Faculty Disclosure

I have no relevant financial relationship to disclose.

Objective

To review the gross and histologic features of unusual findings in the placenta, primarily using case based examples, and briefly discuss their clinical significance.
History of Present Illness

39-year-old G3P2 at 25 3/7 weeks initially presenting of being “very short of breath” and lower extremity edema

Bedside US noted viable fetus with normal growth and a 7 cm solid mass with color flow but no apparent cardiac activity. Thought to be suspicious for acardiac twin at this time.

Detailed ultrasound then performed noting an 8.8 cm mass, suspicious for chorangioma.

Patient found to be anemic (hematocrit = 25.2%) which her dyspnea was attributed to.

A follow-up ultrasound revealed findings concerning for fetal hydrops with high output cardiac failure and polyhydramnios.

Stabilized and sent home with arrangement to go to an outside institution to have evaluation for possible ablation of feeder vessel of chorangioma. Re-presented two days later with worsening SOB and edema.

Given the worsening symptoms, the clinical team felt immediate delivery was necessary. A C-section was performed.
Chorangioma

- Common benign tumor of the placenta
- Proliferation of blood vessels covered by trophoblasts
- Typically develop between 32nd and 37th weeks of gestation
- Usually small, measuring <0.5 cm & not of clinical significance
- Large chorangiomas associated with:
  - Anemia
  - Thrombocytopenia
  - IUGR
  - Fetal Hydrops
  - Polyhydramnios
  - Stillbirth
Large Chorangioma + Fetal Hydrops + Maternal Edema?

Mirror Syndrome

- AKA Ballantyne Syndrome
- Defined as development of maternal edema in conjunction with fetal hydrops
- Named because of the similarity of symptoms between mother and baby
  - Fetal Hydrops
  - Maternal symptoms include:
    - Severe swelling
    - High blood pressure
    - Excessive weight gain over a short time
    - Protein in the urine

Mirror Syndrome

- In contrast with preeclampsia:
  - Low maternal hematocrit
  - Polyhydramnios
  - Rate of intrauterine death at 56%
  - Delivery required to induce remission
Follow-up

Born at 28 weeks, the infant was in the NICU in critical condition for an extended period of time with many complications of prematurity. Now at 17 months of age, she is doing well but continues to have long-term complications including chronic lung disease, retinopathy of prematurity and developmental delay.
History of Present Illness

24-year-old G1P0 with PPROM at 18 weeks 4 days

Multiple fetal anomalies diagnosed by ultrasound including omphalocele, Dandy Walker variant, polyhydramnios and suspected cardiac defect

Placental weight = 342 grams (reference mean = 85 grams)
Gross Fetal Examination

Female fetus, large for gestational age (320 grams, expected 195+/- 44 grams)

Omphalocele
Overlapping toes bilaterally
Enlarged right kidney

Differential Diagnosis

Placental Mesenchymal Dysplasia versus Partial Hydatidiform Mole
Placental Mesenchymal Dysplasia

- Rare (0.02% estimated incidence)
- Also known as “pseudo-partial mole”, “pseudo-mole”
- Karyotype = diploid
  - Subset with androgenetic/biparental mosaicism
- Fetus
  - Often structurally normal and female (4:1)
  - Fetal associations include IUGR, Beckwith-Wiedemann Syndrome (20-30%), fetal/neonatal mesenchymal hamartomas of viscera and skin
  - BWS: characterized by macrosomia, macroglossia, neonatal hypoglycemia, presence of ear pits or creases and abdominal wall defects (umbilical hernia, omphalocele, diastasis recti) and hemihypertrophy

Placental Mesenchymal Dysplasia - Gross features:

- Placentomegaly, >90% 
- Ectatic and tortuous chorionic and stem villous vessels
- Grape-like villous vesicles

Placental Mesenchymal Dysplasia - Microscopic Features

- Abnormal villi interspersed with normal-appearing villi
  - Villi are bulky, with ectatic, thick-walled vessels and loose connective tissue
- Cistern formation
- Thromboses common in both stem and distal villous vessels
- Foci of vascular proliferation
  - Chorangiosis, Chorangiomatosis, Chorangioma
- Increased numbers of fetal nucleated RBCs
Back to the patient…
Placental Mesenchymal Dysplasia - Microscopic Features

Importantly, trophoblastic hyperplasia and pseudoinclusions are not present.

