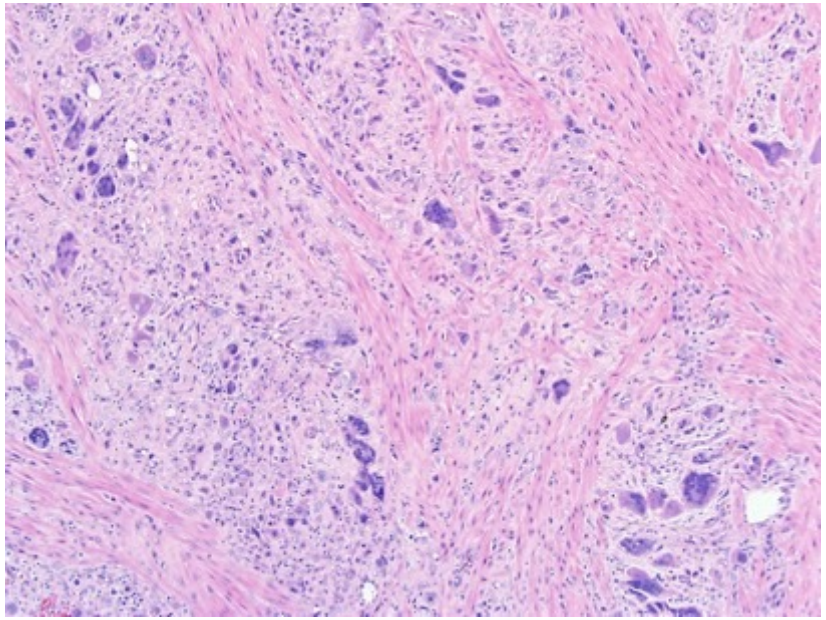
- Uncertain nature of the index gestation

- Antecedent pregnancy may not be the index gestation



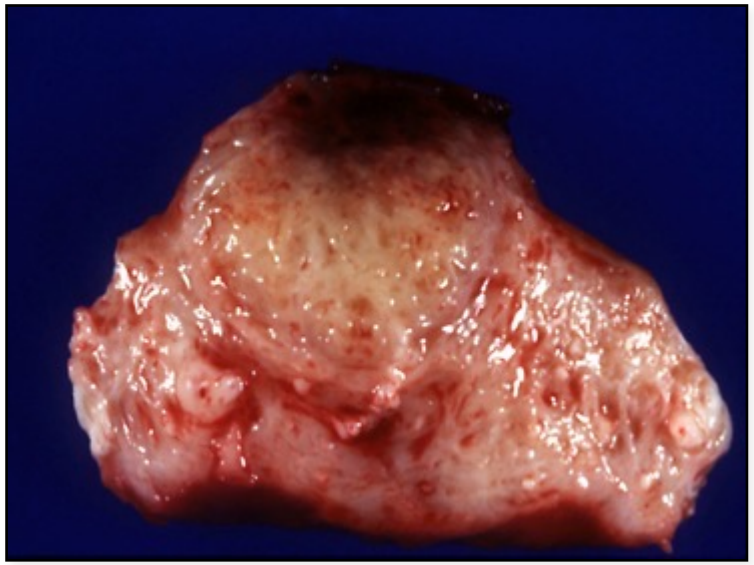
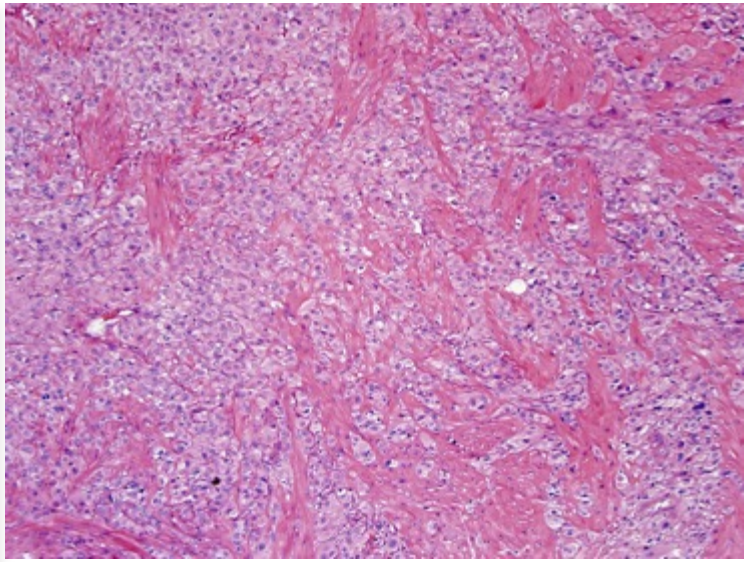
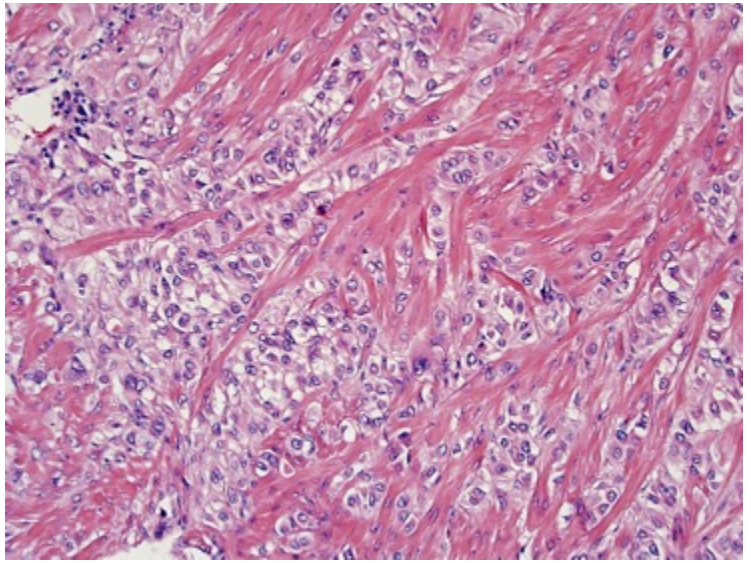
Buza and Hui, Mod Pathology, 2021,34:1658-1672

Exaggerated Implantation Site Reaction (EPS)

- **Reproductive age**
- **Concurrent gestation**
- **Superficial endomyometrium**
- **Non-destructive growth**
- **No mitosis and Ki-67 < 2%**
- **Benign reactive process**

Placental Site Trophoblastic Tumor (PSTT)

