IRAP 2018
Case #1

Crystal Bockoven, MD
Mir Alikhan, MD
Case History

• 74 year old male
• Fatigue, weight loss (30-40 lbs in last 3-6 M)
• Mild jaundice, pallor with scattered ecchymoses, scattered palpable nodes
• PMH: not seen in 20 year
  – No medications
<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>157.9</td>
<td>4.0 -10.0 (10^3)/uL</td>
</tr>
<tr>
<td>Hbg</td>
<td>4.6</td>
<td>13.0-17.0 g/dL</td>
</tr>
<tr>
<td>HCT</td>
<td>16.1</td>
<td>39.0-51.0%</td>
</tr>
<tr>
<td>PLT count</td>
<td>22</td>
<td>150-400 (10^3)/uL</td>
</tr>
<tr>
<td>Atypical Lymphs</td>
<td>45</td>
<td>0%</td>
</tr>
</tbody>
</table>
Blood smear
Diagnosis:

Large B-cell lymphoma, germinal center phenotype

IHC: CD20+, CD3+, CD10+, MUM1 variable, CD5-, Bcl2+, c-myc+ (40-50%)
DIFFERENTIAL DIAGNOSIS
**Differential**

- **Lymphocytic neoplasms**
  - B-cell lymphoma
  - Anaplastic lymphoma
  - Plasma cell neoplasm

- **Metastatic**
  - Melanoma
  - Carcinoma

- **Myeloid neoplasms**
  - Myeloid sarcoma

- **Histiocytic /dendritic cell neoplasms**
  - Follicular dendritic cell neoplasm
  - Interdigitating dendritic sarcoma
  - Histiocytic sarcoma
  - Langerhans cell histiocytosis
CD20 (-)  Lymph node  PAX 5 (-)

CD20 (+)  Bone marrow  PAX 5 (+)
CD68 (+)

CD163 (+)

Lysozyme (+)

S100 (+)
<table>
<thead>
<tr>
<th>Categories</th>
<th>Differentials</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic neoplasm</td>
<td>B cell neoplasm</td>
<td>PAX5, CD20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma cell neoplasm</td>
<td>MUM1, CD138</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>Carcinoma</td>
<td>PanCK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>SOX10</td>
<td>S100</td>
</tr>
<tr>
<td>Myelocytic neoplasms</td>
<td>Myeloid sarcoma</td>
<td>MPO, CD34</td>
<td></td>
</tr>
<tr>
<td>Histiocytic/dendritic cell neoplasms</td>
<td>Follicular dendritic cell neoplasm</td>
<td>CD21, CD23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Langerhans cell neoplasm</td>
<td>CD1a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interdigitating dendritic cell sarcoma</td>
<td>CD163, Lysozyme</td>
<td>S100, CD68</td>
</tr>
<tr>
<td></td>
<td>Histiocytic Sarcoma</td>
<td>CD68, CD163, Lysozyme, S100 OCT2 (weak)</td>
<td></td>
</tr>
</tbody>
</table>
Interdigitating dendritic cell sarcoma (IDCS) vs histiocytic sarcoma

<table>
<thead>
<tr>
<th>IDCS</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often spindled, may be epithelioid CD21 and CD23 - Strongly S-100 and vimentin+ Weakly CD68+</td>
<td>Often epithelioid with abundant cytoplasm S-100 variable Expression of histiocytic markers: - CD68, CD163, lysozyme</td>
</tr>
</tbody>
</table>

Diagnosis

Histiocytic sarcoma (HS)
1970: Mathe proposed term histiocytic sarcoma

Definition (WHO 2016):
- Malignant proliferation of cells showing morphologic and immunophenotypic features of mature histiocytes
- Acute monocytic leukemia must be excluded
**Etiology/Pathogenesis**

<table>
<thead>
<tr>
<th>Sporadic/ de novo</th>
<th>Mediastinal germ cell tumors (teratoma, yolk sac tumor)</th>
<th>Hematolymphoid malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No characteristic cytogenetic alterations identified</td>
<td>Share a common chromosomal abnormality</td>
<td>Commonly a B-cell lymphoma</td>
</tr>
</tbody>
</table>
| Rare subsets:  
- IGH-BCL2 fusion by PCR and FISH  
- IGH and TRB/ TRG rearrangements  
- BRAF mutations | Associated with Isochromosome 12p  
May arise from a pluripotential stem cell | Neoplasic cells can transdifferentiate to a neoplasm of a different lineage |
|                            |                                         | Clonally related |

Medeiros LJ, *Tumors of the Lymph Nodes and Spleen*, AFIP Atlas of Tumor Pathology, 2017
Histiocytic sarcoma as a secondary malignancy: pathobiology, diagnosis, and treatment


Common progenitor model

Dedifferentiation

Transdifferentiation

Common Progenitors

Transcription Factors
- JUMP1
- PU.1
- EBF
- E2A
- PAX-5

Epigenetic Modifications
- Cytokines (e.g. IL-7)

Histiocytic Sarcoma

BRAF Mutations

Therapy Induced Selection Pressure
Transdifferentiation

- **B-cell lymphomas**
  - Follicular lymphoma (most common)
  - Diffuse large B-cell lymphoma
  - Marginal zone lymphomas
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - Acute lymphoblastic leukemia
  - Plasma cell neoplasm

- Histiocytic sarcoma (most common)
- Interdigitating dendritic cell sarcoma
- Langerhans cell sarcoma

Simultaneously or following lymphoma within 2 months to 17 years
**Transdifferentiation**

- More often expresses B-cell transcription factor OCT2 (less often PAX5)

- Higher frequency of monoclonal immunoglobulin gene rearrangements or IGH-BCL2 fusion consistent with t(14;18)

- B-cell lymphoma and HS share clonal identity
  - Analysis of IGH variable regions in cases of histiocytic sarcoma show somatic hypermutation
    - Arose from a germinal center or post-germinal center B-cell

Medeiros LJ, *Tumors of the Lymph Nodes and Spleen*, AFIP Atlas of Tumor Pathology, 2017
Prognosis

- Often aggressive, poor response to therapy
- 60-80% die of progressive disease
- Localized disease & small primary with recurrences in ~20%
- In cases of transdifferentiation the prognosis is worse than *de novo* histiocytic sarcoma

