Clinical History

- 80 year woman
- Post menopausal bleeding
- Endometrial Bx: Endometrial Ca, rule out serous
- CT
  - Bulky uterus
  - Slightly enlarged right common iliac nodes
  - Bilateral lung nodules <5mm ( uncertain significance)
- Laparoscopic hysterectomy, BSO, infracolic omentectomy

Pathology

- Enlarged Uterus with tumour eroding through serosa
- Full thickness myometrial invasion with serosal involvement
- Cervix negative
- Tubes, ovaries negative
- Right common iliac nodes negative (0/2)
- Omentum negative
Presenting Diagnosis

- Endometrial Endometriod Adenocarcinoma NOS versus Metastatic adenocarcinoma from GIT
  - Carcinoma limited to body, fundus
  - Glandular but occasional high grade nuclei
  - Dirty Necrosis
  - Extensive LVI
  - Full thickness invasion with serosal involvement

Working Diagnosis
VIMENTIN
ER PR
p16 p53
CK7
CK20
CDX2 Villin
pCEA
PAX-8

3/28/2017

Additional Immunohistochemistry

CK7 CK20
CDX2 Villin

Immunohistochemical Panel

<table>
<thead>
<tr>
<th>Protein</th>
<th>Endometrial</th>
<th>Endometrioid Adenoc.</th>
<th>Metastatic Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>ER/PR</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>p16</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td>Positive (overexpression)</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>CD125</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>CK7 and CK20</td>
<td>Positive</td>
<td>Both Positive (CK20=CK7)</td>
<td></td>
</tr>
<tr>
<td>CDX2</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Villin</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>pCEA</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>PAX-8</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

Revised Diagnosis

- High Grade Adenocarcinoma, favour metastatic adenocarcinoma
  - Upper GI/Colorectal/Appendiceal/Pancreato-biliary
  - Bladder
Metastatic (Clinical) Work-Up

- Investigations for GI / Pancreato-biliary: Negative
- Investigations for Bladder primary: Negative

Diagnosis???

- Mimics GI/colorectal primary
- Cells show subnuclear and supranuclear vacuolation

<table>
<thead>
<tr>
<th>Presentations</th>
<th>Authors</th>
<th>Year</th>
<th>Title</th>
<th>Volume/Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Damato S, Haldar K, McCluggage WG.</td>
<td>2016</td>
<td>Primary Endometrial Yolk Sac Tumor (YST) with Endodermal-Intestinal Differentiation Masquerading as Metastatic Colorectal Adenocarcinoma</td>
<td>Int J Gyn Pathol 2016;35:316-20</td>
</tr>
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<td></td>
<td>McNamara T, Damato S, McCluggage WG.</td>
<td>2016</td>
<td>Yolk Sac Tumours of the Female Genital Tract in Older Adults Derive Commonly from Somatic Epithelial Neoplasms: Somatically Derived Yolk Sac Tumours</td>
<td>Histopathology 2016; DOI:10.1111/his.13021</td>
</tr>
</tbody>
</table>

- Patients
  - Age 63
  - Postmenopausal bleeding
  - YST in uterus with microscopic focus of Endometroid Adenocarcinoma
  - Stage IV

- Children and young adults
  - Peri/postmenopausal women
  - Somatically derived YST
  - Neoplasia/Retr differentiation of malignant somatic stem cell
  - Pluripotent germ cell/germ cell precursor arrested, misplaced during embryonal migration: germ cell origin

- EGYST
  - Clinical presentation identical to somatic endometrial carcinoma, serum AFP not done

- Immunohistochemistry
  - CK7
  - CK20
  - EMA
  - CDX2
  - AFP
  - SALL4
  - Villin

- S Damato et al UGP 2016:35,316-320
Back to our case

Primary Endometrial (Extra Gonadal) Yolk Sac Tumour with Endodermal-Intestinal Differentiation

Immunohistochemical markers in the diagnosis of EGYST

<table>
<thead>
<tr>
<th>Marker</th>
<th>High Sensitivity (100%)</th>
<th>Low Sensitivity</th>
<th>Pluripotent marker for GCTs (except Chorioca) but positive in somatic carcinomas with intestinal differentiation, 7% RG Endometrial ca +</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALL4</td>
<td>High specificity</td>
<td>Low specificity</td>
<td></td>
</tr>
<tr>
<td>AFP</td>
<td>High specificity</td>
<td>Low specificity</td>
<td></td>
</tr>
<tr>
<td>Glypican 3</td>
<td>High sensitivity</td>
<td>Less specific than AFP</td>
<td></td>
</tr>
<tr>
<td>PAX-8</td>
<td>Positive in neoplasms of mullerian origin; 70-98% Endometrial Carcinomas positive depending on degree of differentiation</td>
<td>Negative in carcinomas of mullerian origin showing intestinal differentiation</td>
<td></td>
</tr>
</tbody>
</table>

???: Revised Diagnosis 2

Endometrial Ca, NOS
- Morphology unusual
- Negative

Metastatic Gastrointestinal adenocarcinoma
- negative
- negative
- positive (focal)
- positive

