Evaluation of Hematuria
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Red Urine-Not Always Blood
• Blood
• Myoglobin
• Metabolites: Porphyrin, bile salts, melanin, methemoglobin, homogenistic acid, urates, tyrosinosis
• Due to food: Beets, blackberries, food coloring
• Due to drugs: Nitrofurantoin, chloroquine, desfuroxamine, iron sorbitol, phenothalein

Microscopic Blood in the Urine-When is it Abnormal?
• Everyone excretes RBCs in their urine
• Normals excrete 66,000 RBCs (0-425,000)/12 hours
• Patients with glomerular disease excrete 40-120 million RBCs/12 hours
• Abnormal Hematuria: >500,000 RBCs/12 hours.

Micro-Hematuria: Scope of the Problem
Using >3 RBC/hpf on 3 occasions over 2-3 weeks:
• Prevalence
  Children: 2-6%
  Adults: 4%
  Men: 2-5%
  Women 5-11%
• 39% may have single episode
• Potential kidney donors: 12%

Detection of Hematuria-The Dip Stick
• Test Performance
  Sensitivity-93-100%
  Specificity-60-80%
  Negative predictive value ~98%
• False Positives: Myoglobin, povidone-iodine, H2O2, bacterial peroxidases
• False Negatives: Presence of ascorbic acid (supplements), formaldehyde (preservative), low pH

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Affiliation / Financial Interest | Organization
--- | ---
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DSMB/Adjudication | Celtic, Takeda
Medical/Scientific Advisor | Biogen, Questcor, Centocor, Lilly, GSK, Abbvie

Medicine/Scientific Advisor Biogen, Questcor, Centocor, Lilly, GSK, Abbvie

Bryant, J. Emergency Med, 2007
Use Urine Microscopy to Verify RBCs

Acanthocytes:
- 98% specific, 52% sensitive if >5% of RBCs in a urine sample; sensitivity >90% if found in 3 consecutive urine samples
- Not inducible by changes in pH, osmolality
- Urine RBCs can be dysmorphic but not indicate glomerular bleeding, such as these (B) commonly found crenated RBCs, caused by osmotic shifts in RBC water

Socioeconomic Impact

- Definitive diagnosis after initial work-up is made in only 50% of cases of microscopic hematuria
- Patients tend to undergo costly work-ups that often involve repeated, invasive urologic and radiologic studies
- After an initial negative work-up 1-3% of patients are found to have a urologic malignancy
- Most urologic associations (American, Canadian, British) suggest follow up for undiagnosed AMH at 6, 12, 24 and 36 months
- Development of gross hematuria, pain/irritation, abnormal cytology warrants repeat urologic evaluation
- Development of hypertension, acanthocytes, proteinuria warrants nephrologic evaluation
- After 3 years of follow up....??

Case #1-Isolated Microscopic Hematuria

A 22 year old Asian male was found to have hematuria during a routine school evaluation. The patient was otherwise healthy, had no complaints, no significant PMH and physical exam was unremarkable including a normal blood pressure on no medications. No FH of kidney disease. SCR was 0.8 mg/dl. Urinalysis showed no protein but did show acanthocytes. 24-hour urine contained 115 mg protein. Would you do a kidney biopsy?

a. No, because the patient does not have abnormal proteinuria and kidney function is normal
b. Yes, because the UA indicates glomerular bleeding
c. Yes, because the patient appears to have a systemic process and the kidney may be involved

Pathology Study 1
N=156
% of patients

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Study 1 N=156</th>
<th>Study 2 N=155</th>
<th>Study 3 N=145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6.4%</td>
<td>37%</td>
<td>83 (13% had no EM)</td>
</tr>
<tr>
<td>IgAN</td>
<td>33.3%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Thin GBM</td>
<td>12.8%</td>
<td>43%</td>
<td>7%</td>
</tr>
<tr>
<td>Mes Prox</td>
<td>23.7%</td>
<td>-</td>
<td>7%</td>
</tr>
<tr>
<td>FSGS</td>
<td>5.1%</td>
<td>-</td>
<td>3%</td>
</tr>
<tr>
<td>MGN, MPGN, HTN,</td>
<td>3.2%</td>
<td>-</td>
<td>3%</td>
</tr>
</tbody>
</table>

Average age of onset 20-30, male preponderance, prevalence higher in Asia than US, UK, Canada, rare in people of African descent. Most common form of GN in Japan, China, Singapore, Taiwan.

