"Glandular lesions and tumors in Uropathology”
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Case 004
Case details:

2016: 82 year male

• **Clinical:** a subcapsular lesion in Liver, **Peripheral type Cholangiocarcinoma**
• Preoperative chemotherapy with Gemcitabine and Carboplatin, good response.
• Clinical suspicion of Liver metastasis from a probable colon primary
• Coloscopy normal
• Liver resection. Subcapsular grey white tumor 4x3x2.5cms.
• **2014-15:**-biopsies and cystectomy-Urothelial carcinoma of bladder.
Bladder

Cystectomy: 2015

• Tumor in diverticulum on right lateral wall of bladder
• Clinically- stage 3 tumor (T3N0M0)
• Gross: diverticulum- 7cm large with an adjacent exophytic tumor measuring 5.5cms on right lateral wall.
  Normal prostate.
• Lymph nodes: normal histology

Biopsies: 2014

• 80 year male: macroscopic hematuria presented in emergency ward.
• Cystoscopy:-
  Many catheter lesions
  A large diverticulum with an adjacent tumor process on the right lateral wall.
Bladder tissue

Cystectomy: 2015

• Tumor in diverticulum on right lateral wall of bladder
• Clinically- stage 3 tumor (T3N0M0)
• Gross: diverticulum- 7cm large with an adjacent exophytic tumor measuring 5.5cms. Normal prostate.
• Lymph nodes: normal

Biopsies: 2014

• 80 year male: macroscopic hematuria presented in an emergency ward.
• Cystoscopy:-
  Many catheter lesions
  A large diverticulum with an adjacent tumor process on the right lateral wall.
Diagnosis

Clear cell adenocarcinoma (CCA) of bladder
Gain of Chromosome: 1p (partiel), 2p (partiel), 3q (partiel), 5q (partiel), 8q (complete), 17q (complete) & 22q (partiel).

Loss of Chromosome: 9p (partiel).
Types of Bladder Adenocarcinoma-WHO 2016

Glandular neoplasms
• Adenocarcinoma, NOS
  Enteric
  Mucinous
  Mixed
• Villous adenoma

Primary adenocarcinoma-
• a rare malignancy,
• 0.5–2% of all malignant bladder tumours.
• Strict definition-tumours derived from urothelium and with an exclusive glandular component.

Urachal carcinoma

Tumors of Mullerian type
Clear cell carcinoma (adenocarcinoma)
Endometroid carcinoma
General considerations:

• *Mesonephric adenocarcinoma*

• 2004:- Clear cell adenocarcinoma (CCA)
• 2016:- CCA- Tumors of Mullerian types
• Extremely rare with single cases and small series published (with a caveat).
• More common in women than men.
• Arises commonly in urethra or bladder.
• Histogenesis-remains uncertain till date.
• It has a classic histology.
• Aggressive neoplasm with associated poor prognosis.
CCA-Distinct histologic pattern

- Papillary, tubulocystic structures, admixed solid areas.
- Basophilic or eosinophilic mucinous (PAS-D resistant) secretions
- Small papillae and fibrovascular cores may be extremely hyalinised
- Cells are flat to cuboidal to columnar, clear or **eosinophilic** cytoplasm
- Hobnail cells are frequently seen.
- Cytologic atypia-moderate to high, many mitosis
Histogenesis: *uncertain*

<table>
<thead>
<tr>
<th>Author</th>
<th>Case number</th>
<th>Histogenetic origin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliva [2]</td>
<td>13</td>
<td>Urothelial; Müllerian</td>
<td>CA125 (+)</td>
</tr>
<tr>
<td>Drew [7]</td>
<td>6</td>
<td>Müllerian</td>
<td>CA125 (+)</td>
</tr>
<tr>
<td>Rivard [8]</td>
<td>6</td>
<td>Wolffian or mesonephric duct</td>
<td>PSA (+)</td>
</tr>
<tr>
<td>Tong [12]</td>
<td>7</td>
<td>Proliferating renal tubules</td>
<td>PAX2 (+), PAX8 (+)</td>
</tr>
<tr>
<td>Sung [29]</td>
<td>12</td>
<td>Urothelial</td>
<td>Chromosomal alterations similar those found in UC</td>
</tr>
<tr>
<td>Hartman [28]</td>
<td>1</td>
<td>NM</td>
<td>Molecular evidence for transition of NM to CCAC</td>
</tr>
<tr>
<td>Brimo [31]</td>
<td>18</td>
<td>Müllerian</td>
<td>HNF-1β (+)</td>
</tr>
<tr>
<td>Current study</td>
<td>4</td>
<td>Proliferating renal tubules/ mesonephric; unknown</td>
<td>PAX8 (+), CA125 (-)</td>
</tr>
</tbody>
</table>

*UC urothelial carcinoma, NM nephrogenic metaplasia*

*Proliferating renal tubules/mesonephric origin for a subset of urethral CCAC*
Contd...histogenesis:

CCAs of FGT & UGT doesn’t arise from a common histogenetic precursor.
• Nephrogenic adenoma (NA): Mazal et al, 2002, Lesions that originate from the proliferation of exfoliated and implanted renal tubular cells in the urothelium.

• CCA is very common in urethra and especially associated with ‘Urethral diverticulum’, which in turn is also frequently associated with NA.

• Histomorphological and immunohistochemical features resembles NA.
  • Is Nephrogenic adenoma a precursor lesion?

_points in favour of renal tubular origin_- Characteristic morphology, PAX8 and Napsin positivity, (HNF1b+ and AMACR+). No usual urothelial carcinoma or urothelial carcinoma in-situ in many cases described and also not seen in the present case.

