Hematuria, Kidney & Bladder Cancer for the Primary Care Provider
Shandra Wilson, MD

Overview
- Hematuria, cases
- What’s new in bladder cancer
- What’s new in kidney cancer

Definition of Microscopic Hematuria
- 3 or more RBC/hpf
- 3 specimens
- 3 weeks
  - No infection
- Of note – USPTF unclear of benefit of screening in asymptomatic population
  - Grade “I” 2012

AUA Best Practice Guidelines, 2001
Non-bloody red urine

- Beets
- Blackberries
- Drugs (pyridium)

Prevalence of Microscopic Hematuria

- 2.5% - 20% of the population

Most Common Causes of Hematuria

- UTI
- BPH
- Nephrolithiasis
- Idiopathic
- Genitourinary cancer
Other Causes of Hematuria
- Radiation cystitis
- Arteriovenous malformation
- Medical renal disease
- Trauma
- Exercise-induced hematuria
- Coagulopathy
- Benign familial/essential hematuria
- Papillary necrosis

Odds of Finding Pathology
- 40-90% of gross hematuria
- 5-10% of microscopic hematuria
- At least 40% of the time no etiology is found for asymptomatic microscopic hematuria

History of Present Illness
- Dysuria?
- Frequency?
- Recent respiratory infection?
- Menstruation?
- Previous episodes, work-up
Past Medical History

- h/o stones
- h/o XRT
- h/o bleeding disorders

Medications

- Pyridium
- Analgesic abuse

Social History

- Smoking
- Exposure to dyes, chemicals
- Exercise patterns
Physical Exam

- Age (cancer)
- Hypertension (associated with nephritis)
- Edema (associated with nephrotic syndrome)
- Pain – suprapubic, flank (infection)
- Possible DRE – (BPH)

Laboratory Evaluation

- UA, microscopy
- Urine culture
- Consider CBC
- Consider Creatinine

Rules to Remember

- Survey upper and lower tracts
- Recheck urine after tx for UTI or stone
- If patient has any of the following – refer to nephrology
  - Dysmorphic RBC’s
  - RBC casts
  - Proteinuria >500mg/dl
Ideal Upper Tract Study

- CT Urogram
  - 3 phases
  - Non-contrast to rule out calculi
  - Contrast to evaluate parenchyma
  - Excretion phase to evaluate GU lining

Lower Tract Evaluation

- Depends on age and risk factors
- Cystoscopy (CT misses CIS which is flat)
  - Not necessary for non-smokers under 40 yo
- Cytology on all patients
  - BTA stat; NMP22; UroVysion unclear positioning in algorithm right now
  - Cytology has accuracy issues too

No Sx of Primary Renal Dz, AUA

- Age > 40
  - Cystoscopy
  - Upper tract imaging
  - Cytology
- Positive Cytology
  - Cystoscopy
  - And treatment
- Negative Cytology
  - Consider BP, cytol 1 yr

- Age <40
  - Non-smoker
  - No chemical exposure
  - Upper tract imaging
  - Cytology
- Positive Cytology
  - Cystoscopy
  - And treatment
- Negative Cytology
  - Consider BP, cytol 1 yr

- Persistent hematuria
  - HTN, proteinuria
  - Eval for renal dz
- Gross hematuria
  - Abnormal cytology
  - Irritative sx:
    - Repeat complete eval

* With complete work-up, the risk of missing malignancy is <1%
Case Studies

- 42 yo mother of one-year-old twins complains of gross hematuria
- How do you proceed?

History and Physical Exam

- No dysuria/frequency/pain
- No h/o respiratory infection or stones
- No history of coagulopathy/non menstrual
- No history of radiation or surgery x c/s
- Non-smoker no chemical exposure
- Now what?

Laboratory Evaluation

- UA shows RBC’s
- CBC normal
- Creatinine normal
- No UTI on culture
- Now what?
No Sx of Primary Renal Dz

- Age > 40
- Cytology:
  - Upper tract imaging
  - Cystoscopy
- Positive Cytology: treatment
- Negative Cytology: Consider BP, cytol 1 yr *

- Age < 40
- Non-smoker
- No chemical exposure
- Upper tract imaging
- Cytology
- Positive Cytology: Cystoscopy, and treatment
- Negative Cytology: Consider BP, cytol 1 yr *

* With complete work-up, the risk of missing malignancy is <1%

Upper and Lower Tract Imaging

- US showed no abnormality of the kidneys
- Bladder US was unclear
- Now what?