Cytogenetic Results

Triploidy

Partial Hydatidiform Mole

- Triploid placenta and fetus, most commonly 69, XXY
- Can have a fetus, usually with multiple fetal anomalies:
  - Severe IUGR
  - Hydrocephaly
  - Syndactyly
  - Midline facial clefting
  - Cardiovascular and renal anomalies
- Grossly and microscopically looks very similar to PMD
### Versus Placental/Mesenchymal Dysplasia

<table>
<thead>
<tr>
<th>Complete Mole</th>
<th>Similarities</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diploid placental karyotype</td>
<td>Usually no embryo/fetus</td>
<td>Villi are avascular</td>
</tr>
<tr>
<td>Large central cisterns</td>
<td>Villi may show ectasia</td>
<td>Trophoblastic proliferation</td>
</tr>
</tbody>
</table>

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<tr>
<th>Partial Mole</th>
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<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross appearance</td>
<td>Triploid karyotype with abnormal fetus</td>
<td>Scallop and pseudoinclusions</td>
</tr>
<tr>
<td>Hydropic villi in the background of normal-appearing villi</td>
<td>Trophoblastic proliferation</td>
<td>No vessel wall thickening</td>
</tr>
<tr>
<td>Villi may show ectasia</td>
<td>Scalloping and pseudoinclusions</td>
<td>Villous edema</td>
</tr>
<tr>
<td>Cistern presence (scarce)</td>
<td>Nucleated fetal RBCs</td>
<td></td>
</tr>
</tbody>
</table>

### Molar versus Non-molar POCs

#### Abnormal Gestation: Diagnostic Reproducibility

- Vang et al. analyzed diagnostic reproducibility of hydatidiform moles
  - 20-30% misclassification by gynecologic pathologists
  - Particularly problematic between partial moles and non-molar pregnancies

* Often ancillary tests are needed to confirm non-molar versus molar gestations.*
**Sets of Chromosomes**

<table>
<thead>
<tr>
<th></th>
<th>Paternal</th>
<th>Maternal</th>
<th>Ploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-molar</td>
<td>1</td>
<td>1</td>
<td>Biparental diploid</td>
</tr>
<tr>
<td>Complete Mole</td>
<td>1</td>
<td>0</td>
<td>Diandric diploid</td>
</tr>
<tr>
<td>Partial Mole</td>
<td>2</td>
<td>1</td>
<td>Diandric triploid</td>
</tr>
</tbody>
</table>

**Parental Contributions**

- **Genotype**
  - **Clinical Significance of Molar Pregnancies**
    - ~75% Regress Spontaneously
    - ~20% Persist
      - Local uterine invasion
      - Metastasize
    - ~2% Recur as mole
    - ~5% Recur as Choriocarcinoma

- **Non-molar vs Molar Products of Conception**
  - **Morphology**
    - Large, cystic villi?
    - Single population vs two populations of villi?
  - **Trophoblastic proliferation**
    - Is it circumferential?
    - Diffusely involving villi?
    - Is there atypia?
36-year-old G3P0202 who presented for a routine ob visit and was diagnosed with a missed abortion at 10 4/7 weeks. Pt with known unicornuate uterus.
Chromosomal Anomalies

- Karyotyping is necessary to confirm the diagnosis
- If a fetus is present, it is usually growth restricted
- Small placenta
- General histologic features:
  - Irregular villous contours
  - Villous enlargement
  - Edema
  - Trophoblastic inclusions
  - Deficient vascularization

Case 4

HPI

21-year-old G2P1011 female presenting to ED with abdominal pain and concern for possible pregnancy (LMP 2 months ago).

Beta HCG 27,937 and US shows irregular intrauterine gestational sac with multiple cystic areas. No definitive embryo or yolk sac.
Follow-up

Pt never followed up with post op visit or beta HCGs.

Pt presents ~7.5 months later with pelvic pain and RUQ pain. US consistent with persistent hydatidiform mole.