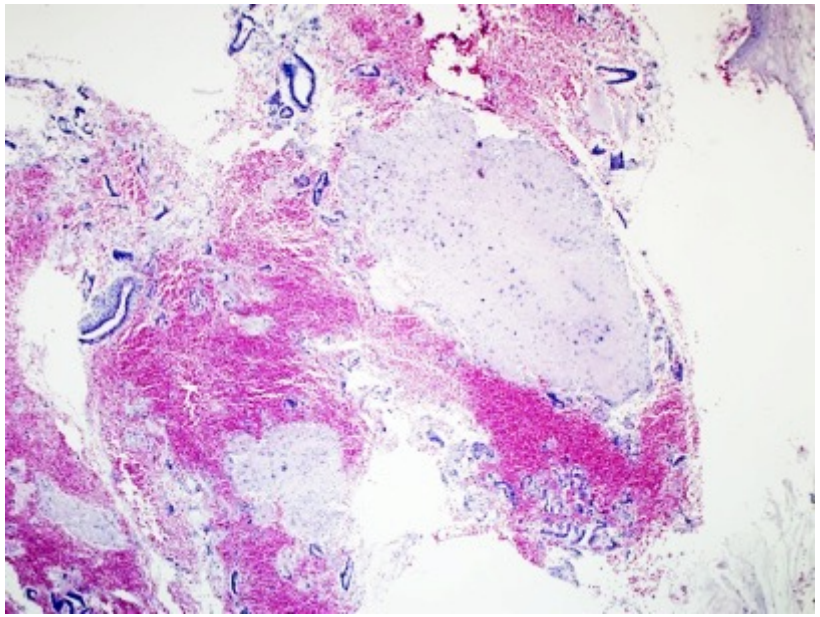
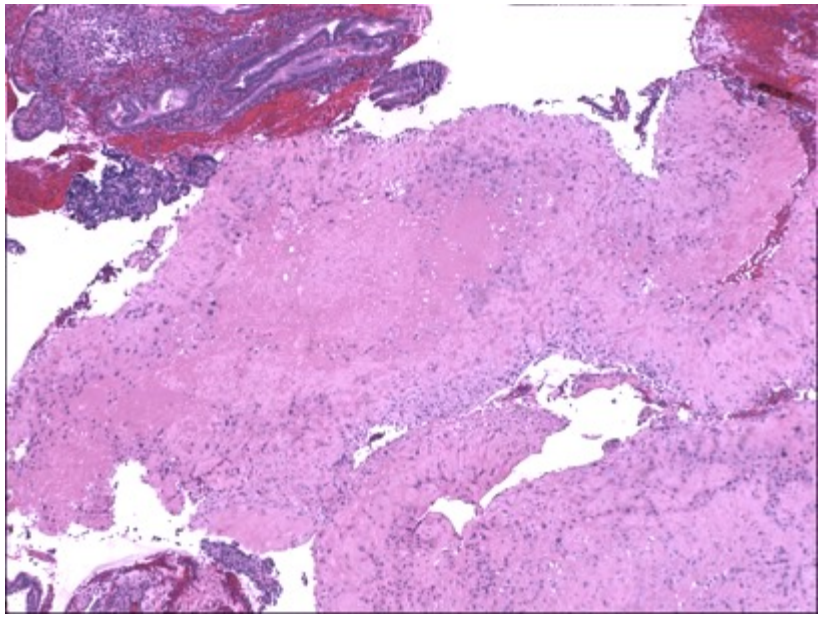
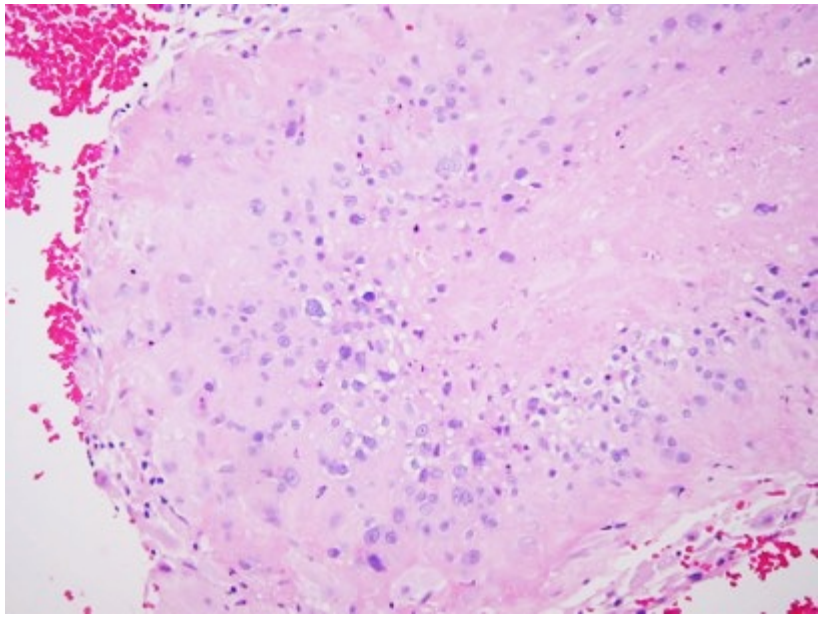
- Reproductive age (>60% after normal pregnancy, 12% after mole and 10% after spontaneous abortion)
- 12-18 months after pregnancy
- Vaginal bleeding or amenorrhea
- HCG: 80% low to moderate level of elevation (mean 700 mIU/ml and median 74.5 mIU/ml)
- FIGO Stage I: 84% and metastasis occurs after 2 or 3 recurrences