Logical Algorithm

- Cytologies should be performed. Her cytology would have been abnormal and cystoscopy, biopsy would have been done showing bladder cancer.
- What happened:
  - Took patient to the operating room for abdominal exploration; husband called me on POD#1 to transfer
  - Entered bladder and spilled tumor throughout abdomen increasing risk of death dramatically
  - Patient required chemotherapy and cystectomy for spilled bladder cancer
  - I am working with patient’s attorneys to find possible reasonable settlement
Case 2

- 59 yo volunteer at Colorado Springs Zoo
- Gross hematuria with flank pain
- Now what?

History and Physical

- No dysuria/frequency/pain
- No h/o respiratory infection
- No history of coagulopathy
- No history of radiation or surgery
- Non-smoker no chemical exposure
- Now what?

Laboratory Evaluation

- UA shows RBC's
- CBC normal
- Creatinine normal
- No UTI on culture
- PSA done 3 months ago: 2.3ng/dl
- Now what?
Upper and Lower Tract Imaging

- CT scan abd shows L kidney stone 1x1cm
- Cytologies are atypical
- Now what?

Rules to Remember

- Survey upper and lower tracts
- **Recheck urine after tx for UTI or stone**
- If patient has any of the following – refer to nephrology for a glomerular problem
  - Dysmorphic RBC's
  - RBC casts
  - Proteinuria >500mg/dl

What Happened

- Pt had his kidney stone treated with shock-wave lithotripsy
- Meanwhile a bladder tumor grew in his bladder for a year
- Finally he underwent cystoscopy, biopsy, and eventually cystectomy
- I have worked with his attorneys to figure out if compensation is reasonable
Case 3

- 23 yo female with malaise goes to ED with microscopic hematuria
- Work up?

History and Physical

- Some dysuria/frequency/pain
- Generally feels crummy
- Possibly pregnant per her report
- No history of coagulopathy
- No history of radiation or surgery
- No chemical exposure
- Has smoked since she was 14yo
- Now what?

Lab Evaluation

- UA shows protein, RBC’s & Bacteria
- HCT 39%
- Creatinine 1.1
- < 100,000 colonies strep on culture
- bHCG negative
- Now what?
Upper and Lower Tract Evaluation

- Renal/bladder US – no obvious tumor
- Cytologies – negative
- Does she need anything else?

No Sx of Primary Renal Dz

Age > 40
- Cytology, Upper tract imaging, Cystoscopy
- Negative: Cystoscopy, Add treatment
- Persistent hematuria, HTN, proteinuria: Test for renal dz
- Gross hematuria, Abnormal cytology: Investigation to rule out complete rule

Age < 40
- Non-smoker
- No chemical exposure
- Upper tract imaging, Cytology
- Positive Cytology: Treat
- Negative Cytology: Consider BP, cytol 1 yr *

* With complete work-up, the risk of missing malignancy is <1%

What Happened

- Pt sent home with antibiotics for UTI
- Pt advised to f/u with gynecology
- Pt returned to the ED 2 more times over 6 months
- Ultimately diagnosed with glomerular disease requiring intensive medical therapy
- Pt sought legal advice for delay in diagnosis
Hematuria Summary

- Algorithm for hematuria is straightforward and makes sense
- Follow the algorithm for hematuria when presented with a patient
- Do not screen for microscopic hematuria unless you want more work
- Remember the stats:
  - 90% of pts with gross hematuria have pathology
  - 90% of pts with microscopic hematuria do not

Bladder cancer
Pioglitazone (Actos) & Bladder Ca

- 115,727 new users of oral hypoglycemic agents
- 470 patients diagnosed with bladder cancer
- 6,699 controls
- Increased risk of bladder cancer (1.83 hazard rate)
  - Highest rate: patient exposed > 24 mo’s (HR 1.99)
  - Cumulative dose > 28,000mg (HR 2.54)

Life Time risk of Bladder Cancer

- 1.17% of men 50-70yo develop TCC
- 0.34% women 50-70yo develop TCC
- Overall risk for all: 2.4% in the U.S.
- 70%-85% do not require cystectomy
How are we doing?

