

## Evaluation of Hematuria

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## DISCLOSURE STATEMENTS

Nothing to disclose

## Red Urine-Not Always Blood

- Blood
- Myoglobin
- Metabolites: Porphyrin, bile salts, melanin, methemoglobin, homogentisic acid, urates, tyrosinosis
- Due to food: Beets, blackberries, food coloring
- Due to drugs: Nitrofurantoin, chloroquine, deferoxamine, iron sorbitol, phenolphthalein

Bryant, J. Emergency Med, 2007

### Definition:

## 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 which is equivalent to 2 or more RBCs/HPF (caveats: recent heavy exercise, menses, sexual activity, instrumentation)

## Definition

- Macroscopic
- Microscopic
- Asymptomatic: Not associated with pain (dysuria, loin pain, renal colic), renal dysfunction, hypertension, proteinuria, or macroscopic hematuria.
- Asymptomatic *Microscopic Hematuria (AMH)* is common and presents the most significant diagnostic and therapeutic challenges

## Micro-Hematuria: Scope of the Problem

Using >3 RBC/hpf on 3 occasions over 2-3 weeks:

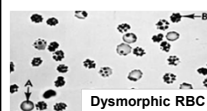
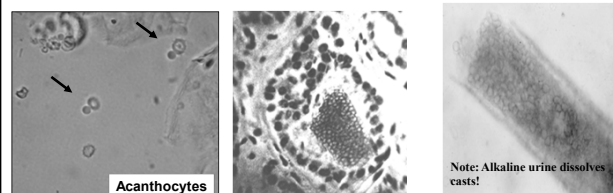
- Prevalence
  - Children: 2-6%
  - Adults: 4%
    - Men: 2-5%
    - Women 5-11%
  - 39% may have single episode
  - Potential kidney donors: 12%

## Detection of Hematuria-The Dip Stick

- Dipstick relies on oxidation of an organic peroxide on the test strip by the peroxidase-like activity of hemoglobin
- False Positives: Myoglobinuria, hemoglobinuria, povidone-iodine, H<sub>2</sub>O<sub>2</sub>, bacterial peroxidases, semen, Ph>9
- False Negatives: Presence of ascorbic acid (supplements), formaldehyde (preservative), low pH
- Test Performance
  - Sensitivity-93-100%
  - Specificity-60-80%
  - Negative predictive value ~98%

Schroder, BMJ, 1994; Huussen J, Neth J Med, 2004

## Use Urine Microscopy to Confirm RBCs Glomerular Hematuria



### Acanthocytes:

- 98% specific, 52% sensitive if >5% of RBCs in a urine sample; sensitivity >80% 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

## Hematuria in Adults

| Diagnosis       | Microscopic<br>(n>2000) | Macroscopic<br>(n>1200) |
|-----------------|-------------------------|-------------------------|
| Cancer          | 0.5-5%                  | 23%                     |
| Nephrolithiasis | 5%                      | 5-11%                   |
| Infection       | 1.7-4%                  | 33%                     |
| BPH             | 3-13%                   | 13%                     |
| Intrinsic Renal | 2-11%                   |                         |
| No Diagnosis    | 43-57%                  | 8-21%                   |

Sutton, JAMA, 263:2475, 1990; Boman, Scand J Urol Neph, 2001; Murakami, J Urol, 144:49, 1990; Sultana, Br J Urol, 78:691, 1999

## Approach to Hematuria *Identify Origin of the Blood*

| Glomerular Hematuria   | Non-Glomerular Hematuria |
|--|--------------------------|
| Micro- or Macroscopic  | Micro- or Macroscopic    |
| Abnormal Morphology<br>Proteinuria, active sediment                          | Normal morphology        |
| May be familial<br>- Check first degree relatives<br>- Look for hearing loss | Isolated finding         |

## To biopsy....or not to biopsy?

What nephrologists think about during the evaluation of microscopic hematuria

## 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?

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

### 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

### Case #1 - Answer

- 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

### Renal Biopsy for Hematuria?

|  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Yes</li> </ul> <p>Proteinuria Present (<math>\geq 500</math> mg/day)<br/>Abnormal Renal Function (Cr<math>\geq 1.3</math>)<br/>Possible Systemic Process<br/>Potential Kidney Donor</p> | <ul style="list-style-type: none"> <li>• No</li> </ul> <p>No Proteinuria<br/>Normal (stable) Renal Function<br/>No Systemic Process</p> <p><b>RATIONALE FOR NOT DOING A BIOPSY:</b> The glomerular diseases that are most likely to cause isolated hematuria have no proven treatments, and in the <i>absence of proteinuria</i> carry an excellent renal prognosis</p> |
|--|---|

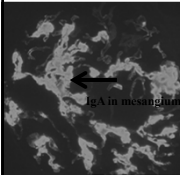
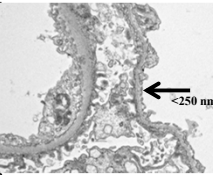

