Gestational Trophoblastic Disease

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Gestational Trophoblastic Disease

GTD includes
• Complete mole
• Partial mole
• Invasive mole
• Placental site trophoblastic tumor (PSTT)
• Choriocarcinoma

Nomenclature

• A spectrum of disease
• Pathologic diagnosis
• In contrast to clinically significant diagnosis requiring active management

Key Points

• Partial and complete mole are abnormal pregnancy events
• Choriocarcinoma is an aggressive malignancy akin to testicular cancer
• Partial and complete moles have the potential to persist, spread, and act like choriocarcinoma

Key Points

• PSTT is generally an indolent malignancy that may be difficult to diagnose
• Treated aggressively, gestational trophoblastic malignancies are highly curable

Key Points

• Benign conditions: partial mole, complete mole
• Malignant conditions: Invasive mole, persistent mole, PSTT, choriocarcinoma, metastatic GTD
Epidemiology of Molar Pregnancy
- Molar pregnancy 7x more common in Asia
  - Taiwan: 1 in 125 pregnancies
  - US: 1 in 1500 live births
- More common in countries with low dietary carotene (vitamin A precursor) and animal fat
- Regions with high incidence of vitamin A deficiency have high rate of moles

Immunobiology of GTD
- Host immune response to paternal antigens on trophoblast cells may contribute to curability
- Histocompatibility between patient and partner is associated with drug resistant choriocarcinoma and greater risk of metastatic GTD
- Prognosis of choriocarcinoma is related to the intensity of lymphocyte and monocyte infiltration at the tumor host interface

Molecular Pathogenesis of GTD
- Complete mole and choriocarcinoma
  - Overexpression of c-myc, c-erbB2, bcl-2
  - Increased expression of p53, p21, Rb, and MdM2
  - Modification of parental imprinting

Pathology
- Complete mole:
  - No fetal or embryonic tissue
  - Diffuse trophoblastic hyperplasia
  - Hydatidiform swelling of the chorionic villi

Hydropic villi of complete mole
Complete mole

Trophoblastic proliferation of complete mole

Invasive mole

Chloriocarcinoma

Pathology

Partial mole:
- **Identifiable embryonic or fetal tissue**
- **Focal trophoblastic hyperplasia +/- atypia**
- **Chorionic villi of varying size**

Partial mole
Partial mole lacks circumfirential trophoblastic proliferation

Complete Mole

Classic Clinical Presentation:
- Vaginal bleeding
- Theca lutein ovarian cysts
  - Due to hyperstimulation from ↑↑ hCG
- Size > dates
- Classic snowstorm ultrasound picture
- Hyperemesis

Pelvic ultrasound showing snowstorm pattern of complete mole
Theca lutein cysts of both ovaries

Complete Mole
- Contemporary Clinical Presentation:
  - Vaginal bleeding
  - Markedly elevated hCG
  - Pathologic diagnosis

Partial Mole
- Classical Clinical Presentation
  - Second trimester preeclampsia
  - IUGR fetus
- Contemporary Clinical Presentation
  - Missed or incomplete Ab
  - Diagnosis usually on histologic review

Natural History
- Complete mole
  - Present with markedly elevated β-hCG
  - Develop uterine invasion in 15%
  - Develop distant metastasis in 4%
- Partial mole
  - Persistent local disease develops in 0-11%
  - Rarely develop metastatic disease

Complete Mole
- Issues with operative intervention:
  - Hemorrhage
  - Uterine atony
  - Dissemination of trophoblast
- Management:
  - Two large bore IVs
  - Pitocin in IV fluid on evacuation
  - Attentive anesthesia

Management of Molar Pregnancy
- Evacuation
  - Assess for medical complications
    - Anemia, hyperthyroidism, preeclampsia, electrolyte imbalances, respiratory insufficiency
  - Mode: hysterectomy vs. suction curettage
    - Rhogam if Rh negative
    - Attentive anesthesia
    - Adequate IV access
Management of Molar Pregnancy

Hormonal follow-up
- weekly until normal for 3 weeks
- monthly for 6 months
- effective contraception

Persistent GTD

- Diagnosis: re-elevation or persistent plateau hCG for at least 3 consecutive weeks
- Risk increased with
  - Complete mole
  - Markedly elevated hCG
  - Excessive uterine size
  - Theca lutein cysts
  - Repetitive molar pregnancy
  - Age > 40

Persistent GTD

Histology (Academic – DO NOT BIOPSY)
- following molar pregnancy: molar tissue or choriocarcinoma
- following a nonmolar gestation: choriocarcinoma
- choriocarcinoma: sheets of anaplastic cytotrophoblast and syncytiotrophoblast (no villi)
- PSTT: mononuclear intermediate trophoblast (no villi)
- NB: choriocarcinoma can rarely involve the fetus

Complete Mole
Choriocarcinoma

Persistent GTD

The confusion:
- Can be local or metastatic
- Can be low or high risk
  - Treatment is based on risk, not stage
- Can follow any type of conception event
- Has a variety of names....