OUR CASE
# FISH Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Histiocytic Sarcoma</th>
<th>Diffuse large B-cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCL6 rearrangements</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IGH-BCL2 fusion</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MYC rearrangements</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### 100% IGK sequence homology

**CLUSTAL O(1.2.4) multiple sequence alignment**

<table>
<thead>
<tr>
<th>LymphNode</th>
<th>BoneMarrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGACCTTTTAATAACTGGTTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAATCTCC</td>
<td>AGACCTTTTAATAACTGGTTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAATCTCC</td>
</tr>
<tr>
<td>TGATCTCCAAGGCCTCTACTTTTAGAAAGTGGGTCCCATCAGCTCAGCGGCAGTGGAT</td>
<td>TGATCTCCAAGGCCTCTACTTTTAGAAAGTGGGTCCCATCAGCTCAGCGGCAGTGGAT</td>
</tr>
<tr>
<td>CTGGGACGGATTCATTTCCTCACCATCAGCAGCTGCAGCCTGATGATTTTTGGAACCTTATT</td>
<td>CTGGGACGGATTCATTTCCTCACCATCAGCAGCTGCAGCCTGATGATTTTTGGAACCTTATT</td>
</tr>
<tr>
<td>ACTGCCAAAATTATAATAGTTCTTTTTTGCGGAGGGAC</td>
<td>ACTGCCAAAATTATAATAGTTCTTTTTTGCGGAGGGAC</td>
</tr>
</tbody>
</table>
Our Case

• B-cell lymphoma likely transdifferentiated to HS. Both tumors had:
  – IGH-BCL2 fusion
  – BCL6 rearrangement
  – Identical IGK gene rearrangements with identical sequences

• Both malignancies presented at the same time

• Our patient died within 1.5 months after diagnosis
Take Home Points

• Malignant neoplasm showing morphology and immunophenotype of mature histiocytes

• Etiology: unknown
  • Sporadic/de novo
  • Mediastinal germ cell tumors
  • Transdifferentiation

• Transdifferentiation
  • Mature B-cell neoplasms directly differentiate into mature histiocytic or dendritic neoplasms
  • B-cell lymphoma and HS are clonally related
   • IGH-BCL2 fusion, identical IGH/IGK gene rearrangements
Questions?
IRAP 2018
Case #2

Anna-Lee Clarke-Brodber, MD
Linda Ernst, MD, MHS
History

- 41 year-old G2P1 female
  - 10 weeks pregnant
  - presents with active heavy vaginal bleeding and passing clots
  - Hemoglobin 6.2 g/dL

- Past history:
  - Ultrasound at 7 weeks with “subchorionic hematoma”
  - Multiple episodes of prior vaginal bleeding
8.5 cm hyperechoic region/suspected subchorionic hemorrhage
Clinical diagnosis

- Active heavy vaginal bleeding & Hb 6.2 g/dL
- Diagnosis: Inevitable abortion

- Underwent suction curettage
- 113 g tissue and blood clot received
  - Including fetus with CRL = 3.4 cm
THINKING...
(PLEASE BE PATIENT)
<table>
<thead>
<tr>
<th>Differential Diagnosis for the Presence of Fetus &amp; Edematous Villi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydropic Abortus</td>
</tr>
<tr>
<td>Placental Mesenchymal Dysplasia</td>
</tr>
<tr>
<td>Partial Hydatidiform Mole</td>
</tr>
<tr>
<td>Complete Hydatidiform Mole with Co-Existent Twin</td>
</tr>
</tbody>
</table>
Villous morphology

- Villous size/shape
  - Simple
- Stroma
  - Capillaries with few nucleated RBC
- Trophoblasts
  - Flattened bilayer
Hydropic Abortus

- Villous size/shape
  - Mild variation
- Stroma
  - Edematous
  - +/- Loss of capillaries
- Trophoblasts
  - Flattened layer
  - Any proliferation is polarized
Placental Mesenchymal Dysplasia

- Villous size/shape
  - Enlarged, edematous stem villi
- Stroma
  - Central cistern in stem villi
  - Vascular proliferation/thick walled
- Trophoblast
  - No proliferation
Partial Hydatidiform Mole

- Villous size/shape
  - Mixed population
  - Irregular shapes
  - Moderately enlarged
- Stroma
  - Central cistern
  - Vessels with fetal RBC
- Trophoblast
  - Patchy proliferation
Complete Hydatidiform Mole (CHM) with Co-existent Twin

- Normal
- Villous size/shape
  - Uniform
- Stroma
  - Non-edematous
- Trophoblast
  - Flat

- Complete Mole
- Villous size/shape
  - Uniformly large
- Stroma
  - Edematous
  - Central cistern
- Trophoblast
  - Circumferential proliferation
Morphology in Case 2
Back To The Gross

Fetus

Placental Tissue

Vesicles
<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydropic Abortus</td>
<td>Villous stromal edema</td>
</tr>
<tr>
<td></td>
<td>No trophoblastic proliferation</td>
</tr>
<tr>
<td></td>
<td>No central cisterns</td>
</tr>
<tr>
<td>Placental Mesenchymal Dysplasia</td>
<td>Stem villous stromal edema</td>
</tr>
<tr>
<td></td>
<td>No trophoblastic proliferation</td>
</tr>
<tr>
<td></td>
<td>No central cisterns</td>
</tr>
<tr>
<td>Partial Hydatidiform Mole</td>
<td>Two villous populations:</td>
</tr>
<tr>
<td></td>
<td>1- Small/normal-sized villi without edema</td>
</tr>
<tr>
<td></td>
<td>2- Enlarged villi with central cisterns and patchy trophoblastic proliferation</td>
</tr>
<tr>
<td>Complete Hydatidiform Mole with Co-Existent Twin</td>
<td>Two villous populations:</td>
</tr>
<tr>
<td></td>
<td>1- Small/normal-sized villi without edema</td>
</tr>
<tr>
<td></td>
<td>2- Enlarged avascular villi with central cisterns and diffuse trophoblastic proliferation</td>
</tr>
<tr>
<td>Partial Mole</td>
<td>Complete Mole</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>69XXY, 69 XXX</td>
<td>46 XX, 46 XY</td>
</tr>
</tbody>
</table>