Superficial Bladder Cancer

- Greater than 98% of patients with bladder cancer have bleeding within 3 months of developing tumor (autopsy studies)
- Yet, recent SEER study evaluated 4,790 patients with NMI bladder cancer. Only 1 received appropriate treatment and follow-up
  - A statistically significant survival advantage was seen in patients who received at least half of the recommended care

Quick Review

- Superficial low grade disease: Strong survival (98%+), recurrence rates 30%
- Non-muscle invasive, high grade disease: Up to 20% require cystectomy; recurrence 60%+
  - Multiple tumors
  - Many recurrences
  - Large tumors
  - Progression in stage or grade
- BCG intravesically (mounts immune response)
  - Surveillance cystoscopy, maintenance treatments
FGFR3 Mutation Related to Favorable T1 disease

- 132 patients with pT1 bladder cancer from 2 academic centers
- FGFR mutations in 37% of cases
- FGFR correlated with lower grade tumors
- Lack of FGFR mutation and CIS were significant for predicting progression in univariate analysis at 6.5 years (P < 0.01)

Decrease in bladder cancer recurrence with Hexaminolevulinate enabled Fluorescence

- 551 participants, prospective study
- Randomization between white light & blue light cystoscopy with Hex (5-aminolevulinic acid)
  - Median time to recurrence 9.4 mo’s white
  - Median time to recurrence 16.4 mo’s 5ALA/blue
  - Cystectomy 7.9% white
  - Cystectomy 4.8% 5ALA/blue (p=0.16)
    - $850 and 2 hours prep for 5-ALA wash
    - 5-ALA is a component of heme synthesis and is taken up by cancerous cells most effectively

National Cancer Database Evaluation

- 40,388 patients with muscle invasive TCC
- Stage 2-4; Age 18-99
- Patients treated with cystectomy: 42.9%
- Patients treated with radiation: 16.6%
- Both figures are stable between 2003-2007
  - Average survival without treatment: 15 mos.
Review: Ileal Conduit Diversion

- **Advantages of Ileal Conduit**
  - Shorter operative time
  - Quicker recovery
  - Ease of care by others
  - Less reabsorption of urine
  - Preferred for radiation patients

- **Disadvantages of Ileal Conduit**
  - External appliance
  - Hernia at least 25%
  - Skin irritation

Continent Cutaneous Diversion

- **Advantages of continent cutaneous diversion**
  - Does not use urethra
  - Minimal change in external body image
  - No appliance required

- **Disadvantages of a continent cutaneous diversion**
  - Need for regular catheterization
  - Risk for reoperation for complications
  - Nitrogen absorption

Orthotopic Continent Diversion

- **Advantages of neobladder**
  - No need for external appliance
  - High daytime continence rate (93%)
  - Least change in lifestyle
  - No need for external appliance

- **Disadvantages of a neobladder**
  - Possible need for regular catheterization (5-20%)
  - Nocturnal incontinence 10-30%
  - Reabsorption of nitrogen
How much has gone on in your world in the last 10 years?

What are we doing differently?
### National Trends, Cont.

- **% receiving chemotherapy:**
  - 27% 2003
  - 34.5% 2007
  - **Our data:**
    - 8.3% 2005
    - 24.6% 2010
  - Now recommended by EORTC w level 1 evidence

U Fediri; J Urol 2011 185(1):72-8

### National Trends Cont.

- Shifting medical climate to “outcomes”
- Complication rates of cystectomy becoming more defined and range from 40-80%
- Peri-operative mortality rate 2.6%
- Mortality higher at low volume hospitals (OR 1.7)

Eur Urol 57(2): Feb 2010, 274-282

### Survival and High v. Low Volume Hospitals

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Survival Rate</th>
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<tbody>
<tr>
<td>Bladder</td>
<td>4%</td>
</tr>
<tr>
<td>Colon</td>
<td>3%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>17%</td>
</tr>
<tr>
<td>Lung</td>
<td>6%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
</tr>
<tr>
<td>Stomach</td>
<td>6%</td>
</tr>
</tbody>
</table>

ROBOTICS! Our world is changing!

Now – Our New World

Robotics History
- Introduced in 2000 in Europe and US
- Laparoscopic surgery using a robotic interface
  - 5:1 and 10:1 magnification
  - 3D visualization
  - Normal surgical manipulation
  - Finger tip instrument control
  - Screen-in-screen technology
  - Fluorescence technology
  - Tremor reducing technology
Robotics History

<table>
<thead>
<tr>
<th>Year</th>
<th>U.S.</th>
<th>International</th>
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<tbody>
<tr>
<td>2002</td>
<td>20</td>
<td>61</td>
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<td>2003</td>
<td>14</td>
<td>61</td>
</tr>
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<td>2004</td>
<td>26</td>
<td>79</td>
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<td>2005</td>
<td>59</td>
<td>90</td>
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<td>2006</td>
<td>235</td>
<td>355</td>
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<tr>
<td>2007</td>
<td>591</td>
<td>526</td>
</tr>
<tr>
<td>2008</td>
<td>200</td>
<td>226</td>
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</tbody>
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Robotic cystectomy