Nonmetastatic GTD

Nonmetastatic disease
- Develops in 15% after a complete mole
- Rare following other gestations
- May present with vaginal or intraperitoneal bleeding or uterine infection
- May also present with irregular vaginal bleeding, ovarian cysts, persistently elevated hCG

Metastatic GTD

Metastatic disease
- Develops in 4% after a complete mole
- Rare following other gestations
- Often associated with choriocarcinoma
- Fragile tumor vessels lead to hemorrhagic metastases
- Propensity for early vascular invasion with widespread dissemination

Metastatic GTD

Presentation of metastatic disease:
- Hemothypsis
- Acute neurologic deficits
- Unexplained systemic symptoms
- Unexplained pulmonary symptoms
Always check an hCG in a woman of reproductive potential with unusual symptoms-- metastatic GTD is often overlooked!

Metastatic GTD

Most common metastatic sites:
- Lung - 80%
- Vagina - 30%
- Brain - 10%
- Liver - 10%
Biopsy is not required -- only radiographic confirmation with an elevated hCG
DO NOT BIOPSY! BEWARE BLEEDING!
Metastatic GTD

Lung metastases presentations:
- Asymptomatic
- Dyspnea
- Chest pain
- Cough
- Hemoptysis
- Right heart strain and pulmonary hypertension

Metastatic GTD

Lung metastases patterns on CXR:
- Pleural effusion
- Alveolar or snowstorm pattern
- Discrete round densities
- Embolic pattern caused by pulmonary arterial occlusion by tumor

- i.e. Anything goes!!!

AP Chest x-ray with large right lower lobe metastasis from GTD

Lateral view, same patient

AP Chest x-ray with right middle lobe metastasis from GTD (arrow)

AP Chest x-ray with alveolar pattern from metastasis from GTD
Metastatic GTD

Lung metastases
• Beware respiratory failure
• Risk factors:
  – >50% lung opacification
  – dyspnea
  – cyanosis
  – anemia
  – pulmonary hypertension

Vaginal metastases
• Presentation:
  – irregular bleeding
  – purulent discharge
• Location
  – fornices
  – suburethrally
• DO NOT BIOPSY!!!!!!!!! (particularly if you are wearing your favorite shoes…)

Cystic anterior vaginal wall metastasis from GTD

Brain metastases presentation:
• Vomiting
• Seizures
• Headache
• Hemiparesis
• Slurred speech
• Visual disturbances
Symptoms result from increased intracranial pressure or intracerebral bleeding

Metastatic GTD Management

Cerebral metastasis
• whole brain radiation plus chemotherapy
  – reduces mortality
• systemic plus intrathecal chemotherapy
• craniotomy for herniation or control of bleeding
  – may also resect resistant tumors
• these patients can be cured!

Liver metastases presentation:
• Jaundice
• Intra-abdominal bleeding
• Epigastric pain
Isolated liver metastasis are rare -- patient presentation is usually due to mets to other sites
Metastatic GTD

**Case Scenario**
47 yo Latina presents to ER
CC: SOB
BP: 170/90
CXR: CHF
hCG: 2,000,000

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Metastatic GTD

**Case Scenario**
22 yo Latina presents to clinic for evaluation
CC: plateaued hCG following molar pregnancy
PE: nonfocal
Chest CT: 40 subcentimeter metastasis

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Metastatic GTD

**Case Scenario**
25 yo Caucasian female with 15 mo child lifeflighted to academic medical center with decreased LOC
Head CT: Hemorrhagic temporal lobe lesion (4 cm) with midline shift
Abdominal CT: 4 cm liver lesion

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Metastatic GTD

**Case Scenario**
27 yo Caucasian female status post SAb presents with abnormal uterine bleeding
hCG +
Given MTXT x 1
hCG persistently positive
US reveals hypervascular 5 cm intrauterine mass