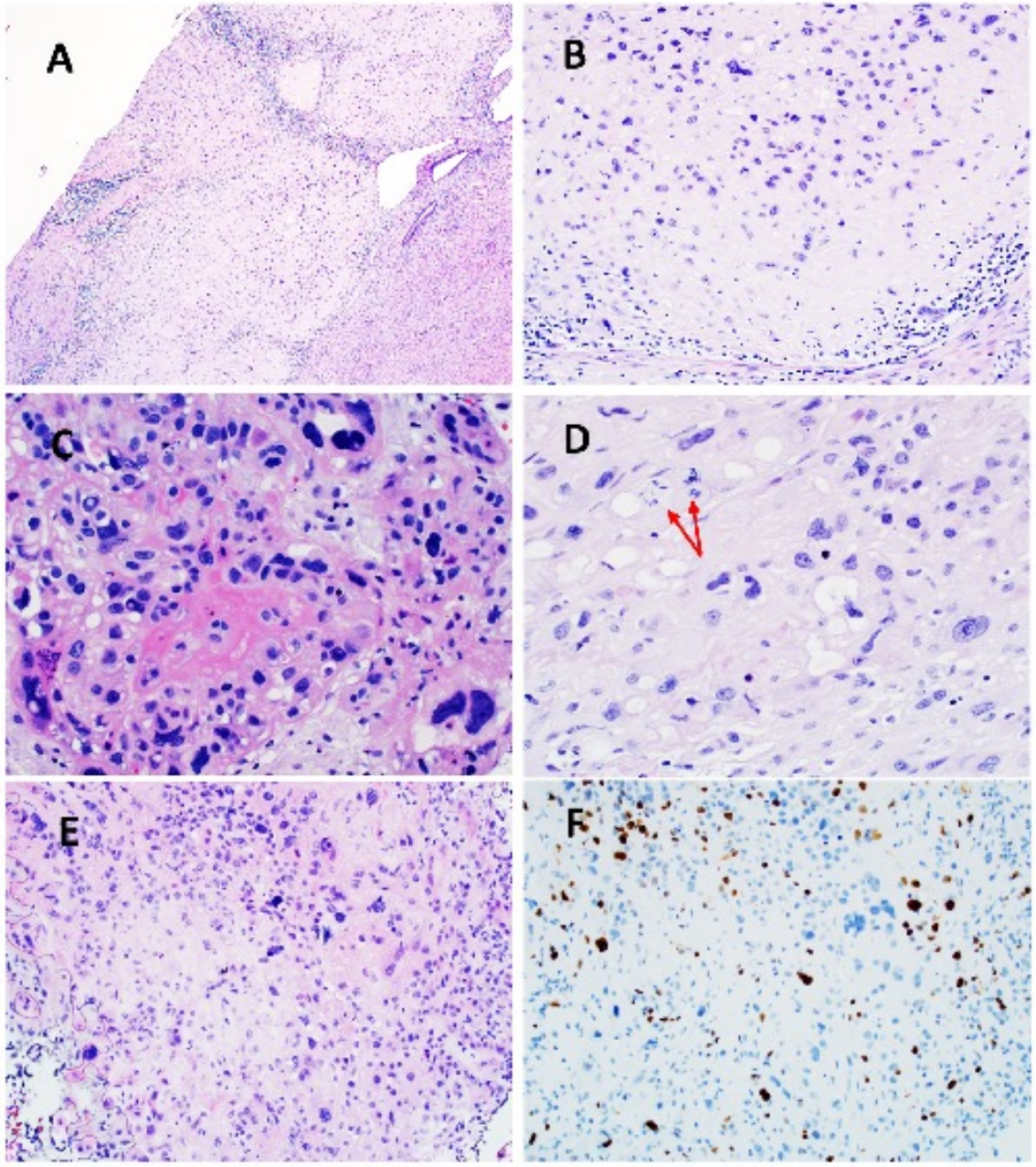
Prognostic Parameters

- Deep myometrial invasion
- High mitotic count (>5/10 hpf)
- Extensive tumor necrosis
- Tumor cells with clear cytoplasm

High FIGO stage, > 35 years of age, > 2 years after index pregnancy, term pregnancy and hCG > 1,000 mIU/ml

Placental Site Nodule (PSN)

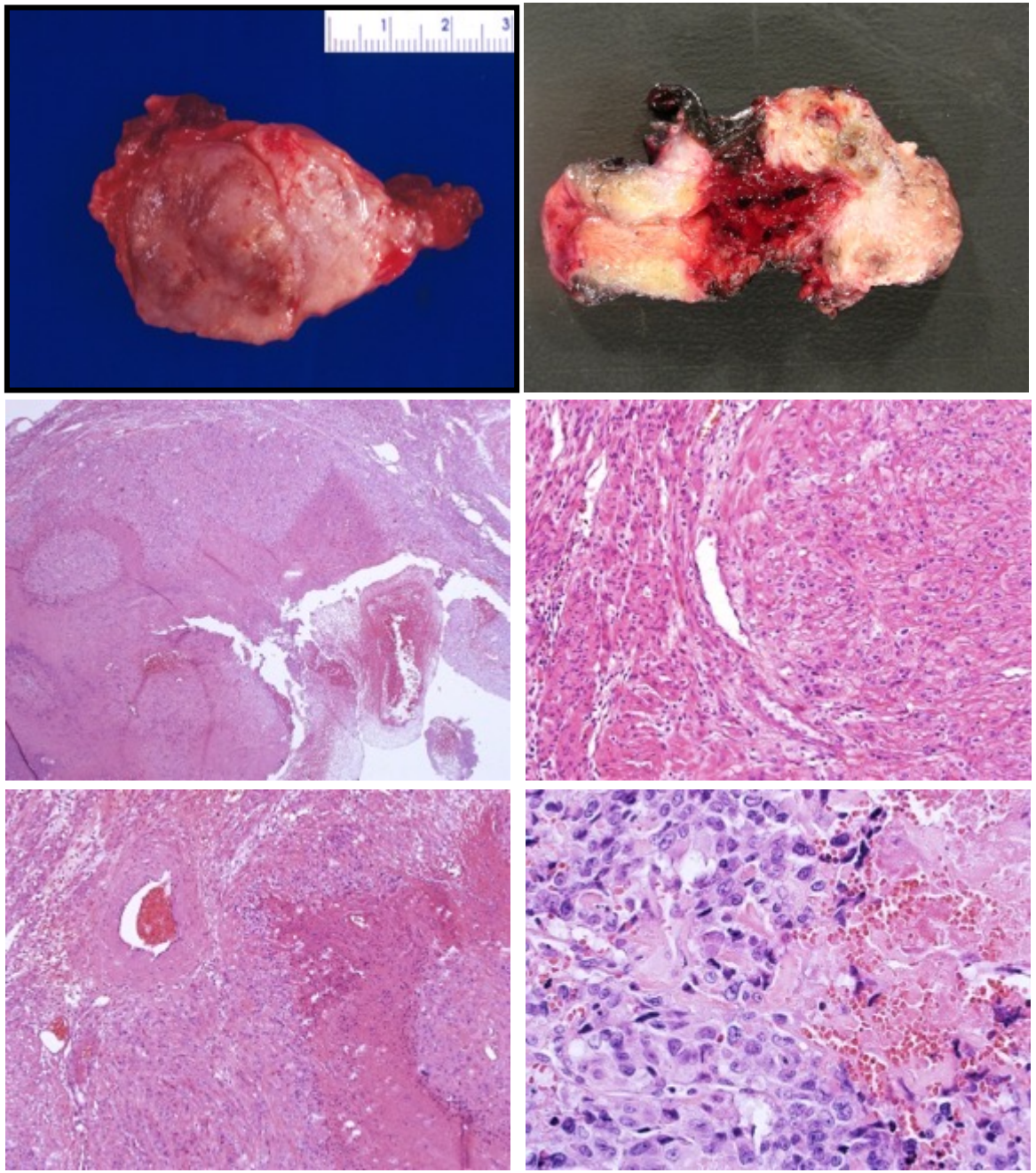






Atypical Placental Site Nodule

- Larger size of the nodule (5-10 mm)
- Hypercellularity
- Marked nuclear atypia
- Increased mitotic activity
- Ki-67 proliferation index of 5-10%

Hui: Arch Pathol Lab Med. 2019 Jan;143(1):65-74.
Kaur et al: 5th WHO Blue Book 2020