<table>
<thead>
<tr>
<th></th>
<th>Robotic</th>
<th>Open</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Mean EBL (ml)</td>
<td>258</td>
<td>575</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OR time (hr)</td>
<td>4.20</td>
<td>3.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to flatus (d)</td>
<td>2.3</td>
<td>3.2</td>
<td>0.0013</td>
</tr>
<tr>
<td>Time to BM (d)</td>
<td>3.2</td>
<td>4.3</td>
<td>0.0008</td>
</tr>
<tr>
<td>Analgesia (mg)</td>
<td>89.0</td>
<td>147</td>
<td>0.0044</td>
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<tr>
<td>Length of stay (d)</td>
<td>5.1</td>
<td>6.0</td>
<td>0.2387</td>
</tr>
<tr>
<td>Decreased QOL</td>
<td>2.3</td>
<td>2.6</td>
<td>0.5622</td>
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Eur Urol 2010; 57(2):196

Our Data

- Estimated blood loss
  - Robotic: 697 cc's
  - Open: 1202 cc's
- Transfusion rate:
  - Robotic: 9%
  - Open: 61%
- Rate of re-operation identical at 14% (hernia, ureteral stricture, wound closure, abscess)
- Death within 30 days of surgery:
  - Robotic: 0%
  - Open: 2.6%
- Same distribution of diversions
  - 27% ileal conduit
  - 3% continent diversion to skin
  - 70% orthotopic neobladder

University of Colorado 2003-2011
How do you do this with a Robot?

http://youtu.be/Kp_u_dKozY
http://www.youtube.com/watch?v=l8akuiW5ZzI&feature=player_detailpage

Robotics and Kidney Cancer

- Evolution:
  - Open nephrectomy
    - Removal of rib
    - Opening in pleural cavity
  - Open partial nephrectomy
  - Laparoscopic nephrectomy
  - Laparoscopic partial nephrectomy
  - Robotic partial nephrectomy (gold standard)

New: Robotic Partial Nephrectomy

<table>
<thead>
<tr>
<th>Laparoscopic v. Robotic Partial Nephrectomy</th>
<th>RPN</th>
<th>LPN</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td>140</td>
<td>156</td>
<td>0.04</td>
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<tr>
<td>Warm ischemic time</td>
<td>19</td>
<td>25</td>
<td>0.03</td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>136</td>
<td>173</td>
<td>.05</td>
</tr>
<tr>
<td>Length of Stay (d)</td>
<td>2.5</td>
<td>2.9</td>
<td>.03</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>2.5</td>
<td>2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Positive margin (n)</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Pelvicaliceal repair (%)</td>
<td>56</td>
<td>56</td>
<td>NS</td>
</tr>
</tbody>
</table>

Urology 2009 73(2):306-10
Review of National Comprehensive Cancer Network (NCCN) Guidelines - Kidney Cancer

- 65,000 Americans will be diagnosed with renal cancer in 2012
- 20% (13,500) expected to die of disease
- RCC has increased by 2% annually for the last 50 years - in part due to scanning
- Only 10% of patients have the triad of flank pain, hematuria, and a flank mass
- Most renal tumors are now found incidentally

UCLA Integrated Staging System

UCLA Integrated Staging
Renal Cell Cancer Review

- It is recommended that patients with stage Ia undergo partial nephrectomy if possible (<4cm)
- Partial nephrectomy is also recommended for stage Ib if technically feasible as well (4-7cm)
- For stage II or greater a radical nephrectomy is usually required
- Although distant recurrence-free survival rates are comparable, thermal ablation has been associated with an increased risk of local recurrence

Renal Cell Cancer Review

- Patient selection is important to identify those who might benefit from cytoreductive nephrectomy
  - Good performance status
  - Pulmonary mets
  - Non-sarcomatoid pathology
- Resection of a solitary metastasis has been shown to be associated with long-term survival in a subset of patients

Renal Cell Cancer Review

- Pazopanib approved in late 2009
  - VEGF, PDGF, and c-KIT receptor inhibitor
  - PFS 11 months v. 2.8 months (placebo)
- Sunitinib approved 2006
  - PDGF, VEGF, c-KIT and CSF
  - 31% 1-year PFS Sunitinib v. 6% for IFN-a
- High-Dose IL-2
  - still considered as a first line
  - 4% remission
  - significant toxicity
- mTOR inhibitors and Sorafenib used in refractory cases
- No convincing data for adjuvant therapy
Summary

- Follow the algorithm for hematuria
- Send patients with renal or bladder masses for surgical evaluation
- Call/email with questions or concerns
  - Shandra.wilson@ucdenver.edu
  - 303-941-7168