Metastatic Adenocarcinoma of the Urachus
A Clinical Pathological Case Presentation
Michelle Longpre, Ted Jones, Nevin Murray, Daniel Rapoport

BUT...

• Before we get into the really interesting case of advanced adenocarcinoma of the urachus

• Some useful tips for Jr. Residents on managing a common case seen at SPH.
TOO THICK FOR METAL CUTTERS...
THE FIRE DEPARTMENT HAS OFTEN TRIED BEFORE YOU GET THERE

REBAR CUTTERS WILL WORK FOR THIS ONE
+ PLASTIC SURGERY CONSULT TO PUT IT BACK TOGETHER AFTER
11-10-17

NEED:
RT: KETAMINE AND PROPOPHOL

ASSIST: IRRIGATION TO KEEP THINGS COOL

TOOLS: BURR DRILL
TONG DEPRESSORS
TOWELS
FACEMASK AND GOWN

BURR DRILL
NOW BACK TO THE URACHUS
History of Mr. BL

- 41 yr old previously healthy male with painless Gross Hematuria in Sept 2010
- Initially treated by GP for UTI
- When this failed to relieve Sx, Urine cytology and CT KUB were ordered by GP
- Urine cytology x2:
  - inadequate cells
  - negative
- Referred to Urology for further work-up of Gross Hematuria

Urologist Work-up

- CT KUB
  - large calcified mass at dome of the bladder

- Cystoscopy
  - Solitary Papillary bladder tumor on the post wall near the dome.
  - 2cm in size
Imaging with contrast

- CT Chest, abdo, pelvis
- 14 Oct 2010
- 6x5.5x5cm partially calcified hypo-attenuating mass in the bladder dome. It is contiguous with a small bowel loop and associated with several enlarged nodes in the peri-sigmoid region.
Embryology of the Urachus

A. Allantois
Mesonephros
Mesonephric duct
Mesonephric diverticulum
Ureteral bud
Ureteral sinus
Cloacal membrane
B. Urachus
Uterine tube
Kidney
Ovary
Uterus
Vagina
C. Urinary bladder
Penis
Testis
Ureter
Ductus deferens
E. Urinary bladder

---

Embryology of the Urachus

A. Chorion
Connecting stalk
Umbilical arteries
Intestine
Yolk sac
Atlantic blood vessels
B. Umbilical vein
C. Urachus
D. Urinary bladder
Intestine
Median umbilical ligament
Uterus
Ureter
Rectum
Normal Anatomy

- Urachus: runs from the umbilicus to the urinary bladder within the space of Retzius between the transversalis fascia and the peritoneum.

Adapted with consent from: Hina Arif Mumtaz

Normal Histology

- The urachus:
  - intramucosal
  - intramuscular
  - supravesical segments

- It contains 3 distinct tissue layers:
  - a canal lined by transitional cell epithelium
  - submucosal connective tissue
  - outer layer of smooth muscle.
  - Metaplastic columnar cells have also been found lining the canal
Benign Pathology

A. Urachal cyst-
Both ends close leaving an open central portion.

B. Urachal sinus-
Drains proximally into the umbilicus.

C. Patent urachus-
Entire length of median umbilical ligament fails to close.

D. Vesico-urachal diverticulum-
Distal communication to bladder persists.

Malignant Pathology

- Makes up <1% of all bladder tumors
- And <10% of all primary Adenocarcinomas of the bladder
- Typically occurs in younger patients (median 47-56yrs)
- Almost always Adenocarcinoma
  - Only rarely have Sarcomatoid, Squamous, or transitional cell elements been reported

Adenocarcinoma

- Usually display an enteric-type histology that is commonly seen in colorectal cancer
- Often have a glandular structure with mucin production
- MORE ABOUT THE HISTOLOGY LATER BY DR. JONES

Origins

- Two theories
  1. Tumors originate from enteric rests left behind from the cloaca during embryological development
  2. Metaplastic Pathway
     1. Support for this comes from the presence of AdenoCa in the GU tract that is not of cloacal origin.

Common Presentation of Urachal Adenocarcinoma

- Most patients present with locally advanced disease at diagnosis
- Symptoms:
  - gross hematuria and irritative voiding symptoms
  - have also reported voiding mucous-like material, consistent with the frequent mucinous enteric elements seen on histopathology.
  - patients may report a suprapubic or umbilical mass, pain or discharge from the Umbilicus.
- Peritoneal carcinomatosis and pseudomyxoma Peritonei may also be present on radiographic imaging.

Presentation continued..