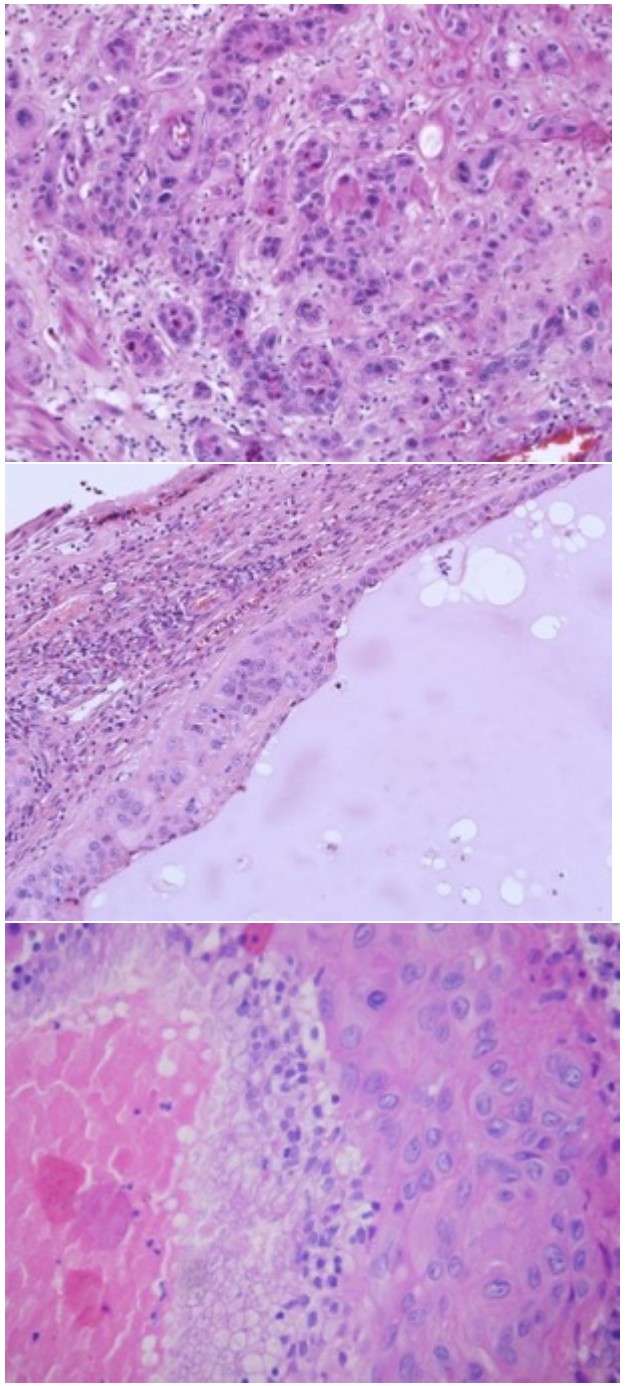


Epithelioid Trophoblastic Tumor (ETT)

- First described by Kurman and Shih in 1998
- Endometrium, cervix, fallopian tube, ovary and other sites
- Reproductive age women with vaginal bleeding with low hCG
- 2/3 after normal pregnancy, 15% after mole and 15% after SAB

Table 7.1 Immunohistochemistry in trophoblastic tumors

	Choriocarcinoma	PSTT	ETT	PSN	APSN
hCG	+ (Diffuse)	+ (Rare cells)	+ (Rare cells)	–/+	–/+
hPL	+	+ (Diffuse)	+ (Rare cells)	+ (Rare cells)	+ (Rare cells)
CD146	+	+ (Diffuse)	–	–	–
GATA3	+	+	+	+	+
P63	+/–	–	+	+	+
SALL4	+	–	–	–	–
Ki-67	>40%	>5%	>10%	<5%	5–10%
HLA-G	+	+	+	+	+
Cyclin E	+	?	+	–	–/+
Inhibin	+	+	+	+	+
HSD3B1	+	+	+	+	+
GPC3	?	+	?	+	?
Cytokeratin	+	+	+	+	+
P40	+/–	–	+	+	+



The most difficult, yet very important differential diagnosis is the distinction from keratinizing squamous cell carcinoma

Table 1 Clinicopathologic characteristics of five cases of epithelioid trophoblastic tumor

Clinicopathologic parameters	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
Patient age (years)	44	42	29	35	42
Presentation	Vaginal bleeding	Menormetrorrhagia	Unavailable	Menormetrorrhagia	Amenorrhea/ovarian enlargement
Prehysterectomy diagnosis	Poorly differentiated carcinoma	Moderately differentiated carcinoma	PSTT	None	Epithelioid mesothelioma of peritoneum
Hysterectomy diagnosis	Adenosquamous carcinoma	Poorly differentiated trophoblastic tumor	PSTT	PSTT with epithelioid features	Epithelioid trophoblastic tumor
Year of initial diagnosis	1987	1997	1991	2000	2004
Tumor size (cm)	4.0	2.5	2.4	4.0	3.0
Anatomic location	Endocervix	Endocervix and lower uterine segment	Uterine corpus (intracavitary and myometrial)	Uterine corpus (outer myometrial)	Endocervix and uterine isthmus
Tumor necrosis	30%	5%	10%	50%	>50%
Mitosis/10 HPF	2	9	48	2	3
Ki-67 index (%)	10	30	86	50	N/D
Follow-up	NERM at 16 years	NERM at 7 years	Died of disease 8 months after surgery	NERM at 3.25 years	Alive with lung metastasis 1 month after surgery

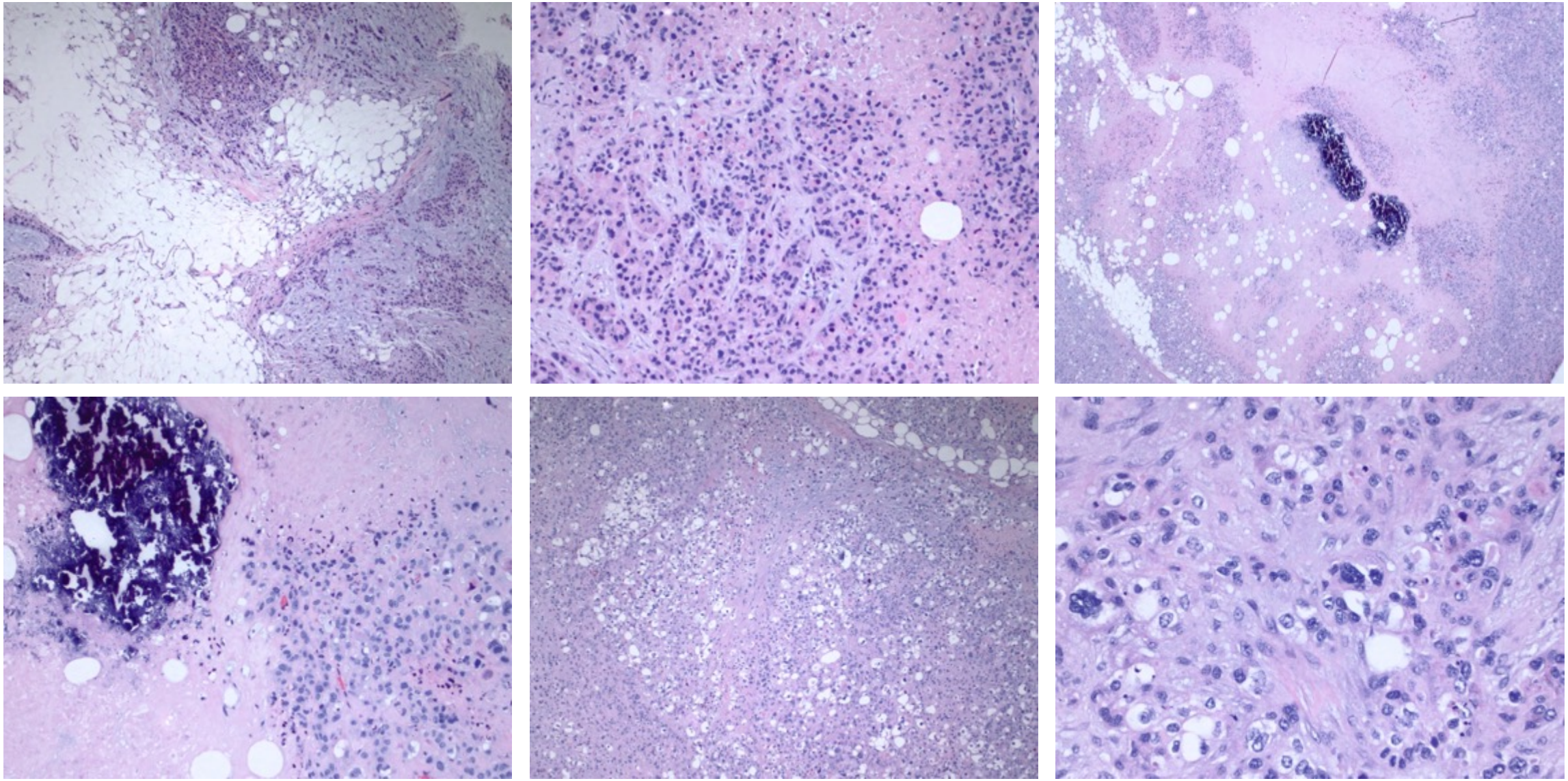
PSTT = placental site trophoblastic tumor; NERM = no evidence of tumor recurrence or metastases; HPF = high-power field; N/D = not done.