**P57<sup>KIP2</sup> STAINING**
<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Morphology</th>
<th>P57&lt;sup&gt;KIP2&lt;/sup&gt; Staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydropic Abortus</td>
<td>Villous stromal edema&lt;br&gt;No trophoblastic proliferation&lt;br&gt;No central cisterns</td>
<td>Positive</td>
</tr>
<tr>
<td>Placental Mesenchymal Dysplasia</td>
<td>Stem villous stromal edema&lt;br&gt;No trophoblastic proliferation&lt;br&gt;No central cisterns</td>
<td>Positive – Trophoblast&lt;br&gt;Negative – Stromal</td>
</tr>
<tr>
<td>Partial Hydatidiform Mole</td>
<td>Two villous populations: 1- Small/normal-sized villi without edema 2- Enlarged villi with central cisterns and patchy trophoblastic proliferation</td>
<td>Positive</td>
</tr>
<tr>
<td>Complete Hydatidiform Mole with Co-Existant Twin</td>
<td>Two villous populations: 1- Small/normal-sized villi without edema 2- Enlarged avascular villi with central cisterns and diffuse trophoblastic proliferation</td>
<td>Positive – Normal fetus&lt;br&gt;Negative – Complete hydatidiform mole</td>
</tr>
</tbody>
</table>
Final Diagnosis

- Twin gestation with:
  - Complete hydatidiform mole.
  - Non-molar co-twin with a embryo/fetus.

- Names used in the literature:
  - Complete hydatidiform mole with co-existent fetus
  - Complete hydatidiform mole with normal fetus
  - Molar twin
Complete Hydatidiform Mole with Coexistent Twin

- Rare occurrence
  - 1/20,000-1/100,000 pregnancies
- Combination
  - Normal Placenta
  - Fetus
  - Cystic Mass (CHM)
**COMPLETE MOLE**

- 10%: 
  - Two sperm (XX or XY) + Egg (No Maternal DNA) → 46XX or 46XY
- 90%: 
  - X sperm + Egg (No Maternal DNA) → Duplication of sperm DNA → Paternal chromosomes only (Androgenetic mole)

**PARTIAL MOLE**

- 75%: 
  - 23X, 23Y, One or two sperm + 23X Egg → 69XXX or 69XY
- 25%: 
  - 46XY + Egg (23X) → Maternal and paternal chromosomes (Triploid)
How does molar twin develop? Two zygotes?

No known reservoir of “empty eggs”

endoreduplication

Diandrogenetic Diploidy (CHM)

Biparental Diploidy (Normal fetus)
Postzygotic diploidization of triploidy

Single zygote!

Triploidy is extremely common

First mitosis

Triploid zygote

Tripolar metaphase spindle = Unstable division

Diandrogenetic Diploidy (CHM)

Biparental Diploidy (Normal fetus)

Niemann et al, Human Reproduction 2008
Complications

**Normal Fetus**
- Preterm labor
- Fetal growth restriction
- Fetal death
  - Intrauterine fetal demise
  - Spontaneous abortion
  - 60% pregnancies that were not electively terminated ended in fetal death
  - Possible mechanism of thrombotic event

**Mother**
- Pre-eclampsia
- Thyrotoxicosis
- Hyperemesis
- Trophoblastic emboli
- Severe maternal hemorrhage
- Persistent Trophoblastic Disease
  - Risk is higher than single complete mole
  - Invasive mole (more common)
  - Choriocarcinoma

Choriocarcinoma

- Recent study showed that many choriocarcinomas with or without a preceding CHM have androgenetic diploidy.

- 2/22 cases involved twins:
  - Biparental term placenta + androgenetic choriocarcinoma in left ovary
  - Biparental 21 week placenta + androgenetic choriocarcinoma in cornu of uterus.

Savage et al, AJSP 2017
Additional History

- ~1 MONTH post-op
- Presents with heavy vaginal bleeding and nausea
- βhCG 110,672
- US: Polypoid intrauterine mass, not consistent with retained products of conception
4.3cm polypoid mass, myometrial invasion
Invasive hydatidiform mole

- Most common form of persistent GTD following a HM
  - Occurs 6-10 x more frequently than choriocarcinoma

- Hydropic villi which:
  - Invade myometrium
  - Invade blood vessels
  - Deported to extrauterine sites

- Sequela of PHM or CHM; can occur simultaneously with intracavitary molar pregnancy

- Not a “true” neoplastic disease, clinically considered to be malignant since it can invade the myometrium and metastasize
  - Distant spread in 20-40% of cases
    » Lung, vagina, vulva, broad ligament

- Death is unusual with modern chemotherapy.
Take Home Points

• Sample POC to include any abnormal appearing tissue even in the presence of fetal parts
• Villous morphology can helpful to recognize molar pregnancy, but trophoblastic proliferation is the most consistent/useful sign of molar pregnancy
• P57$^{\text{KIP2}}$ is very helpful in differentiating partial and complete hydatidiform mole
• Complete hydatidiform mole with co-existent fetus may arise from a triploid embryo undergoing unequal division
Questions?
IRAP 2018: Case #3

Jamaal Rehman, MD
Curtis Hall, MD
History

• 62 y/o Caucasian male

• Malignant melanoma
  - Single ulcerated nodule on lumbar back
  - Widely excised and treated with adjuvant therapy

• Bilateral testicular enlargement with tenderness
  - Negative LDH, HCG, AFP
  - Ultrasound
  - MRI
Ultrasound (right testis)
Differential Diagnosis?
Differential Diagnosis

• Neoplasm
  - Primary vs. Metastatic
• Infarction
• Infection
• Pseudotumors of the testis
  - Vasculitis
  - Lymphocytic orchitis
  - Granulomatous orchitis
  - Fibrous pseudotumors
Additional studies

- **Stains:**
  - AFB (-)
  - GMS (-)
  - PAS (-)

- **Bloodwork:**
  - C-ANCA (-)
  - P-ANCA (-)
**Differential Diagnosis: Vasculitides**

- **Giant cell arteritis**
  - **Sx:** Headache (temporal), double vision, jaw pain
  - **Dx:** Lymphocytes/macrophages/multinucleated giant cells