### Pathologic Diagnosis of Hematuria

Microscopic Hematuria in 165 patients with no other renal or systemic findings:

| Pathologic Diagnosis           | % of Patients      |
|--------------------------------|--------------------|
| None                           | 53 (but 13%-no EM) |
| IgAN                           | 30                 |
| Thin GBM                       | 4                  |
| Mesangial Proliferation        | 7                  |
| FSGS                           | 3                  |
| HTN, Membranous, Int Nephritis | 3                  |

Topham et al, Q.J. Med., 7:329:1994

### Pathology of Common Causes of Isolated Microscopic Glomerular Hematuria

| IgAN   | Thin GBM   | Alport's  |
|--|--|---|
|   |   |    |
| 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. | TBM/Familial benign hematuria is due to an autosomal dominant defect in the alpha 3 or 4 chains of collagen type IV, with heterozygous expression. Isolated thin GBM disease may develop proteinuria and renal insufficiency | ALPORT'S: X-linked is most common. Defect in the alpha 5 chain of type IV collagen. Affected males, female carriers. Many males will develop proteinuria and renal insufficiency within first 2 decades |

### Natural History of Isolated Hematuria

| Biopsy                   | IgAN | Thin GBM | Normal* |
|--------------------------|------|----------|---------|
| # of patients            | 12   | 13       | 20      |
| Mean Age                 | 30   | 35       | 30      |
| Macroscopic Hematuria    | 6    | 1        | 1       |
| Cr Clearance             | 109  | 115      | 113     |
| <b>11 Year Follow-up</b> |      |          |         |
| 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.

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

### Natural History of Isolated Hematuria

100 patients with AMH followed for an average of 32 months

|          | Bx          | F/up        |
|----------|-------------|-------------|
| SBP      | 105+/- 13   | 113+/-11    |
| DB       | 67+/- 7     | 68+/- 8     |
| UPRC     | 0.09+/-0.07 | 0.12+/-0.14 |
| Mean GFR | 99+/-22     | 101+/-24    |
| Scr      | 0.78+/-0.15 | 0.77+/-0.17 |

Adverse renal events ( ARE)

|              |   |       |
|--------------|---|-------|
| CKD          | 0 | 2(2%) |
| Proteinuria  | 0 | 6(6%) |
| Hypertension | 0 | 5(5%) |

Total of 10 pts ARE

- 4 proteinuria ( FSGS, IgAN, minor GN, MPGN)
- 4 HTN ( TBM, FSGS, 2 IgAN)
- 1 prot, HTN, CKD ( IgAN)
- 1 prot, CKD ( IgAN)

Kim et al, KJIM, 2009

### Isolated Hematuria and ESRD-Adults

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

|       | 18-29 | >80   |
|-------|-------|-------|
| Men   | 0.9%  | 8.5%  |
| Women | 7.3%  | 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

### Effect of Proteinuria on the Differential Diagnosis of Hematuria

#### Microscopic Hematuria in 135 patients:

|                      |                           |
|----------------------|---------------------------|
| Proteinuria <0.3 g/d | Proteinuria up to 2.4 g/d |
| Thin GBM 43%         | IgAN 46%                  |
| IgAN 20%             | FSGS 13%                  |
| Normal 37%           | Membranous, MPGN, AIN     |
|                      | Acute prolifer, Alport's  |

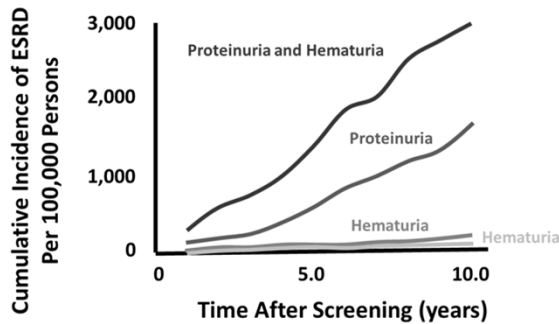
### Proteinuria Changes Everything

In IgAN:

| Proteinuria (g/d) | ESRD over 7-10yrs |
|-------------------|-------------------|
| 0.3-0.99          | 10%               |
| 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

### Kidney Biopsy For Microscopic Hematuria

|  |                                |
|--|--------------------------------|
| Proteinuria Present ( $\geq 500$ mg/day) | No Proteinuria                 |
| Abnormal Renal Function                  | Normal (stable) Renal function |
| Possible Systemic Process                | No Systemic Process            |
| Potential Kidney Donor                   |                                |

YES

NO

### Case #3-Systemic Disease and Macroscopic Hematuria

A patient with a past history of SLE (no nephritis) and clotting due to anti-phospholipid 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