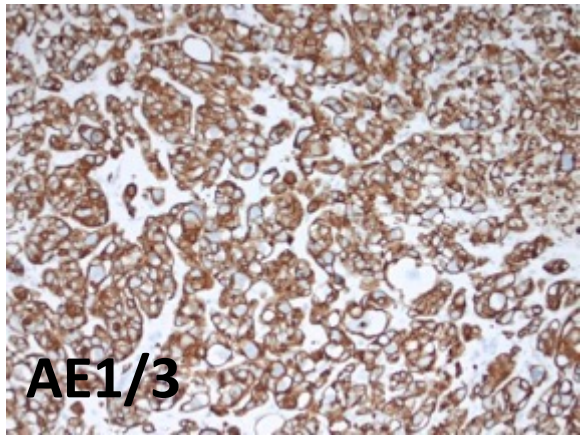
Fadare O et al. Epithelioid Trophoblastic Tumor: Clinicopathological Features with an Emphasis on Uterine Cervical Involvement. Modern Pathology, 2006.

Case Presentation

- 61 years of age, G1P1
- Presenting abdominal pain for 6 weeks with acute exacerbation.
- Reported menstrual-like uterine bleeding with passing tissue to purulent yellow drainage
- Endometrial biopsy one month prior was reported as poorly differentiated cancer with necrosis and calcification (not sent for consultation)
- CT : multiple partially calcified masses involving the enlarged uterus (c/w fibroid) with fistulas to bowel and right pleural effusion
- Exploratory laparotomy, TAH-BSO, lymph node dissections on 7/27/2021
- Operation findings: omental caking and frozen pelvis
- Specimens removed: three omental tissue of 5 to 18 cm in size
- Original diagnosis: poorly differentiated carcinoma with squamous features