Pathology of Common Causes of Isolated Microscopic Glomerular Hematuria

<table>
<thead>
<tr>
<th>Pathology</th>
<th>IgAN</th>
<th>Thin GBM</th>
<th>Alport's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age of onset 50-70, male preponderance, prevalence highest in Asian males, females, rare in people of African descent. Most common form of GN in Japan, China, Singapore, Taiwan.</td>
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<tr>
<td>BDI familial benign hematuria is due to an autosomal dominant defect in the alpha 3 or 4 chains of collagen type IV, with basement membrane expression.</td>
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<tr>
<td>Isolated thin GBM disease may develop proteinuria and renal insufficiency.</td>
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</tr>
</tbody>
</table>

Isolated, Asymptomatic Microscopic Hematuria May:

• Resolve
• Persist Without Kidney Injury
• Persist With Kidney Injury

Natural History of Isolated Microscopic Hematuria

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Number of Patients</th>
<th>Number with Disappearance of Hematuria</th>
<th>Years to Disappearance of Hematuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6</td>
<td>5</td>
<td>4.2</td>
</tr>
<tr>
<td>IgAN</td>
<td>22</td>
<td>2</td>
<td>4.6</td>
</tr>
<tr>
<td>Thin GBM</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Mes Prolif</td>
<td>15</td>
<td>4</td>
<td>4.2</td>
</tr>
<tr>
<td>Minor Abnormalities</td>
<td>13</td>
<td>7</td>
<td>4.5</td>
</tr>
<tr>
<td>FPGN, DPGN</td>
<td>3</td>
<td>2</td>
<td>3.5</td>
</tr>
</tbody>
</table>


Natural History of Isolated Hematuria

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>IgAN</th>
<th>Thin GBM</th>
<th>Normal*</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>12</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Mean Age</td>
<td>30</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Macroscopic Hematuria</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cr Clearance</td>
<td>109</td>
<td>115</td>
<td>113</td>
</tr>
</tbody>
</table>

11 Year Follow-up

Hematuria 10 13 7**
Cr Clearance 100 110 113

*Mean Duration Hematuria 4 years; **5 of the 7 patients developed stones over the 11 year follow-up, suggesting they may have had crystaluria to start.

Niewohof et al., KI, 49:222, 1996

Natural History of Isolated Hematuria

100 patients with AMH followed for an average of 32 months

Kim et al, KJIM, 2009

Case #2-Isolated Microscopic Hematuria

A 69 year old white female developed muscle aches one year ago, was diagnosed with polymyalgia rheumatica. She was treated with prednisone, felt better, but upon taper symptoms became much worse. She then developed left foot drop. A tentative diagnosis of mononeuritis multiplex was made. SCr was 0.7 mg/dl. Urinalysis showed no protein but did show acanthocytes. 24-hour urine contained 178 mg protein. Would you do a kidney biopsy?

a. No, because the patient does not have proteinuria and kidney function is normal
b. Yes, because the UA indicates glomerular bleeding
c. Yes, because the patient appears to have a systemic process and the kidney may be involved

• No biopsy was done. Patient was followed and after several years hematuria resolved, kidney function remained normal. Presumptive diagnosis of IgAN

Case #2-Answer

• ANCA was 1:80
• Sural nerve biopsy was non-diagnostic
• A kidney biopsy was performed and showed pauci-immune crescentic GN

Case #1-Answer

- No biopsy was done. Patient was followed and after several years hematuria resolved, kidney function remained normal. Presumptive diagnosis of IgAN
Proteinuria Present (≥500 mg/day)  
Abnormal Renal Fxn  
Possible Systemic Process  
Potential Kidney Donor

<table>
<thead>
<tr>
<th>Proteinuria Present</th>
<th>Abnormal Renal Fxn</th>
<th>Possible Systemic Process</th>
<th>Potential Kidney Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Proteinuria</td>
<td>Normal (stable)</td>
<td>No Systemic Process</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

Isolated Hematuria and ESRD-Adults

107,192 Japanese were screened with a single urine dipstick:

- 18-29: Men 0.9%, Women 7.3%
- >80: Men 8.5%, Women 15.3%

10 years later the odds ratio for developing ESRD was calculated:
- Men vs. Women: 1.4
- Hematuria vs. no hematuria: 2.3
- Proteinuria vs. no proteinuria: 15

Iseki et al, Kidney Int, 1996

Isolated Hematuria and ESRD-Adolescents/Young Adults

Over 1 million Israeli conscripts were screened for AMH, mean age 17 (16-25). Diagnosis, ≥5 RBC/hpf, 3 occasions, confirmed by microscopy, other etiologies and co-morbidities (e.g. proteinuria) excluded