- **Granulomatosis w/polyangiitis (Wegener’s)**
  - **Sx:** Upper airway (rhinitis, sinusitis)
  - Lower airway (lung: pneumonia, hemoptysis)
  - Kidney involvement

- **Eosinophilic granulomatosis w/polyangiitis**
  - **Sx:** Asthma, allergic rhinitis
  - **Dx:** Mostly eosinophils → kidney involvement
Diagnosis

Ipilimumab-mediated vasculitis
Melanoma

• An “immunogenic” tumor
  - Host immune system actively responds to melanoma
  - T-cell infiltration at the primary site is prognostic of OS
  - Absent lymphocytes have higher sentinel node metastasis

• Immunotherapeutic agents
  - Past melanoma therapy: Dacarbazine, IL-2
  - Recent advancements (checkpoint inhibitors):
    Augment lymphocyte activation in response to tumor
T-cell activation

**Primming phase**
- Dendritic cell
- T cell
- Lymph node

**Effector phase**
- T cell
- Cancer cell
- Peripheral tissue

**Activation signals**
- MHC
- TCR
- B7
- CD28

**Inhibitory signals**
- B7
- Antibody
- CTLA-4

**Negative regulation**
- PD-1
- PD-L1
Ipilimumab

- Human monoclonal antibody against CTLA-4
  - FDA approved (2015) as adjuvant for advanced melanoma
  - Blocks APC B7 from interacting with T-cell CTLA-4
  - Amplifies T-cell response against tumor

- Administration
  - 4 total doses, over 12 weeks, 10 mg/kg (adjuvant setting)
  - $30,000/dose

- Current testing of its effect on other tumors
Immune-Related Adverse Events (IRAEs)

• Side-effect profile
  - 65% of patients experience some side effect
  - Most are “mild-to-moderate” (grade 1-2)
  - Death in <1% of patients
  - Incidence and severity related to dose (i.e. heavier patients)
  - Most side effects occur within weeks of induction therapy

• Autoimmune organ damage
  - Most common: Skin, GI tract
  - Rare: Hepatic, endocrine, and neurologic events
Overlap of IRAEs among checkpoint inhibitors

- Similar IRAEs among all checkpoint inhibitors
  - Mechanism of why some occur over others is unknown

- **PD-1/PD-L1: Dermatologic symptoms**
  - Oral mucositis (ulcerations, dry mouth)

- **CTLA-4: GI & CNS symptoms**
  - Colitis (diarrhea)
  - Hepatitis (elevated AST/ALT)
  - Hypophysitis (panhypopituitarism)
Immune-Related Adverse Events (IRAEs): Dermatologic

• Skin (~45% of patients)
  - Sx: Maculopapular rash
  - Stevens-Johnson and TEN (~3%, with 1 death)
  - Dermatitis, papillary dermal edema, epidermal spongiosis
  - Perivascular lymphocytic infiltrate (CD4+, CD8+)
  - Apoptotic melanocytes

https://www.hindawi.com/journals/scientifica/2013/857519/fig3
Immune-Related Adverse Events (IRAEs): Gastrointestinal

- GI (~33% of patients)
  - Sx: Diarrhea, abdominal pain, blood in stools, nausea
  - Intestinal perforation (1%)
  - Enterocolitis (5%), 4 deaths
  - Colitis, crypt destruction, loss of goblet cells
  - Predominantly neutrophilic and lymphocytic infiltrates

https://www.hindawi.com/journals/scientifica/2013/857519/fig6
Immune-Related Adverse Events (IRAEs): Miscellaneous

- **Endocrine (~5% of patients)**
  - Thyroiditis: hypothyroidism, hyperthyroidism
  - Hypophysitis: Pituitary enlargement and panhypopituitarism

- **Hepatic (~2% of patients)**
  - Immune-related hepatitis: diffuse T-cell infiltrate
  - Elevated LFTs (ALT & AST) and hyperbilirubinemia
  - Liver failure, 1 death

- **Ocular (~1% of patients):** conjunctivitis
Immune-Related Adverse Events (IRAEs): Vasculitis

- **Vasculitis (6 total cases)**
  - 4/6 cases: Testes, retina, uterus, and brain
  - 2/6 cases: Systemic vasculitis associated with giant cell

- **Isolated testicular vasculitis**
  - Usually ANCA (+)
  - Drug reaction: Minocycline
    - Immunosuppressive therapies
    - Immune checkpoint inhibitors
Isolated Testicular Vasculitis

• Antigen presentation
  - Antigen is unknown
  - Dendritic cells present to T-cells in adventitia and media of vessel wall

• Inflammatory cytokine release
  - Macrophages → IL-1, IL-6
  - Blood vessel T-cells → IL-17, IL-21, and IFN-gamma
    Intimal hyperplasia, neoangiogenesis
Vasculitis: Checkpoint inhibitors

- Induce ANCA and Proteinase 3
- Overlap with other ANCA-associated vasculitides
- Predominantly induce CD8(+) T-cells
  - Granulomatous drug reaction in skin (Nivolumab)
  - Colitis in gastrointestinal system (Ipilimumab)
Patient course of therapy and follow-up

- Elected for adjuvant Ipilimumab
  - 1st dose (day 0): 10 mg/kg No symptoms
  - 2nd dose (day 21): 10 mg/kg
    - Pruritic rash (~ day 24)
    - GI discomfort (~ day 24)
    - B/L testicular pain (~ day 28) Tx: Orchietectomy
      D/C Ipilimumab

- Currently followed with PET scan and MRI
Take-home points

• Clinical history is essential

• Important to follow advancements in treatments, especially side-effect profile
  - Checkpoint inhibitors are a recent phenomenon
  - Their potential and pitfalls will be realized in years to come
  - Their application amongst tumors in most organ systems brings along certain complications
Questions?
IRAP 2018
Case #4

Amandeep Kaur, MD
Thomas Victor MD, PhD
Clinical history

- 25 yr. old African American female
- No significant PMH
- Presented at 38 weeks of an uncomplicated pregnancy (G1P0) with painful contractions
- Severe pre-eclampsia with chorioamnionitis
- Delivered a healthy baby boy
Week 1
- Post partum hemorrhage
- Acute kidney injury (AKI)
- Pulmonary embolism
- Lymphadenopathy