Original Dx: Poorly Differentiated Carcinoma with Squamous Features

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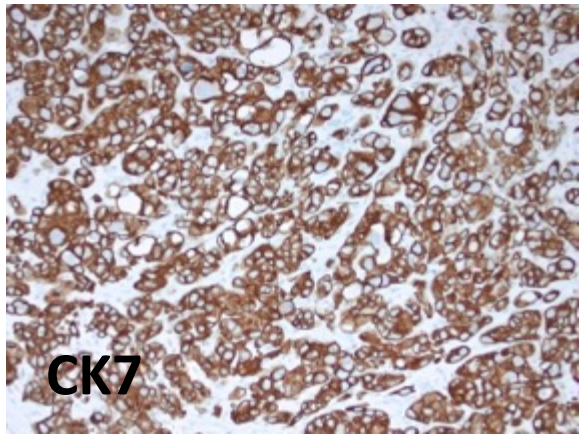
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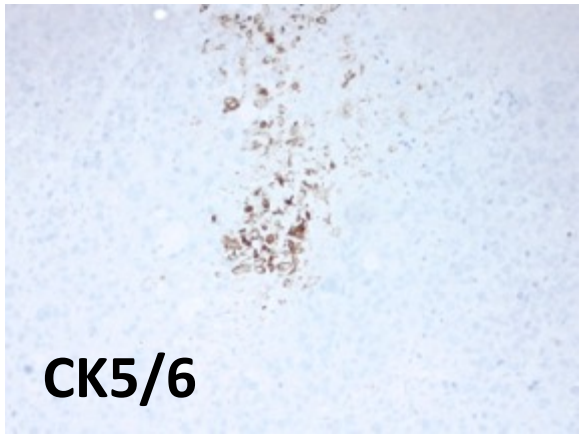
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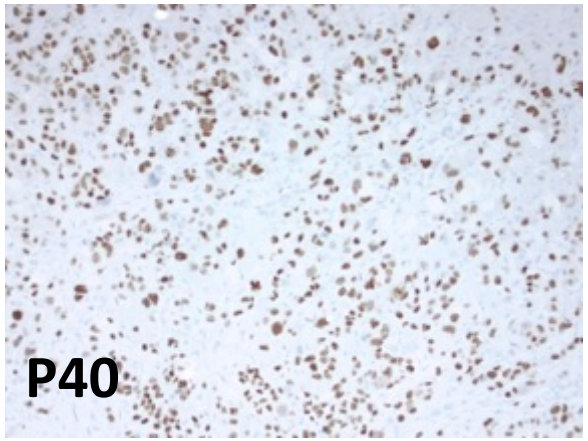
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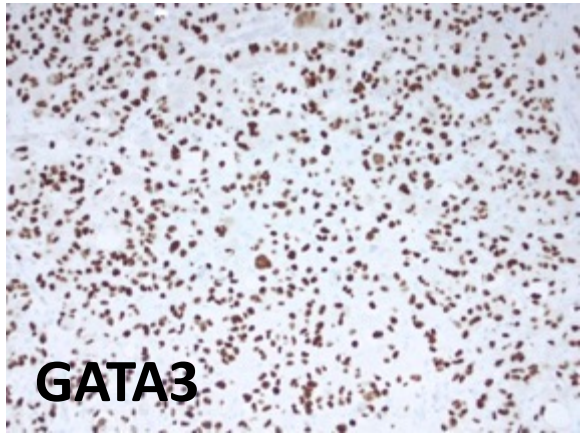
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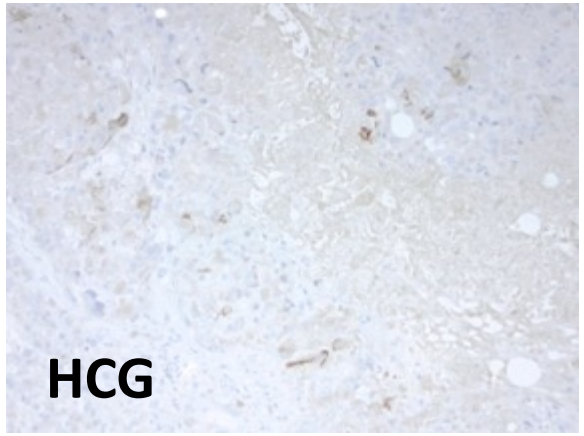
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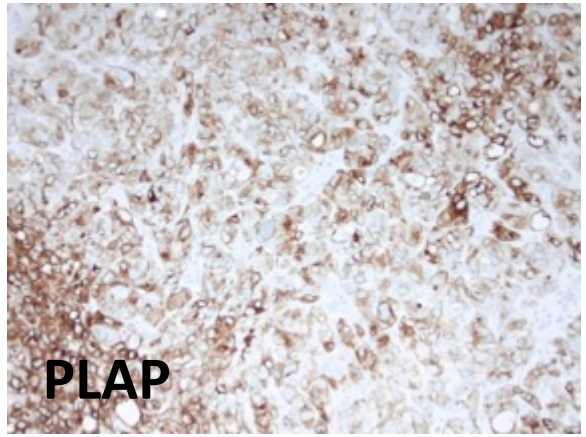
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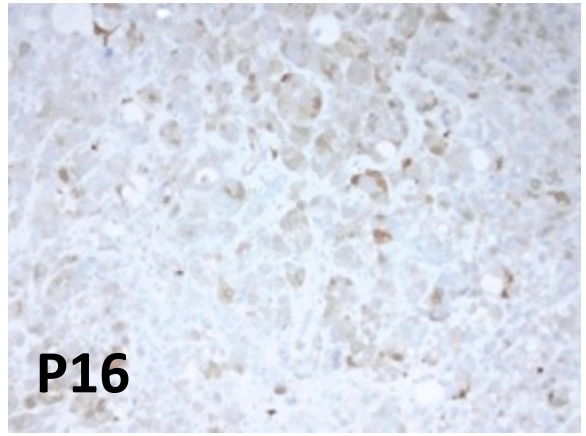
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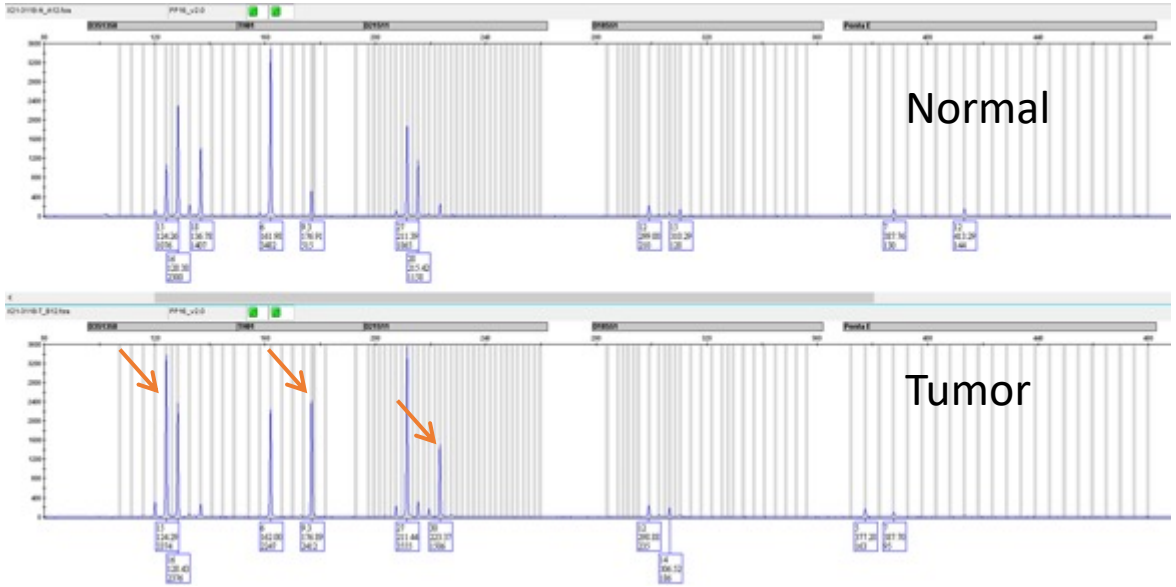
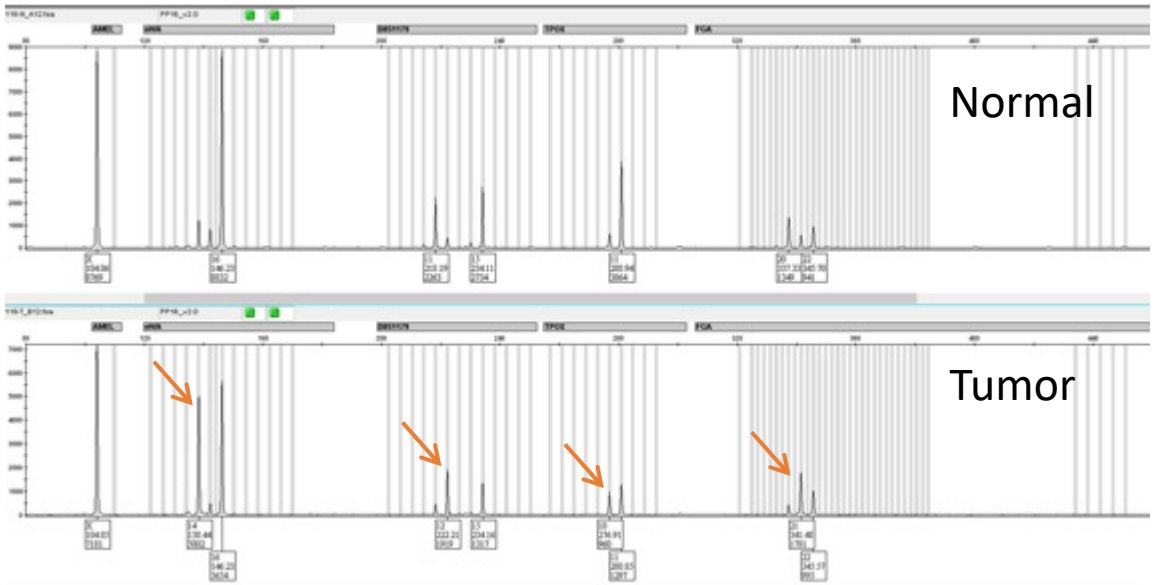

Normal
Tumor


Normal
Tumor

Metastatic Epithelioid Trophoblastic Tumor (ETT)

GTD - 2020 WHO UPDATES

- Definite diagnosis of PHM requires DNA genotyping (WHO2020)
- Subtyping of CHM for prognosis requires DNA genotyping (WHO2020)
- Genotyping is important for diagnosis of gestational choriocarcinoma at extrauterine site (WHO2020) and risk scoring for patient management
- Recognition of intraplacental and intramolar choriocarcinoma (WHO2020)
- Recognition of atypical placental site nodule (WHO2020)