Presented several days later to L&D with severe cramping and vaginal bleeding. Tissue protruding from cervical os, removed with forceps.
Complete Hydatidiform Mole

- Diffusely hydropic villi with cistern formation
- Circumferential trophoblastic hyperplasia
  - Can vary between villi
    - Involves both cytotrophoblast & syncytiotrophoblast
  - Atypia is present – nuclear pleomorphism & cytoplasmic vacuolization in syncytiotrophoblast
  - Can have mitoses
**Early Complete Moles**

- Can be diagnostically challenging
- Features more subtle, less developed
  - Smaller, less edematous villi
  - Bulbous villi → “knuckle-like” or “cauliflower-like”
  - Cisterns poorly formed
  - Trophoblastic proliferation not as pronounced
  - Blue myxoid stroma
  - Karyorrhexis

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**Exaggerated Placental Site**

- Nonneoplastic but exuberant proliferation of EVT in the implantation site associated with pregnancy
  - “Excessive” physiologic response of EVT
  - Occur concomitant with pregnancy so chorionic villi are almost always present

Frequently seen in complete moles, its presence may be helpful in the differential diagnosis.

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*Differentiation of EPS from a normal implantation site is arbitrary as there are no specific criteria.*
p57KIP2

- p57 is a paternally imprinted gene on chromosome 11p15.5
- Maternally expressed if maternal DNA is present
- Villous cytotrophoblasts are p57 negative in androgenetic complete mole
- Villous cytotrophoblasts are p57 positive in normal placenta, partial mole and hydropic abortus
- Syncytiotrophoblast is always p57 negative
- Extravillous trophoblasts are always positive even in complete mole

Can you have fetal tissue in complete moles?

- Traditionally taught complete moles are never associated with an embryo or fetal tissue
  - MOST cases embryos are absent but in rare cases one may be present
  - Fetal blood vessels and fetal nucleated red blood cells may be encountered in complete moles, particularly in early moles

The presence of these elements does not rule out a complete mole.
HPI

37-year-old G3P2 who initially presented with pelvic pain she thought was related to her IUD. Had IUD in place following the birth of her last child (2013). Pelvic pain resolved. Represented with breakthrough bleeding. Was amenorrheic until ~2 months prior. Ultrasound at that time showed LUS mass thought to be most consistent with a fibroid.

Following a MVA had positive UPT thought to possibly represent an SAB or ectopic.

Had imaging done at an outside hospital that identified 10 cm LUS mass and concern for metastatic disease.

Beta HCG was found to be 121,000.
Choriocarcinoma

- Malignant tumor of cyto- and syncytiotrophoblast – always associated with a preceding pregnancy:
  - Follows complete hydatidiform mole (50%)
  - Normal and ectopic pregnancies (25%)
  - Miscarriages (25%)
- Prior pregnancy can be years ago
- Presents with vaginal bleeding and/or signs and symptoms of metastasis

Choriocarcinoma

- Intravascular growth—likes to grow in blood vessels
- No inherent blood supply—no angiogenesis – takes blood supply from invasion of host vessels
  - Prominent hemorrhage and necrosis
- First malignant tumor to respond to chemotherapy, high cure rate using 5 drug regimens, +/- radiation therapy
- Non-gestational choriocarcinoma occurs in ovary, testis, and many other sites, not as sensitive to tx as gestational choriocarcinoma
World Health Organization (WHO) prognostic scoring system is important in the medical management of patients with complete hydatidiform moles, partial hydatidiform moles, and choriocarcinomas.

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Prognostic Score</th>
</tr>
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<tbody>
<tr>
<td>Mat</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td>0</td>
</tr>
<tr>
<td>Histologic grading</td>
<td>0</td>
</tr>
<tr>
<td>Tumoral size (mm)</td>
<td>0</td>
</tr>
<tr>
<td>Number of embryos</td>
<td>0</td>
</tr>
<tr>
<td>Presence of chorionyctosis</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk Categories:
- 0-3: Good prognosis
- 4-6: Intermediate prognosis
- 7-9: Poor prognosis

WHO staging for Gestational Hydatidiform Mole (2000):
- Stage 0: Complete hydatidiform mole
- Stage 1: Partial hydatidiform mole
- Stage 2: Choriocarcinoma

Unknowns

Case 1
Molar or Non-Molar?

Diagnosis

Monosomy X

Unknowns

Case 2
Molar or Non-Molar?

Diagnosis

Monosomy X and Trisomy 16
Molar or Non-Molar?

Diagnosis

Placental Mesenchymal Dysplasia

We can Diagnose it if we Consider it. Diagnostic Pitfall for Placenta: Placental Mesenchymal Dysplasia

Questions?