- ESRD due to glomerular disease was double in the hematuria + group
- HR of about 19 for ESRD in hematuria + group
- Annual prevalence of AMH was 0.2-0.5%
- Cannot use these data to recommend mass screening, but can use these data to recommend good follow up if AMH is discovered

Vivante et al., JAMA, 2011

Proteinuria Changes Everything

In IgAN:

- Proteinuria (g/d)  
  - 0.3-0.99: ESRD over 7-10yrs 40%
  - 1-1.99: 25-35%
  - 2-2.99: 40%
  - >3: 60%

Hall et al, Clin Nephrol 2004

Natural History of Hematuria with Proteinuria

Iseki et al, Kidney Int, 1996
Case #3-Systemic Disease and Macroscopic Hematuria

A patient with a past history of SLE (nephritis) and clotting due to antiphospholipid syndrome was taken off AZA 3 months ago. She called to say she saw blood in her urine. SCr was 0.7mg/dl, P/C ratio was 0.9, and INR was 3.5 on her usual dose of warfarin. What is the next step?

a. Stop the anticoagulation because she is bleeding due to a high INR
b. Restart immunosuppression with AZA, and add high dose prednisone 1mg/kg/d
c. Do a kidney biopsy
d. Perform a urinalysis
e. Do cystoscopy

Urine Microscopy Showed Acanthocytes

What will you do now?

a. Stop the anticoagulation as she is bleeding due to a high INR
b. Restart immunosuppression with AZA, and add high dose prednisone 1mg/kg/d
c. Do a kidney biopsy
d. Do cystoscopy

WARFARIN RELATED NEPHROPATHY

AKI appears shortly after INR acutely increases to >3.0.

• WRN is common: Seen in 33% (CKD) and 16% (no-CKD) of warfarin-treated patients whose INR acutely rises to >3.0
• Patients with WRN have increased mortality (one-year mortality rate 31.0% versus 18.9% in no-WRN patients).
• WRN accelerates the progression of CKD
• WRN should be suspected on biopsy of patients on warfarin if the RBC casts are disproportionate to the degree of underlying glomerular injury
• WRN may be part of a broader Anticoagulant-Related Nephropathy-ARN, so switching anticoagulants is questionable

WRN is Common

• 103 CKD patients on warfarin therapy with serial measures of INR and serum creatinine
• Of these, 49 patients experienced at least one INR>3.0 and had Scr measured before and after the INR.3.0
• 18 of these patients (37%) had an unexplained increase in Scr>0.3 mg/dl associated with INR>3.0

Biopsy Findings in WRN

- RBC in Bowman’s space
- Glomeruli normal in appearance
- Dense RBC casts causing tubular obstruction
- RBC casts do not contain Tamm-Horsfall protein

Case #3-Answer

Kidney Biopsy Showed IgAN
No Histologic Evidence of LN or WRN
Case #4-Macroscopic Non-Glomerular Hematuria

A 58 year old African American male complained of red urine and was found to have new hematuria. He had a SCr of 1.5 mg/dL and about a 500 mg/d urine protein excretion. These levels have been stable for years, and were attributed to long-standing, poorly-controlled hypertension. Blood pressure was now controlled. He was a former smoker, quit 5 years ago. He developed a DVT 2 months ago, and was on warfarin with an INR of 2.5. Urinalysis showed no bacteria, WBC, or casts, but he did have many eumorphic RBCs that were of uniform size. Renal ultrasound showed echogenic, 8cm kidneys. What next?

a. Perform a kidney biopsy for suspected GN
b. Strain urine for kidney stones
c. Send urine cytology
d. Do cystoscopy

Differential Diagnosis of Non-Glomerular Hematuria

- GU Cancer
- Nephrolithiasis (also hypercalcuria, hyperuricosuria)
- BPH
- Cysts
- Infection
- Anatomic Lesions (e.g. aneuva/malformation; hemangioma; angiomyolipoma; renal varixes)
- Hematologic (coagulopathy; platelet dysfunction; hemoglobinopathy)
- Ischemia/infarct; emboli; exercise; malignant HTN

Risk Factors for Urothelial Cancers

- Age (>40)
- Sex (males >> females)
- Smoking
- Episodes of macroscopic hematuria
- Irritative voiding symptoms; previous GU history
- Exposure to aromatic amines/benzenes
- Pelvic radiation
- Exposure to cyclophosphamide
- Phenacetin use (heavy)
- Exposure to aristolochic acid (herbal weight-loss)
- Parasitic infection (Schistosoma haematobium)