Extragonadal (somatic) YST
- Only one GC marker +ve

<table>
<thead>
<tr>
<th>Marker</th>
<th>Metastatic Gastrointestinal adenocarcinoma</th>
<th>Extragonadal (somatic) YST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>negative</td>
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</tr>
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</tr>
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<td>negative</td>
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</tr>
<tr>
<td>p53</td>
<td>positive</td>
<td>Positive</td>
</tr>
<tr>
<td>p53A</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>p53B</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>GSTP1</td>
<td>positive</td>
<td>Positive</td>
</tr>
<tr>
<td>CDX2</td>
<td>positive</td>
<td>Positive</td>
</tr>
<tr>
<td>V903</td>
<td>positive</td>
<td>Positive (focal)</td>
</tr>
<tr>
<td>HSPH1</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>CA125</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>TTF1</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>PAX-8</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
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</tr>
<tr>
<td>AFP</td>
<td>negative</td>
<td>negative</td>
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</table>
Unusual morphology for primary endometrial Ca
Morphology and IHC GI primary but metastatic work up negative

Extragonadal (somatic) Yolk sac tumor, but
Only 1 of 3 GST markers (SALL4) positive &
more specific YST markers (AFP, Glypican) negative

Diagnosis after External Consultation
• Could be somatic EGYST
  • but both AFP and Glypican 3 negative
• Primary Intestinal type Endometrial Adenocarcinoma/ Endometrial Carcinoma showing intestinal differentiation
  • Diagnosis of exclusion (Rule out metastatic adenocarcinoma of GI origin)

Primary Intestinal type Endometrial Adenocarcinoma/ Endometrial Carcinoma showing intestinal differentiation
• Endometrial primary: 2 case reports
  • Endometrial adenocarcinoma with simultaneous endocervical and intestinal-type mucinous differentiation: report of a rare phenomenon and the immunohistochemical profile. Buil-Galindo et al. Diagn Pathol 2013;8:128
• Vaginal primary: 22 cases reported
  • Most recent: Primary intestinal type adenocarcinoma of the vagina. Sar A, Nation JD, Duggan MA et al. CJP 2016;8:10-20
  • 4 cases, Age 32-74 yrs range
  • Arise from metaplastic intestinal epithelium in the squamous epithelium, cloacal remnants, or entrapped rectal mucosa post vaginal tear repair
  • CDX2+, CK20+, CK7+patchy, pCEA+
  • PAX8-, p16-, p53 wild type, ER-

Primary Intestinal type Endometrial Adenocarcinoma/ Endometrial Carcinoma showing intestinal differentiation
• Etiology of intestinal differentiation within endometrium unclear
  • ? Neometaplasia: Mullerian epithelium undergoes metaplasia along an intestinal lineage
  • Metaplastic mullerian epithelium retains CK7 positivity
  • ER negative subset thought to behave in a more aggressive manner
  • Does Intestinal differentiation represent aggressive phenotype in the endometrium (too few cases)

Follow up of our case
• Taxol and carboplatin as standard protocol for gynecologic malignancies (pT3a, FIGO IIIA)
• Radiation
• Last follow up November 2016
  • 9 months post surgery
  • No evidence of disease recurrence/metastasis
When faced with such a lesion in the uterus

- Warrants careful clinico-pathologic work up to exclude metastasis from GI tract/pancreas/bladder
- Extragonadal Yolk Sac of somatic derivation (with intestinal-endodermal differentiation)
- Need high index of suspicion: YST may be present with or without adenocarcinoma in varying proportions with morphologic and immunohistochemical overlap
- Primary Intestinal type Endometrial Adenocarcinoma / Endometrial adenocarcinoma with intestinal differentiation
- Diagnosis of exclusion
- Use a broad IHC panel
  - CK7, CK20, CDX2, Villin, Vimentin, ER, PR, p16, p53, WT-1, SALL4, PAX-8, Glypican-3, AFP

Acknowledgements

- Gyn-Oncology Disease Site team (Juravinski Hospital and Cancer Center, McMaster University, Hamilton, Ontario, Canada)
  - Professor Dean Daya (Department of Pathology and Molecular Medicine)
  - Dr Alice Lytwyn (Departments of Pathology and Molecular Medicine & Health research methods, evidence, impact and Clinical Epidemiology)
  - Dr Waldo Jimenez (Gyn Oncologist)
  - Dr Bindi Dhesy (Medical oncologist)
- Professor Glen McCluggage (Department of Pathology, Royal Group of Hospitals, Belfast)
- Professor Esther Oliva (Department of Pathology, Massachusetts General Hospital, Harvard University, Boston)

Important Information Regarding CME/SAMs

The Online CME/Evaluations/SAMs claim process will only be available on the USCAP website until September 30, 2017. No claims can be processed after that date! After September 30, 2017 you will NOT be able to obtain any CME or SAMs credits for attending this meeting.

Molecular based classification for endometrial cancers
(The Cancer genomic Atlas-TGCA)

- POLE mutation
- Microsatellite instability
- Copy number low: microsatellite stable with low mutation rates: FIGO 1 and 2 Endometrioid Adenocarcinoma
- Copy number High: recurrent TP53 mutation, high copy number aberrations, low mutation rates: Serous Ca & FIGO 3 Endometrioid Adenocarcinoma
- p53 overexpression: Primary Intestinal Type Endometrial Adenocarcinoma???


5 Ravishankar et al AJP 2017-1:1-11