WHO
WHAT
WHERE
WHEN
WHY
HOW
QUESTIONS
ANSWERS

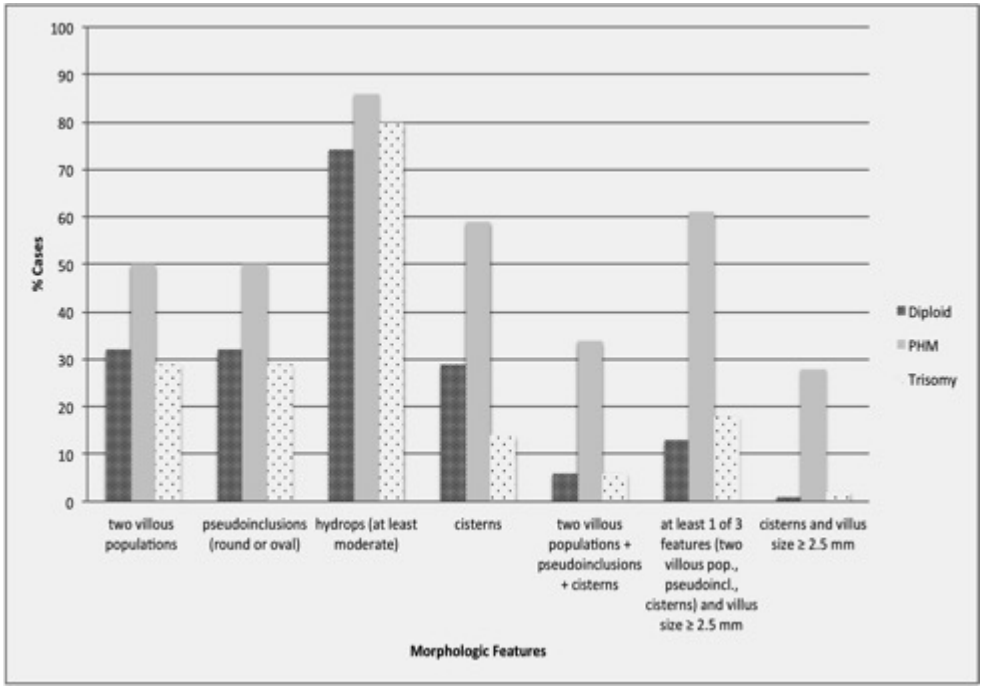
High grade carcinoma morphology at an extrauterine site in a young woman without history of gestational trophoblastic disease

- High index of suspicion is essential
- Molecular genotyping is powerful in separating primary carcinoma from metastatic gestational trophoblastic tumors
- Molecular genotyping is important for FIGO/WHO risk scoring of GTN

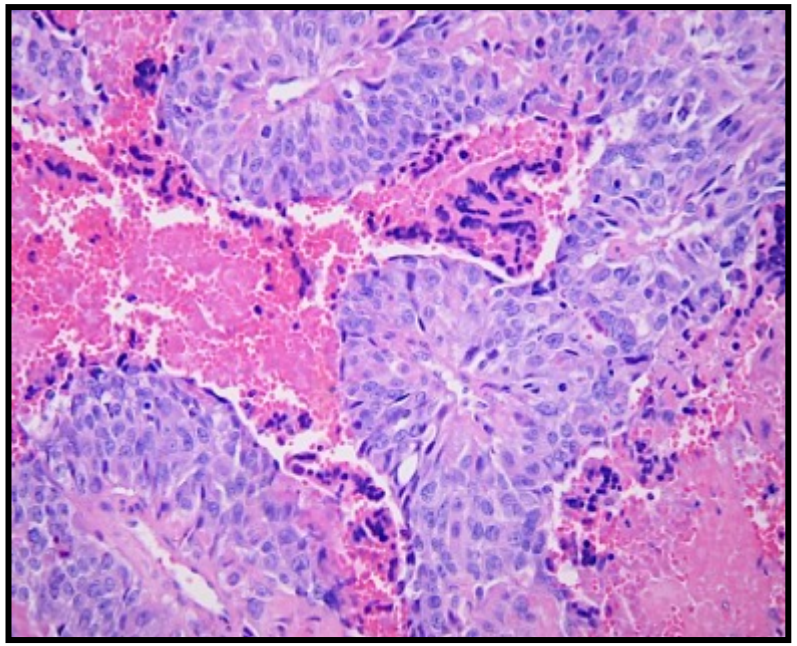
TABLE 2. *Morphologic parameters*

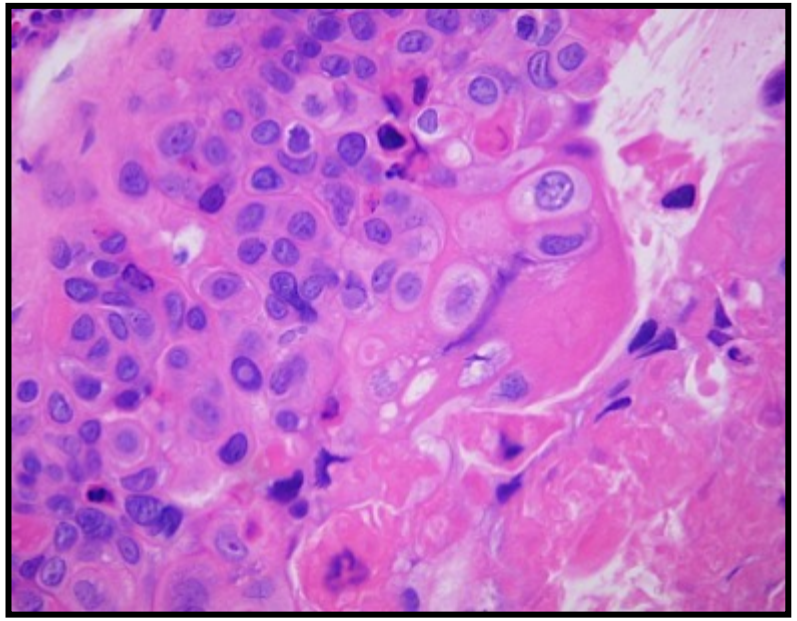
	PHM (n = 56)	Trisomy (n = 51)	Nonmolar diploid (n = 31)
Maximum size of chorionic villi: range (mean)	1–6 mm (3.2 mm)	0.9–4.5 mm (2.1 mm)	1–4 mm (2.0 mm)
2 villous populations	28 (50%)	15 (29.4%)	10 (32.2%)
Round or oval trophoblastic pseudoinclusions	28 (50%)	15 (29.4%)	10 (32.2%)
Villous hydrops (at least moderate)	48 (85.7%)	41 (80.4%)	23 (74.2%)
Cistern formation	33 (58.9%)	7 (13.7%)	9 (29.0%)
Trophoblastic hyperplasia (at least moderate)	10 (17.8%)	4 (7.8%)	2 (6.4%)
Single trophoblast inclusions	9 (16.1%)	12 (23.5%)	7 (22.5%)
Nucleated fetal red blood cells	38 (67.8%)	32 (62.7%)	20 (64.5%)
Syncytiotrophoblast knuckles	52 (92.8%)	51 (100%)	27 (87.1%)
Syncytiotrophoblast lacunae	53 (94.6%)	47 (92.2%)	27 (87.1%)
Irregular villous contour	52 (92.8%)	46 (90.2%)	22 (71.0%)

PHM indicates partial hydatidiform mole.