- Diagnosis:
  - supported by the presence of normal transitional cell epithelium overlaying the tumor
  - However, destruction of this layer frequently occurs. Making the Diagnosis more difficult
- Urachal VS nonurachal adenocarcinomas
  - with some studies suggesting a better prognosis for the urachal cohort
- nonurachal adenocarcinoma:
  - cystitis cystica or cystitis glandularis transitioning through to the malignancy
Ultrasound:
Complex solid / cystic mass. +/- calcification

Doppler:
Vascular lesion  with low resistance flow

CT Scan:
Asymmetric midline thickening / mass at the bladder dome
Focal regions of low attenuation (mucin) - 60%
Punctate, stippled, curvilinear or peripheral calcifications - 50-70%
Muscle invasion +/- metastases at the time of presentation - 95%

MRI:
Better assessment of invasion and spread
Improves surgical planning

Sheldon et al Criteria

- tumor in the dome of the bladder;
- absence of cystitis cystica and cystitis glandularis;
- predominant invasion of the muscularis or deeper tissues with a sharp demarcation between the tumor and surface bladder urothelium that is free of glandular or polypoid proliferation;
- presence of urachal remnants within the tumor;
- extension of tumor into the bladder wall with involvement of the space of Retzius, anterior abdominal wall, or umbilicus;
- no evidence of a primary neoplasm elsewhere.


MD ANDERSON

- Location in the bladder dome or elsewhere in the midline of the bladder
- Sharp demarcation between tumor and normal surface epithelium
- Supportive criteria:
  - Enteric-type histology
  - Absence of urothelial dysplasia
  - Absence of cystitis cystica or cystitis glandularis transitioning to the tumor

Sheldon et al. Staging

- Stage I—no invasion beyond the urachal mucosa;
- Stage II—invasion confined to the urachus;
- Stage III—local extension to the...
  - (a) bladder, (b) abdominal wall, and (c) viscera other than the bladder;
- Stage IV—metastasis to...
  - (a) regional lymph nodes
  - (b) distant sites.

Work-up

- PE: Palpate the umbilicus and suprapubic area for masses, pain or discharge
- If considering an occult primary: Breast exam, prostate and rectal exam
- Cystoscopy + TURBT + EUA
- Radiological evaluation with: contrast CT or MRI
- Metastatic workup: CT chest
- If considering an occult primary: SOB, colonoscopy, esophagogastroduodenoscopy, breast Mammogram
Markers

- Consistent with other enteric-type adenocarcinomas, urachal cancers may express detectable serum levels of:
  - carcinoembryonic antigen (CEA), CA125 and cancer antigen (CA) 19-9
  - these markers were elevated in approximately half of patients, with reductions in markers occurring in parallel with radiographic response to systemic chemotherapy

TURBT

- 7 Oct 2011
- EUA was negative
- 24g of tissue removed
Colonoscopy

- 25 Oct 2010
- Colonoscopy to rule out a colonic primary
- No mucosal lesions found

Pathology TURBT

- Collect Oct 7, 2010
- Invasive mucinous adenocarcinoma
- Immunostains:
  - +CK20, CDX2
  - - p63 and CK7
- The stains are consistent with either mucinous urachal or intestinal adenocarcinoma
What is the next step??

- Summary so far:
  - 41 yr old healthy male with mucinous Urachal Adenocarcinoma
  - Abutting the Colon
  - Enlarged LN on CT scan
  - Surgery vs Chemotherapy (primary vs adjuvant vs neoadjuvant)

Operation Performed

- Oct 27, 2010
- Radical Cystectomy with removal of the urachus and umbilicus
- nerve sparing, and orthotopic neobladder (studer pouch)
- Bilateral extended LND
- Removal of peritoneal lesions suspected to be solitary mets
Pathology Cx

- Invasive mucinous adenocarcinoma
- Invades 3mm into perivesical fat
- 35mm in size
- Peritoneal deposit: extensive involvement of peritoneum with multiple large deposits positive for AdenoCa
- All margins negative
- No LVI seen
- LN:
  - Right: One of 4 LN positive, no extranodal spread
  - Left: No positive LN
Pathology of Adenocarcinoma of the Urachus

DR. EDWARD JONES
Clinical Professor
Department of Pathology & Laboratory Medicine

Risk Factors For Recurrence

- Overall outcomes have not been linked to choice of radical vs partial cystectomy
- However, En-Bloc removal has lead to better survival
- Surgical Margins
  - Few long-term survivors
- Peritoneal Carcinomatosis
- Positive LN
- Distant metastasis
  - There is no difference in outcomes with Distant metastasis vs Lymph node involvement
Fig. 3. Median survival from diagnosis of metastatic disease (26 cases) was 24 months with median follow-up of 29 months (range 2 to 100).
Medical Oncology

4 Nov 2010 seen by Medical Oncology

- Given gemcitabine, cisplatin x4 cycles
- Tolerated well initially, but required dose adjustment for neutropenia and fatigue.