Week 2
- Hypoxemic respiratory failure
- Vesicular rash
- Serology - positive ANA, anti-centromere, anti dsDNA, anti chromatin, anti SSA, antiphospholipid Ab, low complement levels

Week 3
- Severe thrombocytopenia
- Persistent fevers
- PS: occasional schistocytes

- anemia, thrombocytopenia
- creatinine-1.7, uric acid-12.8

- BUN:Cr ratio 70:2.7
• In light of severe acute kidney injury with proteinuria
• A renal biopsy was performed
34 intact glomeruli
No sclerotic glomeruli
Differential Diagnosis?
Differential Diagnosis

1. Class IV lupus nephropathy
2. Atypical Hemolytic uremic syndrome (aHUS)
3. Antiphospholipid antibody syndrome (APLAS)
4. Hemophagocytic lymphohistiocytosis (HLH)
Class IV lupus nephropathy

LM:
- Mesangial proliferation
- Thickened GBM (wire loop)
- Endocapillary hypercellularity

IF:
- Full house

EM:
- Mesangial, subendothelial, and subepithelial deposits
- Tubulo-reticular inclusions
Lupus nephropathy
Thrombotic microangiopathies (aHUS, APLAS)

LM:
- Thrombi
- Endothelial swelling or denudation
- Fragmented red blood cells
- Mesangiolysis

IF:
- Negative

EM:
- No deposits
Hemophagocytic lymphohistiocytosis

LM:
- Thrombotic microangiopathy
- Histiocytic glomerulopathy
- Acute tubular necrosis
- Interstitial fibrosis
- Tubular atrophy

IF:
- Negative

EM:
- Histiocytes in glomeruli
- No deposits
Courtesy of Dr. Chang, University of Chicago
Immunofluorescence

Sparse 2+:
- C3
- C1q

Negative:
- IgG
- IgA
- IgM
- Kappa
- Lambda
- Fibrinogen
Differential Diagnosis

1. **Class IV lupus nephropathy**
   EM: Mesangial, subendothelial, and subepithelial deposits
   IF: Full house

2. **Atypical Hemolytic uremic syndrome**
   EM: No histiocytes in glomeruli

3. **Antiphospholipid antibody syndrome**
   EM: No histiocytes in glomeruli

4. **Hemophagocytic lymphohistiocytosis**
Diagnosis

Histiocytic glomerulopathy with thrombotic microangiopathy
Diagnosis of Hemophagocytic lymphohistiocytosis (HLH)

Table 2. Diagnostic criteria for HLH

1. Familial disease/known genetic defect or
2. Clinical and laboratory criteria (5/8 criteria should be fulfilled)

- Fever
- Splenomegaly
- Cytopenia ≥ 2 cell lines
  - Hemoglobin < 90 g/L (below 4 weeks of age, < 100 g/L)
  - Platelets < 100 × 10⁹/L
  - Neutrophils < 1 × 10⁹/L
- Hypertriglyceridemia and/or hypofibrinogenemia
  - Fasting triglycerides ≥ 3 mmol/L
  - Fibrinogen < 1.5 g/L
- Ferritin ≥ 500 μg/L*
- sCD 25 ≥ 2400 U/mL

  Decreased or absent NK cell activity
  Hemophagocytosis in BM, CSF, or lymph nodes
Final Diagnosis

Hemophagocytic lymphohistiocytosis
Hemophagocytic lymphohistiocytosis

- HLH is an aggressive and life-threatening syndrome of excessive immune activation
- It is caused by defective lytic capability of cytotoxic T lymphocytes and NK cells
- Age: Infants from birth to 18 months of age
- Types: Primary and secondary
# Primary HLH

<table>
<thead>
<tr>
<th>HLH type</th>
<th>Defective gene</th>
<th>Function</th>
<th>Notable clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial HLH type 2</td>
<td>PRF1</td>
<td>Pore formation</td>
<td>No notable clinical findings</td>
</tr>
<tr>
<td>Familial HLH type 3</td>
<td>UNC13D</td>
<td>Vesicle priming</td>
<td>Increased incidence of CNS involvement</td>
</tr>
<tr>
<td>Familial HLH type 4</td>
<td>STX11</td>
<td>Vesicle fusion</td>
<td>Mild, recurrent HLH; colitis</td>
</tr>
<tr>
<td>Familial HLH type 5</td>
<td>STXB1P2</td>
<td>Vesicle fusion</td>
<td>Colitis; hypogammaglobulinemia</td>
</tr>
<tr>
<td>Syndromes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Griscelli syndrome type 2</td>
<td>RAB27A</td>
<td>Vesicle docking</td>
<td>Partial albinism; silvery-gray hair</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>LYST</td>
<td>Vesicle trafficking</td>
<td>Partial albinism; bleeding tendency; recurrent pyogenic infection</td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome type 2</td>
<td>AP3B1</td>
<td>Vesicle trafficking</td>
<td>Partial albinism; bleeding tendency; immunodeficiency</td>
</tr>
<tr>
<td>EBV-driven</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked lymphoproliferative disorder type 1 (XLP-1)</td>
<td>SH2D1A</td>
<td>T cells, NK cells, and NK T cell signaling</td>
<td>Hypogammaglobulinemia; lymphoma</td>
</tr>
<tr>
<td>X-linked lymphoproliferative disorder type 2 (XLP-2)</td>
<td>BIRC4</td>
<td>Signaling pathways involving nuclear factor kappa-light-chain enhancer of activated B cells</td>
<td>Mild, recurrent HLH; colitis</td>
</tr>
<tr>
<td>IL2-inducible T cell kinase deficiency</td>
<td>ITK</td>
<td>Signaling in T cells</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>CD27 deficiency</td>
<td>CD27</td>
<td>Lymphocyte costimulatory molecule</td>
<td>Combined immunodeficiency</td>
</tr>
<tr>
<td>X-linked immunodeficiency with magnesium defect (XMEN)</td>
<td>MAGT1</td>
<td>T cell activation via T cell receptor</td>
<td>Combined immunodeficiency; chronic viral infections; lymphoma</td>
</tr>
</tbody>
</table>

George, Blood Reviews, 2014
Secondary HLH

1. Viral infections
   - CMV, EBV, HSV, HIV, Parvovirus, Influenza A, H1N1, Post vaccination

2. Other infections
   - Bacteria, Protozoal (Malaria, Leishmania), Fungi (Candida, Aspergillus), Mycobacteria, Mycoplasma