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**Take home message:**

All GTD needs thorough evaluation for metastatic disease
Evaluation must be expeditious
DO NOT BIOPSY ANYTHING!!!!!!!
Metastatic GTD
FIGO anatomic staging system:
• Stage I: confined to the uterus
• Stage II: extension to genital structures (vagina, adnexa, broad ligament)
• Stage III: lung metastases
• Stage IV: all other metastatic sites

Substages:
– A: no risk factors
– B: one risk factor
– C: two risk factors

Risk factors:
– hCG > 100,000
– > 6 months since antecedent pregnancy

WHO prognostic scoring system
• Points assigned based on certain clinical variables
• Allows appropriate selection of chemotherapy
• Low risk: score ≤ 4
• Intermediate risk: score 5-7
• High risk: score > 8

• Time since and type of antecedent pregnancy
• Blood group
• hCG level
• Location of mets; size of largest met
• Number of mets
• Prior chemo drugs
• Age

Metastatic GTD
Diagnostic Evaluation
• History and Physical
• hCG levels
• labs: TFTs, LFTs, renal function, CBC
• CXR
• if vaginal/lung mets and/or choriocarcinoma, CT or MRI head, abdomen, and pelvis
  – rare to have brain or liver mets if pelvic exam and CXR normal

GTD Management
Depends on
• Stage of disease
• Risk factors (WHO score)
• Desire for future fertility
• Ability to be compliant
**GTD Management**

**Surgery**
- Hysterectomy if:
  - patients have completed childbearing
  - locally persistent disease
  - PSTT (relatively chemo resistant)
  - control uterine hemorrhage or sepsis
  - resect bulky tumor to decrease need for chemo
- Uterine wedge resection
- Thoracotomy
- Liver wedge resection to control hemorrhage
- Neurosurgery

**Chemotherapy**
- Single agent: actinomycin D or methotrexate
  - For low risk/low stage patients
  - Even with Stage II/III patients, low risk, response rates are 84-87%
- Combination: EMACO vs MAC vs EMA
  - For high risk and Stage IV patients
- Treat two-three cycles beyond negative hCG (best done by a gyn onc)

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**Metastatic GTD Management**

**Laboratory follow-up**
- Stage I/II/III:
  - hCG weekly until normal x 3 then monthly x 12
  - contraception x 12 months
- Stage IV:
  - weekly hCG until normal x 3 then monthly x 24
  - increased risk of late recurrence
  - Contraception x 24 months

**Relapse**
- Risk: 2% with nonmetastatic disease
  - 4% with low risk metastatic disease
  - 13% with high risk metastatic disease
  - Stage I - 3%, Stage II - 8%, Stage III - 4%, and Stage IV - 9%
- Recurrence within 3 months in 50% and 18 months in 85%

**Subsequent pregnancies**
- Complete mole - normal reproductive future
- Partial mole - reassuring data
- After two molar pregnancies, recurrence risk is 15-23%
- Therefore, 1st trimester US in subsequent pregnancy is not unreasonable
- Also, pathologic evaluation of the placenta and 6 wk pp hCG levels
GTD Management
Subsequent pregnancies
• After GTD, similarly normal pregnancy outcomes
• Similar management recommendations

Metastatic GTD Management
hCG Assays
• hCG molecules in GTD can be more degraded and/or heterogenous-- assay needs to detect intact hCG as well as metabolites and fragments
  – hence, “tumor beta”
• cross-reactivity with LH
  – prevent menopausal rise of LH in 30-40 yo with OCPs during chemo

Gestational Trophoblastic Disease
Summary
• Keep it simple, don’t get confused by terminology
• hCG levels must plateau or rise over three weeks for a diagnosis of GTD
• Initial evaluation with physical exam and CXR
• I honestly do a total body CT

Gestational Trophoblastic Disease
Summary
• Disease can progress rapidly-- metastatic survey must be done ASAP (ADMIT!)
• WHO scoring system more predictive of poor outcome that FIGO staging
• Single agent methotrexate and actinomycin-D are very effective in low-risk disease
• EMA-CO is the most effective combination regimen for high-risk disease

Gestational Trophoblastic Disease
Summary
• Even patients with brain mets/Stage IV disease can be cured
  – Think Lance Armstrong!
• These women need aggressive expeditious management
• Women with GTD are best managed by a gynecologic oncologist with experience in GTD

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