• Points in favour of urothelial origin- Not many, only CK7 and GATA3 positivity.
Differentiel diagnoses:

- **Nephrogenic adenoma** – size, low ki-67, how is atypia?
- **Atypical nephrogenic metaplasia**- solid islands, necrosis & few mitosis, increased Ki-67.
- **Clear cell variant of urothelial carcinoma/Clear cell carcinoma**- PAX8-, Napsin- Hepatocyte nuclear factor-1β-, Uroplakin 2 +.
- **Metastatic Clear cell Renal cell carcinoma**- CAIX, Vimentin, CD10.
- **Prostatic adenocarcinoma**- NKX 3.1, PSA, P501s
- **Metastatic CCA from ovary or endometrium** - mainly clinical/radiology
- **Cervical or Vaginal CCA**- mainly clinical/radiology
Napsin A:

- It’s an aspartic protease.
- It is predominantly expressed in Lung and Kidney.
- Lungs: Cytoplasm of alveolar ‘Type II’ pneumocytes.
- Adenocarcinoma of lung
  - Kidneys: Cytoplasm of proximal tubular epithelial cells. (Renal Cell Carcinoma < Papillary RCC.)
- Ovarian CCA
- Arias Stella reaction.
- Why is Napsin positive in CCA?
# Differential Diagnosis of Atypical Nephrogenic Metaplasia and Clear Cell Adenocarcinoma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ANM</th>
<th>Clear cell adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male predominance</td>
<td>Female predominance</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Hematuria and voiding symptoms</td>
<td>Hematuria and voiding symptoms</td>
</tr>
<tr>
<td>Biologic behavior</td>
<td>Benign</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Location</td>
<td>No apparent predilection</td>
<td>(21% died within 4 yrs)</td>
</tr>
<tr>
<td>Size</td>
<td>Small (mean, 3.9 mm)</td>
<td>Urethra^b</td>
</tr>
<tr>
<td>Microscopic findings</td>
<td>Absent</td>
<td>Large</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Absent or inconspicuous</td>
<td></td>
</tr>
<tr>
<td>Stromal edema</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Luminal mucin</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Clear cell change</td>
<td>May be seen</td>
<td>Common</td>
</tr>
<tr>
<td>Hobnail cells</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Infiltrative growth</td>
<td>Usually absent</td>
<td>Present</td>
</tr>
<tr>
<td>Psammoma bodies</td>
<td>Absent</td>
<td>May be seen</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Invariably present</td>
<td>May present</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear enlargement</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear hyperchromasia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear pleomorphism^a</td>
<td>Minimal</td>
<td>Present</td>
</tr>
<tr>
<td>Immunostaining</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>34βE12</td>
<td>Positive (occasionally negative)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>Positive</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cytokeratin 20</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>EMA</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MIB labeling index</td>
<td>≤5%</td>
<td>&gt;15%</td>
</tr>
<tr>
<td>bcl-2</td>
<td>Occasional positivity</td>
<td>Positive</td>
</tr>
<tr>
<td>DNA ploidy</td>
<td>Aneuploid pattern may be seen</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

^a PSA: prostate specific antigen; 34βE12: high-molecular-weight cytokeratin; EMA: epithelial membrane antigen.

^b Nuclear pleomorphism is more pronounced in clear cell adenocarcinoma.

^c Clear cell adenocarcinoma of the urinary bladder is rare, and the diagnosis should be made with extreme caution.
Take home message

• Need for multi-institutional study.
• The characteristic histomorphology of Clear cell adenocarcinoma of bladder.
• Differential diagnosis of Clear cell tumors of bladder
• Urothelial carcinoma, clear cell variant versus Clear cell adenocarcinoma (CCA) of urogenital tract.
• Pax 8
• Utility of Napsin A

Fortunately CCA is rare,

BUT occurrence of clear cells in bladder tumors is not .................
Case 2: Sarcomatoid Clear cell adenocarcinoma of Bladder

- 2008: 45/F Heart transplant-diffuse myocarditis
- 2017: 54 years-Tumor posterior bladder wall. No lesion elsewhere on scanning. No history of any tumor in the past.
- 2018: 55 years-Lung metastases

- Immunohistochemistry:
  Positive-CK7, Vimentin, GATA3, PAX8, P53
  Negative-CK20, Uroplakin2, P63, ER, WT1, BHCG
Diagnosis

Sarcomatoid Clear cell adenocarcinoma of bladder
Thanks!!!
**Mesonephros/Wolffian ducts:**
Males: urogenital structures that include the epididymis, vas deferens, and seminal vesicles that differentiate from this structure.
Female: Degenerates. Epoophoron and Skene's glands may be present. Also, lateral to the wall of the vagina a Gartner's duct or cyst could develop as a remnant.

**Mullerian ducts Paramesonephric ducts:**
Females - fallopian tubes, uterus, cervix, and the upper two third of the vagina.
Males - in the male, they are lost. Or rudimentary testis appendix
Probable points/criterias for CCA-

• A need to devise strict diagnostic criterias is very important
• NA like areas (Classic papillary, tubular, tubulo-papillary morphology and Hobnail cells)
• PAX8 +
• If predominantly solid areas & cells are positiv for PAX8 and or Napsin, accept.
• Rule out primary in Female genital tract and kidney (although it’s the solid variant which enters into DD of Clear Cell RCC, but not the classic one).
• Papillary, tubulopapillary Prostate adenocarcinomas?, no, but go ahead with NKX 3,1 in the panel.
• No GATA3 in the panel.
• Catch hold of someone reliable- PAX8, Napsin etc