3. Malignancies
   - Leukemia, Lymphoma, Solid tumors (Germ cell tumors)

4. Rheumatological diseases Macrophage activation syndrome (MAS)
   - SLE, sJRA, Scleroderma, Sjogrens, Kawasaki, MCTD

5. Immune deficiency syndromes
   - SCID, CVI, CGD, BMT/SCT
Pathogenesis
Histiocyte Cytokine Storm

Schulert, Annual Review of Medicine, 2015
Kidney and MAS

Table 2. Renal lesions in MAS

<table>
<thead>
<tr>
<th>Glomerular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease</td>
</tr>
<tr>
<td>Collapsing glomerulopathy</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td>‘Histiocytic glomerulopathy’</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tubulointerstitial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>Microcystic tubular dilatation</td>
</tr>
<tr>
<td>Interstitial nephritis, with polymorphic T lymphocytes and CD68+ macrophages</td>
</tr>
<tr>
<td>Tubular atrophy and interstitial fibrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic microangiopathy</td>
</tr>
</tbody>
</table>
Prognosis - Histiocytosis with AKI

121 patients fulfilling diagnostic criteria for HLH between 2007 and 2013

- 26 patients with incomplete data or lost to follow-up

95 patients with complete follow-up and no missing data

- AKI
  - n= 59 (62%)
    - Survivors at 6 months
      - n= 22 (37.3%)
        - Chronic Kidney Disease*
          - n= 7 (31.8%)
        - Complete renal recovery
          - n= 15 (68.2%)
    - Non survivors at 6 months
      - n= 37 (62.7%)
        - Deceased with AKI
          - n= 28 (75.7%)
        - Deceased with complete renal recovery
          - n= 9 (24.3%)

- No AKI
  - n= 36 (38%)
    - Survivors at 6 months
      - n= 20 (55.6%)
    - Non survivors at 6 months
      - n= 16 (44.4%)
Follow-up

- Started on Anakinra, IvIg, Mycophenolate and Prednisone
- All labs came back to normal
- Patient discharged and doing well
- Bone marrow biopsy is planned to exclude lymphoma
- Continued on Mycophenolate and Prednisone
- Still has nephrotic range proteinuria
Take Home Message

• HLH is an under-recognized potentially fatal systemic disease

• Since the prognosis with AKI is very poor, greater awareness of these kidney biopsy manifestations is needed to ensure its prompt recognition and appropriate treatment
Questions?
IRAP 2018
Case #5

Julio A. Diaz-Perez, MD
Thomas L. Cibull, MD
23 yo Female

- Hx. Multiple dysplastic melanocytic nevi
- Hx. Metastatic melanoma
- In follow-up

New scalp lesion

- Frequent user of tanning beds
Differential diagnosis?
Differential diagnosis?

- Metastatic melanoma
- Melanoma arising in a nevus
- Intradermal nevus inflamed consistent with partial regression – halo effect
- Combined melanocytic nevus with a Spitz nevus component
Ruling out melanoma

<table>
<thead>
<tr>
<th>Our case</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small size</td>
<td>Size beyond 10 mm</td>
</tr>
<tr>
<td>Small tumor thickness</td>
<td>Depth involvement</td>
</tr>
<tr>
<td>Symmetric</td>
<td>Asymmetry</td>
</tr>
<tr>
<td>Intact epidermis</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Circumscribed</td>
<td>Poor circumscription</td>
</tr>
<tr>
<td>Basal epidermal melanocytes</td>
<td>Pagetoid melanocytosis</td>
</tr>
<tr>
<td>Mild confluence of melanocytes</td>
<td>High confluence of melanocytes</td>
</tr>
<tr>
<td>Zonation / homogeneity</td>
<td>Lack of zonation and maturation</td>
</tr>
</tbody>
</table>
Metastatic melanoma
Melanoma arising in a preexisting dermal nevus
Ruling out nevus with halo effect

<table>
<thead>
<tr>
<th>Our case</th>
<th>Halo effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non pigmented</td>
<td>Depigmented ring</td>
</tr>
<tr>
<td>Dense mononuclear infiltrate</td>
<td>Dense mononuclear infiltrate</td>
</tr>
<tr>
<td>Few apoptotic nevus cells</td>
<td>Apoptotic nevus cells</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>Peripheral changes</td>
</tr>
</tbody>
</table>
Differential diagnosis?

- Metastatic melanoma
- Melanoma arising in a preexisting dermal nevus
- Intradermal nevus inflamed consistent with partial regression – halo effect
- Combined melanocytic nevus with a Spitz nevus component
BRCA associated protein (BAP) - 1

Courtesy of Jarish Cohen, UCSF
Final diagnosis

- Combined melanocytic nevus including a component of epithelioid melanocytic nevus (Spitz) associated with BAP-1 loss (BAPoma)
Spitz nevus

• Tumor of spindled and epithelioid melanocytes

• Aka:
  – Juvenile melanoma
  – Spindle and epithelioid cell nevus

• Trunk most common; also lower extremities, head and neck

• Usually single papule (<6 mm)
Spitz melanocytic neoplasm

- What we have called Spitz nevus represents a group of molecularly and morphologically heterogeneous melanocytic neoplasms
The Spitz spectrum

- Conventional Spitz
- Superficial spreading Spitz
- HRAS-mutant Spitz
- Kinase-fusion Spitz
  - ALKoma
  - NTRKoma
  - ROSoma
  - REToma
  - BRAFoma
- Epithelioid with BAP-1 loss
  - BAPoma
- Spitzoid Melanoma

LeBoit, Conference, 2016
Weng, Conference, 2017
Wiesner, Nat Com, 2014

HRAS-mutation
Kinase fusions
BAP-1 loss

CDKN2A deletion
TP53 inactivation

TERT promotor mutations
PTEN loss
ARID2A mutation
Spitz HRAS-mutated
(Desmoplastic)

• Aka:
  – 11p Spitz
  – Bastian nevus

• Young adults

• Symmetrical & sharply demarcated
• Horizontal orientation

• Melanocytes in mitosis

• Good prognosis

• Detection: FISH

van Engen-van Grunsven Am J Surg Pathol. 2010
Bastian BC. Am J Pathol. 2000
Kinase-fusion Spitz
(Wedge shaped pigmented)