Hematuria in Adults-Cancer as a Function of Age, Symptoms, and Type of Hematuria

Age 50+ and gross hematuria are worrisome combination


Case #4-Answer

- This patient had cystoscopy that revealed a transitional cell carcinoma of the bladder
- It was felt that anticoagulation unmasked the cancer
- The proteinuria and elevated SCr along with smaller, echogenic kidneys on US were felt to be consistent with hypertensive nephrosclerosis
- The TCC was successfully removed

Approach to Patients with Asymptomatic Non-Glomerular Hematuria

- Image Upper Tract (radial CT or MRI-US) → Appropriate Referral
- Cytology (?) → Cystoscopy
- Age >40 or risk factors for bladder CA → Risk factors for bladder CA → Cystoscopy → R/O crystaluria, prostate exam → Consider angiogram → Observation
Performance Characteristics of Urine Cytology as a Screening Test for Bladder Cancer

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro Hematuria</td>
<td>0.45</td>
<td>0.86</td>
<td>0.11</td>
<td>4%</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>0.55</td>
<td>0.99</td>
<td>0.43</td>
<td>18%</td>
</tr>
</tbody>
</table>

Chou and Dana, Ann. Int. Med, 2010

Urine Cytology: Cost Effective?

The American Urologic Society recommends urine cytology only in patients with risk factors for significant disease because:

- Sensitivity is poor
- Cystoscopy is so good at detecting TCC that urine cytology provides unique information in very few cases:
  - In a series of 660 patients with TCC urine cytology was the only positive test in 4 (.06%). Therefore, the cost of cytology is high when cost is examined on the basis of unique diagnoses.

<table>
<thead>
<tr>
<th>Cytology</th>
<th>$8369</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystoscopy</td>
<td>$3235</td>
</tr>
</tbody>
</table>

Holland and Mariami, J. Urol., 2004

Bonus Case

A 40 year old white woman presented with flank pain and red urine. She had similar episodes twice before. She did not recall if she had other symptoms with these, specifically colds or other acute illnesses, but this time she had a sore throat that began about 3 days ago. She has not seen a physician regularly. Someone on her father’s side of the family required dialysis. Her father died of a stroke at age 45. Blood pressure was 145/95. Exam showed a red throat, clear lungs, unremarkable heart, and obesity, with a tender left flank. Urine dipstick showed large blood, 1+ protein, and no leukocytes. Urine sediment had too many RBCs to count, and they appeared to be eumorphic. SCr was 1.3 mg/dL. Which is correct?

a. You should quantify proteinuria and set up a kidney biopsy to rule out GN
b. You should send urine studies for calcium, oxalate, citrate, and sodium
c. You should get a detailed neurologic history
d. You should check complement component C3 and C4 levels
e. You should hospitalize, push fluids, and give narcotics for pain control

A Word About Loin-Pain Hematuria Syndrome

- The glomerular diseases most commonly associated with upper respiratory tract infections are IgAN and post-strep GN.
- IgAN occurs during the infection, usually soon after it is apparent
- Post-strep occurs after the infection is resolved; the lag is usually several days to a couple of weeks
- There is not much proteinuria and this amount could be accounted for by the hematuria
- The RBCs do not appear to be dysmorphic
- Loin Pain Hematuria Syndrome is a diagnosis of exclusion
- Stones are possible, and a flat plate could be helpful, unless the stones were radio-lucent; also would not expect an increased SCr with stones under most circumstances
  - But this patient appears to have either CKD or AKI, and a relevant family history ANSWER: C → PCKD with cyst rupture

Group Discussion

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A Word About Loin-Pain Hematuria Syndrome

- Unexplained, disabling chronic flank pain and hematuria:
- Syndrome characterized by flank pain and micro- or macroscopic hematuria, often in Caucasian (93%) females (70%). No clear urologic etiology, although 50% have a history of nephrolithiasis, and most have abnormal urine risk factors for stones.
- Renal biopsy of these patients shows hemorrhage into multiple tubules. Glomeruli are normal on light and immunofluorescence, but EM often shows thin (51%) or thick (20%) GBMs.
  - Presumed Mechanism: Glomerular hematuria causes tubular obstruction, back-leak of glomerular filtrate, renal parenchymal swelling, with stretching of the renal capsule causing pain, plus an abnormal pain response. Correlation with stones remains obscure.
References