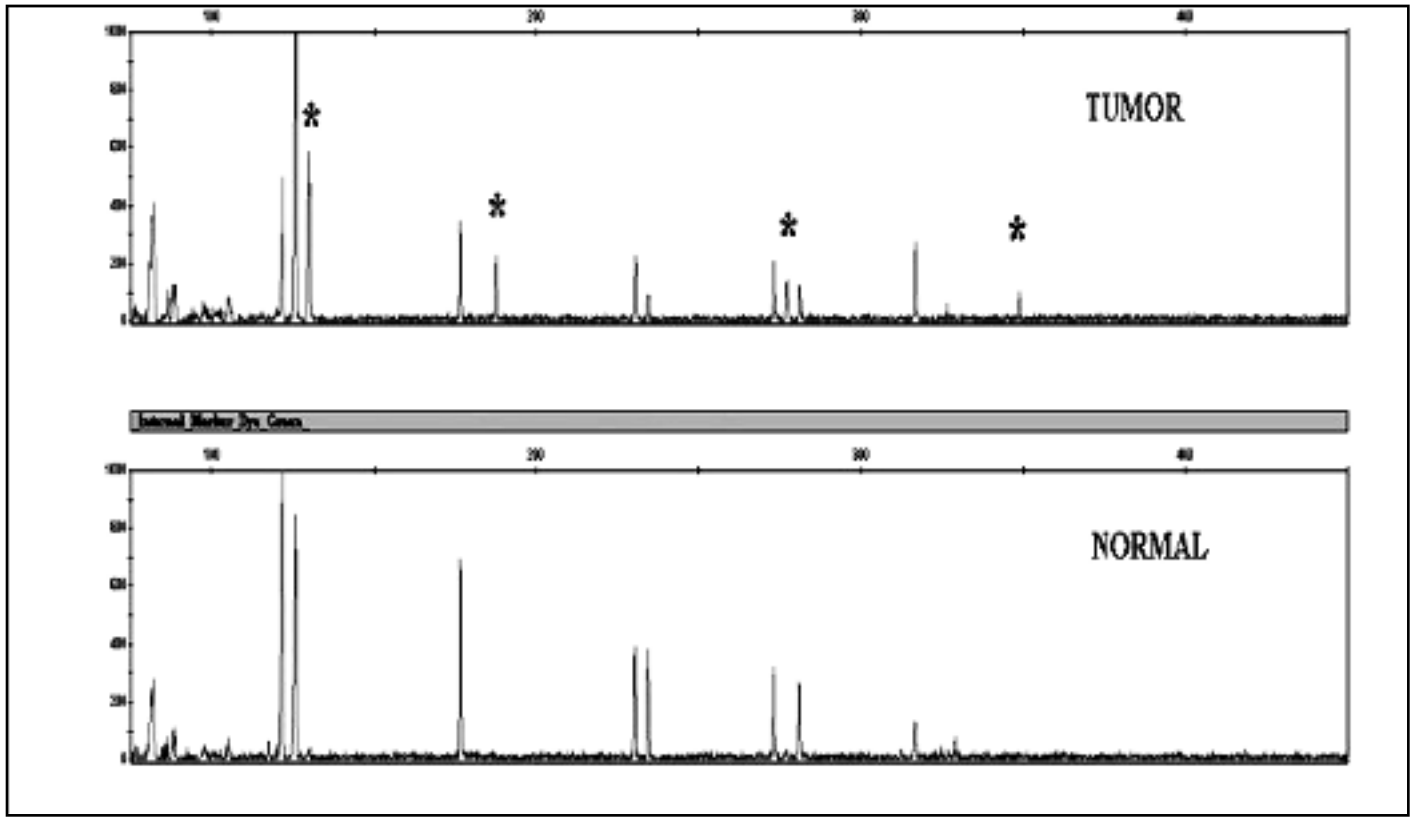


No single or combined histological parameters are specific for histologic diagnosis of PHM

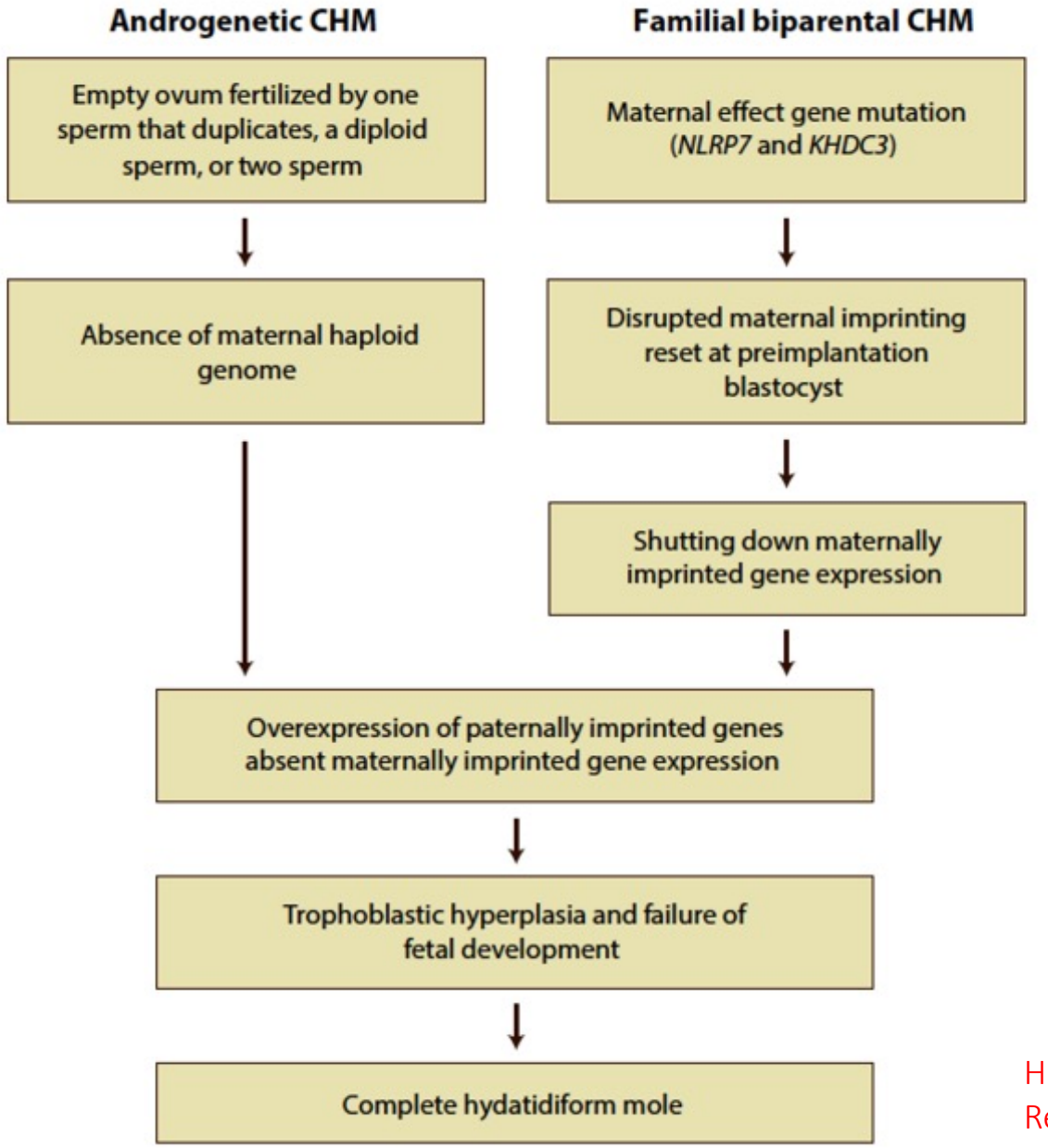




ETT vs. Squamous cell carcinoma



Xu M, et al. Modern Pathology 22:232-238, 2008.



Hui, Buza, Murphy, Ronnett: Annual Review of Pathology: Mechanism of Disease, 2017, 12:449-485.

Pearls

- Significant clinical implications of both over- and underdiagnosis of hydatidiform moles
- Morphologic overlap with mimics, especially for partial mole
- Ancillary tests are necessary in most cases to confirm the diagnosis
  - p57 immunohistochemistry
  - Molecular genotyping – also prognostication in CHM
- Algorithmic approach