The role of Chemotherapy in Andenocarcinoma of the Urachus

DR. NEVIN MURRAY
Clinical Professor
Medical Oncologist at the BCCA
Palliative Systemic Chemotherapy

- **Single agent therapy**
  - 5FU (GIFUFA or GIFUINF) or capecitabine (GIAVCAP)
  - 25-30% RR

- **Doublet therapy**
  - 5FU + irinotecan (GIFOLFIRI)
    - Main toxicity is GI
  - 5FU + oxaliplatin (UGIFOLFOX)
    - 55-60% RRs
    - Equivalent in first line
    - Usually sequence
  - Capecitabine based combos are an option if pump or IVAD access not available (UGICAPOX or UGICAPIRI)

- **Doublet therapy plus bevacizumab**
  - FOLFIRI + bevacizumab (UGIFFIRB)

Progress Timeline in Advanced Colorectal Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Panel 1</th>
<th>Panel 2</th>
<th>Panel 3</th>
<th>Panel 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962-1995</td>
<td>5-FU</td>
<td>5-FU/ LV</td>
<td>5-FU/ LV</td>
<td>5-FU/ LV</td>
</tr>
<tr>
<td></td>
<td>Leucovorin</td>
<td>Capecitabine</td>
<td>Capecitabine</td>
<td>Capecitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irinotecan</td>
<td>Irinotecan</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Median Survival</td>
<td>6 to 12 months</td>
<td>14 to 16 months</td>
<td>20 to 23 months</td>
<td>23 - ?? months</td>
</tr>
</tbody>
</table>

Can we afford this?
Can we CURE more patients??
Estimated Costs of Therapy for Metastatic Colon Cancer/cycle

- Infusional 5FU ~ $50
- Capecitabine ~ $700
- FOLFOX ~ $1,750
- FOLFIRI ~ $250
- plus bevacizumab + $1,750
- plus cetuximab + $3,350
- plus panitumumab ~ $2,500

Adjuvant Therapy for Colon Cancer

- Goal
  - to eradicate micrometastatic disease
- In whom?
  - High risk stage II - T4, obstruction, high grade, < 8 nodes examined
  - Risk of Recurrence ~ 20%
  - Stage III
  - Risk of Recurrence ~ 40 to 80%
Adjuvant Therapy for Colon Cancer
Current BCCA Guidelines

- Hi risk stage II, and stage III not suitable for FOLFOX
- 6 months of 5FU based therapy
- capecitabine preferred (BCCA code: GIAJCAP) - less toxic, more HFS
- Monthly IV bolus 5FU/LV still an option (GIFFAD)
- 30% proportional reduction in risk of recurrence and death
- **Selected high-risk stage II may be considered for FOLFOX

Stage III Colon Cancer
- 6mos X 5FU-oxaliplatin aka FOLFOX (BCCA code: UGIAJFFOX)
  - Further 24% risk reduction in recurrence 6mos X 5FU-based monotherapy
  - Consider a cumulative 50-55% proportional reduction in risk of 3-5 year recurrence compared to surgery alone
  - Neuropathy is a problem

### Regimen Administration Decrease in Risk of Recurrence vs Surg alone Toxicities

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Administration</th>
<th>Decrease in Risk of Recurrence vs Surg alone</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>Oral 1250mg/m2 BID q14/21d X 24 weeks (8 cycles)</td>
<td>30-35%</td>
<td>HFS, stomatitis, diarrhea, bili, neutropenia Rare: DPD def TRM: 0.7%</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>IVAD Q2weekly infusional 5FU +LV+ oxaliplatin X 24 weeks (12 cycles)</td>
<td>50-55%</td>
<td>Neuropathy (early &amp; late), N/V, alopecia, stomatitis, diarrhea, neutropenia, thrombocytopenia Rare: ILD TRM: 1%</td>
</tr>
</tbody>
</table>
**CRC Management Summary**

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Surgery +/- Adjuvant Chemotx (RT if rectal)</td>
<td>Surgery + Adjuvant Chemotx (RT if rectal)</td>
<td>Palliative Chemotx +/- Surgery</td>
</tr>
<tr>
<td>5yS &gt;90%</td>
<td>5yS 75-80%</td>
<td>5yS 50-65%</td>
<td>MS 6m-21m</td>
</tr>
</tbody>
</table>

*Should be considered for Onc Referral*

---

**Back to MR. BL Pre-chemo**

- CT Abdo/pelvis/chest
- 10 Dec 2010
- Persistent 1.2cm pelvic LN in the right pelvis, unchanged from previous
- No lung mets, has previous granulomatous disease
Imaging Post Chemotherapy

- 8 JUNE 2011
- Persistent pelvic LN in the right pelvis, decrease in size.
- No new mets seen
Cystoscopy F/U

- 29 Mar 2011
- Good capacity
- Continent

- MARKERS: CEA (No other markers done)
  - MARCH 2011: 1.1
  - MAY 2011: <0.5
  - AUG 2011: 0.8
REFERENCES


Moore, Keith L. Before We Are Born: Essentials of embryology and birth defects. 6th ed.

THANK YOU

• Special thanks to:
  • Dr. Ted Jones
  • Dr. Nevin Murray
  • Dr. Daniel Rapoport
  • Dr. Peter Black
  • Dr. Allen Rowley
  • Dr. Jean Buckley