### WARFARIN RELATED NEPHROPATHY

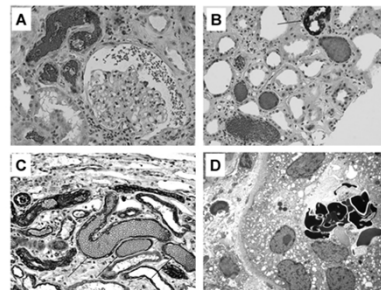
- AKI appears shortly after INR acutely increases to >3.0.
- WRN is common: Seen in 33% (CKD) and 16% (no-CKD) of warfarin-treated patients whose INR acutely rises to >3.0
  - Patients with WRN have increased mortality (one-year mortality rate 31.0% versus 18.9% in no-WRN patients).
  - WRN accelerates 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

Brodsky; Nephrology Clinical practice 2010

### 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

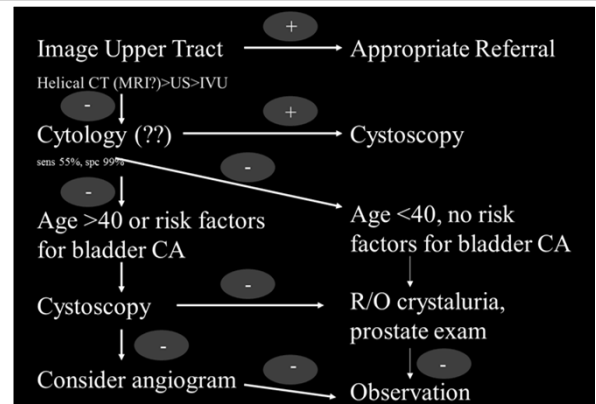
A 58 year old African American male complained of red urine and was found to have new hematuria. He had a SCR of 1.5 mg/dL and about a 500 mg/d urine protein excretion. These levels have been stable for years, and were attributed to long-standing, poorly-controlled hypertension. Blood pressure was now 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, 9cm kidneys. What next?

- Perform a kidney biopsy for suspected GN
- Strain urine for kidney stones
- Send urine cytology
- Do cystoscopy

## Differential Diagnosis of Non-Glomerular Hematuria

- GU Cancer
- Nephrolithiasis (also hypercalcuria, hyperuricosuria)
- BPH
- Cysts
- Infection
- Anatomic Lesions (a-v fistula/malformation; hemangioma; angiomyolipoma; renal varicies)
- Hematologic (coagulopathy; platelet dysfunction; hemoglobinopathy)
- Ischemia/infarct; emboli; exercise; malignant HTN

## Approach to Patients with Asymptomatic Non-Glomerular Hematuria





### Performance Characteristics of Urine Cytology as a Screening Test for Bladder Cancer

|                 | Sensitivity | Specificity | PPV  | Prevalence |
|-----------------|-------------|-------------|------|------------|
| Micro Hematuria | 0.45        | 0.86        | 0.11 | 4%         |
| Gross Hematuria | 0.55        | 0.99        | 0.43 | 18%        |

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.

cytology \$8369      cystoscopy \$3235

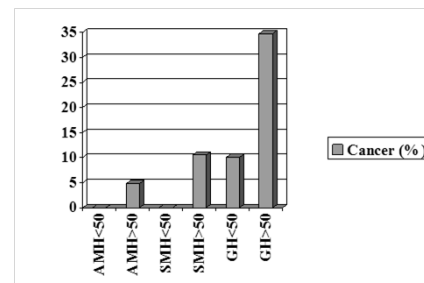
total cost = (cost of test)(#of tests)/(#of unique diagnoses)

Hofland and Mariani, J. Urol., 2004

### Risk Factors for Urothelial Cancers

- Age (>50)
- Male sex
- Smoking
- Episodes of macroscopic hematuria
- Analgesic abuse (Phenacetin)
- Irritative voiding symptoms, previous GU history
- Exposure to aromatic amines/benzenes
- Exposure to cyclophosphamide
- Pelvic irradiation
- 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

Sultana et al, Br. J. Urol., 78:691, 1996

## 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

## Bonus Case

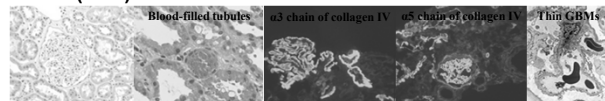
A 40 year old white woman presented with flank pain and red urine. She had similar episodes twice before. She did not recall if she had other symptoms with these, specifically colds or other acute illnesses, but this time she had a sore throat that began about 3 days ago. She has not seen a physician 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

- 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

## 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.

## **When No Diagnosis is Made**

- **If no diagnosis is made after initial evaluation, patients should be followed every six months**
- **It is not clear how often to repeat urologic studies.**
- **In one large study of 225 patients (Murakami et al, 1990) 91% of the serious (eg cancer, stones) lesions were found at the initial visit.**
- **An additional 9% (22 cases, 4 malignancies) were discovered over the next 1.5 years with extensive urologic testing every 6 months.**