• Induced by various kinase gene fusions
  – ALK, NTRK1, NTRK3, ROS1, RET, BRAF

• Darkly pigmented

• Extension into the dermis or subcutis
  – Wedge-shaped, bulbous lower border

• Detection:
  – IHC: ALK (D5F3), NTRK1 (EP1058Y), ROS1 (D2D6), RET (EPR287)
  – FISH
BAP1 (-) Spitz (BAPoma)

(Epithelioid and polypoid)

- Wiesner nevus
- Polypoid - combined
- Large, epithelioid melanocytes
- Chronic inflammation
- May be marker for syndromic BAP-1 mutation
- Less aggressive
- Detection: IHC BAP1 (-)

Busam, JAMA Dermatol, 2013
BAP1 (-) SPITZ NEVUS (BAPOMA)

Loss or depletion of BAP1
  ↓
Decreased H4K20me1
  ↓
Increased EZH2 expression and H3K27me3
  ↓
Rescue with EZH2 deletion or inhibition
  ↓
Repression of Polycomb genes

<table>
<thead>
<tr>
<th>Tumours with somatic BAP1 mutations</th>
<th>Total</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uveal melanoma</td>
<td>60</td>
<td>28</td>
<td>47</td>
</tr>
<tr>
<td>Skin</td>
<td>33</td>
<td>13</td>
<td>39</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td>60</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Atypical Spitz tumours</td>
<td>18</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Spitz naevi</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Common acquired naevi</td>
<td>29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>121</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Kidney</td>
<td>18</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Prostate</td>
<td>176</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Ovary</td>
<td>98</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>62</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Breast</td>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>355</td>
<td>3</td>
<td>09</td>
</tr>
<tr>
<td>Other</td>
<td>322</td>
<td>2</td>
<td>04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BAP1 mutation status</th>
<th>Mutated</th>
<th>Wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical/histopathological data</td>
<td>n = 35</td>
<td>n = 39</td>
</tr>
<tr>
<td>BAP1 expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>4</td>
<td>38</td>
</tr>
</tbody>
</table>

White, Science 2012
Wadt, Pigment Cell Melanoma Res. 2012
Hunter, NEJM, 2015
Koopmans, Modern Pathology, 2014
Goldstein, Nature genetics 2011
Carbone, Nature Reviews Cancer 2013
NorthShore Center for Medical Genetics

Genealogy Diagram

- 60 (Bone)
- 97
- 82 (d. heart failure)
- 72 (Breast mast. recur in spine)
- 85
- 89 (a/w)
- 52 (Breast met. to lungs unilat. mast.)
- 58 (Skin - Basal cell)
- 68
- 66
- 64
- 58
- 47 (Meningioma - Cerebral benign)
- 32 (a/w)
- 57 (a/w)
- 56 (a/w)
- 35 (a/w)
- 35 (a/w)
- 35 (a/w)
- 24 (Skin - Melanoma 1st scalp, removed 4 lymph nodes in neck - recur at same spot, interferon
- 2nd: leg
- pale skin
- h/o of occasional light tanning bed use
- gets moles removed regularly
- >100 moles currently
- 50 year C. loss of
- apol
- Cancer ? = Yes

Cancer - 1st primary = Skin - Melanoma
# The Spitz spectrum targeted therapy

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Mutation</th>
<th>Drug</th>
<th>Stage in development</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRAS-mutant</td>
<td>HRAS</td>
<td>Tipifarnib</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Kinase-fusion</td>
<td>ALK</td>
<td>Crizotinib</td>
<td>FDA approved in cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceritinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NTRK</td>
<td>Cabozantinib</td>
<td>FDA approved in cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LOXO-101</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>RET</td>
<td>Cabozantinib</td>
<td>FDA approved in cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vandetanib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ROS</td>
<td>Crizotinib</td>
<td>FDA approved in cancer</td>
</tr>
<tr>
<td></td>
<td>BRAF</td>
<td>Sorafenib</td>
<td>FDA approved in cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tramefinib</td>
<td></td>
</tr>
<tr>
<td>BAP-1 loss</td>
<td>BAP-1</td>
<td>Tazemetostat</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>
Take home message

• Spitz tumors
  – Genetic aberrations usually correlates with the histology
  – IHC and FISH, auxiliary techniques

• Spitz tumors are biologically distinct

• Spitz tumors show specific mutations
  – Tetraploid tumors = FISH unreliable
Questions?
IRAP 2018
Case #6

Muhammad Ahmad, MD
William G. Watkin, MD
Patient data

- A 70 year old female presented with weight loss (10 lbs), abdominal fullness and bloating – 3 weeks
Patient data

- CT scan: large amount of ascites and a lobulated soft tissue mass in left adnexa measuring 5.8 x 3.2 x 3.2 cm.

- CA-125: 14.8 (normal)
Gross findings
IT'S NOT LUPUS
Differential diagnosis

• Carcinoma:
  ➢ High-grade serous carcinoma
  ➢ Endometrioid carcinoma

• Female adnexal tumor of probable Wolffian origin (FATWO)

• Neuroendocrine tumor

• Yolk sac tumor
## Stains summary - Positive

<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin OSCAR</td>
<td>Positive</td>
</tr>
<tr>
<td>EMA</td>
<td>Positive</td>
</tr>
<tr>
<td>SALL-4</td>
<td>Positive</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Positive</td>
</tr>
<tr>
<td>p53</td>
<td>Moderate intensity staining</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Patchy positive staining</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Weakly positive staining</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>Scattered positive staining</td>
</tr>
<tr>
<td>CDX-2</td>
<td>Patchy positive staining</td>
</tr>
<tr>
<td>Calretinin</td>
<td>Patchy positive staining</td>
</tr>
</tbody>
</table>
# Stains summary - Negative

<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>Negative</td>
</tr>
<tr>
<td>CK20</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytokeratin AE1/AE3</td>
<td>Negative</td>
</tr>
<tr>
<td>WT-1</td>
<td>Negative</td>
</tr>
<tr>
<td>p16</td>
<td>Negative</td>
</tr>
<tr>
<td>PAX-8</td>
<td>Negative</td>
</tr>
<tr>
<td>GATA-3</td>
<td>Negative</td>
</tr>
<tr>
<td>Inhibin</td>
<td>Negative</td>
</tr>
<tr>
<td>TTF-1</td>
<td>Negative</td>
</tr>
<tr>
<td>Napsin</td>
<td>Negative</td>
</tr>
<tr>
<td>GFAP</td>
<td>Negative</td>
</tr>
<tr>
<td>CD56</td>
<td>Negative</td>
</tr>
<tr>
<td>ER</td>
<td>Negative</td>
</tr>
</tbody>
</table>
High-grade serous carcinoma

- Branching papillary fronds, slit-like fenestrations, glandular complexity
- Moderate to marked nuclear atypia with marked pleomorphism
- Prominent nucleoli, nuclear stratification
- Frequent mitoses & stromal invasion
- Variable psammoma bodies

# Serous carcinoma – staining pattern

<table>
<thead>
<tr>
<th>Stain</th>
<th>Serous carcinoma</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>p16</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>WT-1</td>
<td>Positive (78%)</td>
<td>Negative</td>
</tr>
<tr>
<td>SALL-4</td>
<td>Negative (&gt;60%)</td>
<td>Positive</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>Negative</td>
<td>Scattered positive staining</td>
</tr>
</tbody>
</table>
Endometrioid carcinoma

- Vast majority are low-grade
- Predominately intraluminal exophytic growth
- Pushing or infiltrative border
- Back-to-back small to large, tubular to convoluted glands, cribriform, trabecular, solid growth
## Endometrioid carcinoma – staining pattern

<table>
<thead>
<tr>
<th>Stain</th>
<th>Endometrioid carcinoma</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>ER</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>SALL-4</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>Negative</td>
<td>Scattered positive staining</td>
</tr>
</tbody>
</table>
FATWO

- Diffuse, trabecular, tubular or sieve like patterns
- Cells are cuboidal to columnar with minimal cytoplasm
- May have prominent hyalinized stroma or fibrous bands that creates lobular appearance
- Sheets of tumor cells may have a spindly appearance
- Mild cytologic atypia with few cells with prominent nucleoli.
### FATWO – staining pattern

<table>
<thead>
<tr>
<th>Stain</th>
<th>FATWO</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK AE1/AE3</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>CK7</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>WT-1</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>SALL-4</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>EMA</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>Negative</td>
<td>Scattered positive staining</td>
</tr>
</tbody>
</table>
Neuroendocrine tumor

- Organoid architecture: solid nests, trabeculae, cords, glandular, acinar, cribriform
- Small to medium cells with eosinophilic to amphophilic and finely granular cytoplasm
- Nuclei are uniform, central, round / oval, with "salt and pepper" (finely stippled) chromatin
- Rich vascular network
# Neuroendocrine tumor- staining pattern

<table>
<thead>
<tr>
<th>Stain</th>
<th>Neuroendocrine tumor</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromogranin</td>
<td>Diffusely positive staining</td>
<td>Patchy positive staining</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Diffusely positive staining</td>
<td>Weakly positive staining</td>
</tr>
<tr>
<td>CD 56</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>EMA</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>SALL-4</td>
<td>Negative</td>
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</tbody>
</table>
Yolk sac tumor

- May present with abdominal pain, rapidly growing mass and increasing alpha fetoprotein (AFP)
- Usually in children or young adults
- Numerous patterns:
  - Reticular or microcystic
  - Polyvesicular vitelline pattern
  - Endometrioid
  - Glandular
  - Intestinal differentiation

- Schiller-Duval body is pathognomonic
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<td>WT-1</td>
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<tr>
<td>Calretinin</td>
<td>Negative</td>
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</tr>
<tr>
<td>CK7</td>
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<td>Negative</td>
</tr>
<tr>
<td>EMA</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Cytokeratin AE1/AE3</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Diagnosis

Yolk sac tumor of distal fallopian tube

or

Distal fallopian tube tumor with yolk sac differentiation with probable somatic derivation
Discussion
Somatically derived yolk sac tumors

- YST of the female genital tract in older adults derive commonly from somatic epithelial neoplasms
- Arising through neo-metaplasia (aberrant differentiation) or retro-differentiation
- Pure glandular YST may arise secondary to total overgrowth of an epithelial neoplasm
- Often significant immunophenotypical and morphological overlap with epithelial neoplasms
Somatically derived yolk sac tumors

- A case series of 18 YST cases of the female genital tract in adults aged 40 or over
- Most of the YSTs occurred in association with a somatic epithelial neoplasm
- Variety of morphological phenotypes
- High-grade serous carcinoma: most common
Somatically derived yolk sac tumors

- One case with a pure YST: endometriotic cyst in the same ovary
- All other cases: YST exhibited a predominantly glandular morphology closely mimicking primary ovarian adenocarcinomas
- Morphological overlap between a YST and a clear cell carcinoma has been highlighted in the literature
- Given the high-grade nuclear features in the glandular YST components, a HGSC might also be in the differential diagnosis.
Somatically derived yolk sac tumors

- A high index of suspicion for a combined epithelial neoplasm and YST
- EMA, BerEP4 & CK7: used for YST v/s Mullerian adenocarcinoma
- Diagnosis made based on the morphology together with +ve staining with a variety of markers
Somatically derived yolk sac tumors

- In six cases, the neoplasms comprised pure YSTs with no somatic epithelial component.

- Since four of these exhibited a predominantly glandular morphology, an epithelial element may have been present originally and been totally overgrown by the YST component.
Somatically derived yolk sac tumors

- Treatment regimen dilemma
- Argument for epithelial-based regimen
- Regimen against predominant component
- Combined therapy against both components
Back to our patient

- Status post 5 cycles of chemotherapy (Taxol based)
- Active with good energy
- No current symptoms or complaints
Take Home Points

• YST of the female genital tract in older adults derive commonly from somatic epithelial neoplasms
• Arising through neo-metaplasia (aberrant differentiation) or retro-differentiation
• Pure glandular YST may arise secondary to total overgrowth of an epithelial neoplasm
• Significant immunophenotypical and morphological overlap with epithelial neoplasms
Questions?
That's all Folks!